

A critical review of the recent literature and selected therapy guidelines since 2006 on the use of lamotrigine in bipolar disorder

Anja Tränkner
Christian Sander
Peter Schönknecht

Department of Psychiatry
and Psychotherapy, University
Hospital Leipzig, Leipzig, Germany

Abstract: The anticonvulsant drug lamotrigine (LTG), a sodium channel blocker and inhibitor of glutamate release, has been found to have antidepressant effects in the treatment of bipolar disorder. It is recommended by certain therapy guidelines as a first-line agent for acute and maintenance therapy in bipolar depression, but there have been only some promising results of placebo-controlled trials on its acute antidepressant effects, and the recommendation in therapy guidelines has been reconsidered. On the contrary, positive results for maintenance therapy could be confirmed, and LTG is still a well-tolerated option, especially in patients with predominant depressive episodes. Antimanic effects are not shown in the literature, and its use is not advised in any guidelines that were examined. In conclusion, the findings of the present review article on treatment guidelines for bipolar disorder question the role of LTG in acute depressive states, and critically discusses its use, particularly in acute depressive states.

Keywords: lamotrigine, bipolar disorder, bipolar depression

Introduction

Bipolar disorder (BD) is a chronic mood disorder with episodes of elevated or irritable mood, referred to as mania (or a milder form, hypomania), and episodes of depressive symptoms. The aggregate lifetime prevalence for bipolar 1 disorder (BD1) is 0.6%, for bipolar 2 disorder (BD2) is 0.4%, and for subthreshold BD is 1.4%.¹ Treatment of different affective conditions is challenging; distinct treatment strategies, not only for acute episodes, but also for prevention of relapse of either depression or mania are essential. Different guidelines dealing with this problem are published, and because of newly approved drugs and an increase in studies that are being conducted, publications need to be edited permanently. We would like to discuss the changing role of lamotrigine (LTG) in selected treatment guidelines based on findings in publications dealing with LTG actions in the acute treatment and prevention of BD, mainly by including publications cited by the named guidelines (see Table 1). When the first guidelines were published pertaining to LTG as a treatment option for BD, only data with positive and supportive results were available, and it was strongly recommended as a first-line agent. When meta-analyses including more modest or even negative results were published, the role of LTG was reconsidered.

LTG, an antiepileptic drug that has been approved by US Food and Drug Administration (FDA) since 1993, acts through the inhibition of the sodium-dependent release of glutamate by blocking voltage-sensitive sodium-channels.² Additionally, LTG diminishes neuronal transmission through blocking N-type calcium-channels

Correspondence: Peter Schönknecht
Department of Psychiatry and
Psychotherapy, University Hospital
Leipzig, Leipzig, Germany, Semmelweisstr,
10, DE-04103 Leipzig, Germany
Tel +49 341 972 4506
Email peter.schoenknecht@medizin.
uni-leipzig.de

Table 1 Included guidelines and a summary of their recommendation for LTG use in depression and mania in acute or maintenance therapy are shown

Therapy guideline	Acute treatment: depression	Acute treatment: mania	Maintenance treatment	Main studies included
NICE guideline ¹⁰	Not recommended for initiated single use in BD I	Not recommended	Add-on therapy	Bowden et al ²⁹ Calabrese et al ^{21,37} Ichim et al ³⁶ Nierenberg et al ³⁵
WFSBP guideline ¹¹⁻¹⁵	Level: "B" (2002) Category of Evidence: "B" Recommendation Grade: "3" (2010)	Category of Evidence: "E," negative evidence	Level: "A"	Hurley ⁴⁶ Ichim et al ³⁶ Kusumakar and Yatham ⁴⁷ Nierenberg et al ³⁵ Nolen et al ²⁸ Schaffer et al ²⁷ van der Loos et al ³² Walden et al ⁴⁸⁻⁵⁰
CANMAT and ISBD guideline ⁹	First-line agent	Not recommended	First line agent, especially for depressive episodes	Goldsmith et al ⁵ Calabrese et al ^{1,23} Frye et al ²⁴ Geddes et al ²² Geddes et al ²² Maina et al ⁵¹ Nolen et al ²⁸ Sharma et al ⁵² Suppes et al ⁵³ Bowden et al ³⁸ Calabrese et al ²¹ Frye et al ²⁴ Geddes et al ²² Goodwin et al ²¹
BAP guideline ⁸	Recommendation Grade "A", Category of Evidence: I	No information given	Category of evidence: I, especially for depressive episodes	Bowden et al ^{29,38,54} Brown et al ^{25,26} Calabrese et al ^{21,30,37} Dosssett et al ⁵⁵ Frye et al ²⁴ Ghaemi et al ⁵⁶ Goodwin et al ³¹ Geddes et al ²² Goldsmith et al ⁵ Ketter et al ⁴¹ Calabrese et al ^{23,37,62} Goldsmith et al ⁵ Smith et al ⁴⁴ van der Loos et al ³²
S3 guideline ¹⁷	Recommendation Grade: "0"	No recommendation possible, insufficient data	Recommendation grade: "B" for depressive episodes No information given for manic episodes	Licht et al ⁴³ Mokhber et al ⁵⁷ Nierenberg et al ³⁵ Nierenberg ⁵⁸ Nolen et al ²⁸ Rubio et al ⁵⁹ Schaffer et al ²⁷ Schieber et al ⁶⁰ Spaulding et al ⁶¹ van der Loos et al ³²
Ministry of Health clinical practice guidelines: bipolar disorder ⁶	Add-on treatment in patients already on lithium, Recommendation Grade "A"	Not recommended	When antidepressant effect occurred in acute state, Recommendation grade: "A"	

Note: Studies cited by guidelines were given.

Abbreviations: LTG, lamotrigine; NICE, National Institute for Health and Clinical Excellence; WFSBP, World Federation of Societies of Biological Psychiatry; CANMAT, Canadian Network for Mood and Anxiety Treatments; ISBD, International Society for Bipolar Disorder; BAP, British Association for Psychopharmacology.

and the potassium outward current.³ In mice treated with LTG (32 mg/kg), Prica et al⁴ showed a significant decrease in immobility time in a forced swimming test as an animal model for depression. By adding the sodium-channel activator, veratrine, this effect was reversed. This could not be repeated using different antidepressants, so the authors presumed that sodium channel blocking is a potential antidepressant mechanism of LTG.

Clinically, LTG is generally well tolerated, and the most common adverse events (AE) include headache, nausea, and rash.^{5,6} In trials comparing LTG with placebo (PLC), AE and rates of withdrawal due to AE did not differ significantly between groups. Seo et al⁶ found no association between the rates of AE and LTG dose when comparing doses of 50 mg and 200 mg LTG per day. In Stevens–Johnson syndrome, a hypersensitive reaction of the skin tissue and blood vessels due to drug exposure and in toxic epidermal necrolysis (also called Lyell’s disease, which is a more severe skin reaction as seen in Stevens–Johnson syndrome), the incidence in patients treated with LTG is approximately 0.13% for monotherapy and 0.08% in adults receiving LTG as adjunctive therapy.⁶ To avoid this condition, it is recommended that LTG be tapered over a 6-week period.⁷

Methods

We performed a search for the latest updates of treatment guidelines for BD among the following: the British Association for Psychopharmacology guidelines 2009;⁸ the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorder guidelines 2009;⁹ the National Institute for Health and Clinical Excellence (NICE) guidelines 2006;¹⁰ the World Federation of Societies of Biological Psychiatry guidelines;^{11–15} the Ministry of Health Clinical Practice Guideline: Bipolar Disorder;¹⁶ and the S3 guidelines on diagnostics and therapy of BD.¹⁷ The search was conducted using the electronic databases MEDLINE and PubMed, and the Cochrane Library. We obtained relevant articles on LTG from citation indices of the named guidelines (for a detailed presentation, see Table 1). We then performed a search for English language articles in the same electronic databases using the keywords “lamotrigine” and “bipolar depression,” as well as “lamotrigine” and “mania.” Obtained articles were selected if they were randomized controlled trials (RCT) with PLC, Phase III studies and meta-analyses including RCT; or Phase III studies or meta-analyses including RCT; or Phase III studies (Tables 2 and 3). The retrieved articles were compared with previous findings from the reference

lists and three more reviews were added,^{18–20} in addition to the single studies named in the guidelines (Table 2).

Results

LTG and treatment of BD

The first RCT comparing LTG over PLC in bipolar I depression was conducted in 1999 by Calabrese et al.²¹ A total of 195 patients received either LTG 50 mg/day, LTG 200 mg/day, or PLC as monotherapy. For the primary outcome measure, which was defined by a difference of 5.0 points in the 17-item Hamilton Rating Scale for Depression (HAM-D), the study failed. Nevertheless, the authors found a response within the first 3 weeks, and statistical significance using last observation carried forward (LOCF) could be shown in week 5 for patients taking 200 mg of LTG compared to the PLC group in the Montgomery–Åsberg Depression Rating Scale (MADRS), the Clinical Global Impressions scale for Improvement, and the Clinical Global Impressions scale of Severity (CGI-S). In 2009, Geddes et al conducted a meta-analysis of five RCTs published by GlaxoSmithKline (GSK) including Phase III studies and the RCT by Calabrese et al,⁸ and found a small but consistently positive effect of LTG monotherapy compared to PLC when the results were pooled.²²

When examined in detail, four of five studies were underpowered and failed to show a superiority of LTG over PLC. The relative risks of response (>50% reduction in the baseline scores of HAM-D and MADRS) and remission (<8 on HAM-D and <12 on MADRS) were calculated. The pooled risk ratio (RR) for a reduction of >50% in HAM-D was 1.27 (95% CI: 1.09–1.47, *df* = 4, *P* = 0.772) and 1.22 in MADRS (95% CI: 1.06–1.41, *df* = 4, *P* = 0.538). When the authors distinguished between mild (HAM-D < 24) and severe depression (HAM-D ≥ 24), a significant therapeutic effect of LTG compared to PLC (RR = 1.47, 95% CI 1.16–1.87, *P* = 0.001) could be found only in patients in a severe state of depression (regression coefficient = 0.30, 95% CI: 0.14–0.60, *P* = 0.04). There was no significant difference between BP 1 and BP 2 patients (regression coefficient = –0.06, 95% CI: –0.35 to 0.24, *P* = 0.705).

In 2008, Calabrese et al²³ published a similar overview of the results of these four Phase III studies by GSK, as well as the Lamictal 602 study,²¹ and the authors found that only in the Lamictal 602 study was there a significant reduction in the HAM-D score in the LTG group compared to the PLC group (*P* < 0.05). This result could not be repeated in the other four trials, and LTG and PLC did not statistically differ in terms of changes in the 17-item or 31-item HAM-D scores.

Table 2 Overview of included studies on the use of LTG in BD

Authors	Design	Sample	Duration	Treatment	Results
Bowden et al ³⁸ Jadad: 1	Open, multicenter study	75 patients, 41 rapid cycling	48 weeks	LTG: 25 mg/day week 1, increased to 200 mg/day, max 500 mg/day Add-on or monotherapy	MRS, HAM-D, and GAS (all patients); $P < 0.05$ LOCF: rapid cycling patients improved less in GAS and MRS; no difference in HAM-D change LTG versus PLC: $P = 0.02$ Lithium versus PLC: $P = 0.03$
Bowden et al ³⁹ Jadad: 4	Double-blind RCT	175 patients Bipolar I Maintenance treatment	72 weeks	LTG (100–400 mg/d) Lithium (serum levels of 0.8–1.1 mEq/L) Monotherapy	CGI-S: OFC versus LTG: $P = 0.002$ overall MMRM, MADRS: OFC versus LTG: $P = 0.002$, overall MMRM YMRS: OFC versus LTG: $P = 0.001$, overall MMRM CGI-S: OFC versus LTG: $P = 0.008$ overall MMRM, overall effect size = 0.22, MADRS: OFC versus LTG: $P = 0.005$, overall MMRM, overall effect size = 0.23
Brown et al ²⁵ Jadad: 4	Double-blind RCT	410 patients Bipolar I depression	7 weeks	LTG escalation regimen up to 200 mg/day according to Lamictal package insert ⁷ GSK, 2005 OFC: 6/25, 12/25, 6/50, or 12/50 mg/day	
Brown et al ²⁶ Jadad: 4	Double-blind RCT	410 patients Bipolar I depression	25 weeks	LTG escalation regimen up to 200 mg/day according to Lamictal package insert ⁷ GSK, 2005 OFC: 6/25, 12/25, 6/50, or 12/50 mg/day	
Calabrese et al ³⁰ Jadad: 4	Double-blind RCT	463 patients Bipolar I maintenance treatment	72 weeks	LTG (50, 200, 400 mg/day) lithium (serum levels of 0.8–1.1 mEq/L) Monotherapy	LTG (200/400 mg/day) versus PLC: $P = 0.029$ lithium versus PLC: $P = 0.029$
Calabrese et al ²¹ Jadad: 3	Double-blind RCT	195 patients Bipolar I depression	7 weeks	LTG (50 and 200 mg/day) Monotherapy	LTG (50 mg/day): HAM-D-17, $P = 0.24$ LTG (200 mg/day): HAM-D-17, $P = 0.08$ Additional pharmacotherapy: LTG 50%, PLC 56%, $P = 0.177$
Calabrese et al ³⁷ Jadad: 3	Open-label, multicenter	324 patients, 182 randomly assigned to maintenance phase	26 weeks	LTG (25 mg/day week 1–2; 50 mg/day, weeks 3–4; 100 mg/day week 5; max. 300 mg/day) Adjunctive treatment and monotherapy	
Chang et al ³⁴ Jadad: 1	Open-label, multicenter	109 patients Bipolar 2 depression	52 weeks	LTG (maximum dose 145.5 ± 113.2 mg/day) Adjunctive treatment	CGI-BP-S depression score (baseline to 52 weeks endpoint): $t = 13.6$, $df = 108$, $P < 0.001$
Frye et al ²⁴ Jadad: 5	Double blind crossover RCT	31 patients Bipolar 1/2, unipolar treatment-refractory depression/mania	18 weeks	LTG (maximum dose, 500 mg/day) GBP (maximum dose, 4800 mg/day) Monotherapy	CGI-BP response rate: LTG: 52%, GBP: 26%, PLC: 23%
Goodwin et al ³¹ Jadad: 4	Pooled analysis of two double blind RCT	638 patients Bipolar I disorder	78 weeks	LTG (50–400 mg/day fixed dose or 100–400 mg/day flexible dose) Lithium (serum levels of 0.8–1.1 mEq/L) Monotherapy	LTG versus PLC: $P < 0.001$ Lithium versus PLC: $P < 0.001$ LTG versus lithium: $P = 0.629$
Ichim et al ³⁶ Jadad: 2	Double-blind RCT	30 patients Bipolar I, mania	4 weeks	LTG (25 mg/day first week, 50 mg/day second week, 100 mg/day for last 2 weeks) Lithium (800 mg/day) Monotherapy	MRS score: LTG improvement 34.4 to 14.3, $P = 0.0002$ Lithium: improvement 31.6 to 13.2, $P = 0.0005$, no difference Same in BPRS, CGI-S and GAF scales

Licht et al ⁴³ Jadad: 3	Open randomized trial	155 patients Bipolar I maintenance treatment	Up to 5.8 years	LTG (100–400 mg/day) Lithium (serum levels of 0.5–1.0 mmol/L) Mono-therapy 6 months after randomization	Crude HRR (95% CI, LTG relative to lithium): 0.92 (0.60–1.40) Mania: crude HRR (95% CI): 1.91 (0.73–5.04) Depression: crude HRR (95% CI): 0.69 (0.41–1.22) LTG versus PLC: $P = 0.024$
van der Loos et al ³² Jadad: 5	Double-blind RCT	124 patients Bipolar I/2 depression	8 weeks	LTG (25 mg/day weeks 1 and 2; 50 mg/day weeks 3 and 4; 100 mg/day weeks 5 and 6; 200 mg/day weeks 7 and 8) Adjunctive treatment to lithium (serum levels of 0.6–1.0 mmol/L)	LTG versus PLC: time to relapse, median time 10.0 months versus 3.5 months; no formal statistic test done
van der Loos et al ³³ Jadad: 5	Double-blind RCT	124 patients Bipolar I/2 depression	68 weeks	LTG (200 mg/day) Paroxetine in nonresponders (20 mg/day) Adjunctive treatment to lithium (serum levels of 0.6–1.0 mmol/L)	
Nierenberg ³⁵ Jadad: 2	Open-label, multicenter study	66 patients Bipolar I/2 depression	16 weeks	LTG (50 mg/day for first 2 weeks; 50 mg for weeks 3 and 4; target dose of between 150 and 250 mg/day) Inositol (2.5 g to 5 g with a target dose of between 10 g and 25 g) Risperidone (0.5 mg and 1.0 mg with titration up to 6 mg) Adjunctive treatment	All between-group comparisons were not significant ($P > 0.10$)
Nolen et al ²⁸ Jadad: 3	Open randomized trial	19 patients Bipolar depression	10 weeks	LTG (25 mg/day for the first week; 50 mg/day in week 2; 100 mg/day in week 3; 200 mg/day in week 4; 300 mg/day in week 5; and finally 400 mg/day in weeks 6–10) Tranylcypromine (20 mg/day, increased each week with 20 mg/day to a maximum of 100 mg/day in weeks 5–10)	LTG versus tranylcypromine: no significant difference
Schaffer et al ²⁷ Jadad: 3	Double-blind RCT	20 patients Bipolar I/2 depression	12 weeks (Table 1) single studies	LTG (25 mg/day for 2 weeks; 50 mg/day for another 2 weeks; after week 5, a maximum of 200 mg/day) Citalopram (10 mg/day for 2 weeks, 20 mg/day for the next 2 weeks, up to a maximum of 50 mg/day) Adjunctive treatment	LTG versus citalopram: $P = 0.78$ No significant difference

Note: Jadad: a score for evaluation of RCT, developed by Jadad et al.⁶³

Abbreviations: LTG, lamotrigine; BD, bipolar disorder; MRS, mania rating scale; HAM-D, Hamilton Rating Scale for Depression; GAS, Global Assessment Scale; LOCF, last observation carried forward; RCT, randomized controlled trial; PLC, placebo; GSK, GlaxoSmithKline; OFC, olanzapine/fluoxetine combination; CGI-S, Clinical Global Impressions-Severity of Illness Scale; MIMR, mixed model repeated measure; MADRS, Montgomery-Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; CGI-BP-S, Clinical Global Impression-Bipolar Version-Severity Scale; CGI-BP, Clinical Global Impression Scale modified for Bipolar Disorder; GBP, gabapentine; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; HRR, hazard rate ratio; CI, confidence interval.

Table 3 Meta-analyses and review articles used in this publication and listing of included trials

Authors	Design	Studies included
Amann et al ¹⁸	Meta-analysis	SCAA2008 SCAA2009 SCA100223 SCA30924 SCA40910 SCAA2010 SCAB2005 Calabrese et al ^{21,30,37} Bowden et al ²⁹ Brown et al ²⁵ van der Loos et al ³²
Calabrese et al ²³	Report of five RCT	SCA100223 SCA30924 SCA40910 SCAA2010 SCAB2001
Cipriani et al ¹⁹	Meta-analysis	SCAA2008 SCAA2009
Geddes et al ²²	Meta-analysis and Meta-regression of five RCT	lchim et al ³⁶ SCA100223 SCA30924 SCA40910 SCAA2010 SCAB2001 Raw data sets conducted by GSK
Goldsmith et al ⁵	Review	Calabrese et al ^{21,30,37,64} Bowden et al ²⁹ Frye et al ²⁴ Obrocea et al ⁶⁵
Yildiz et al ²⁰	Meta-analysis of RCT	GW609 (GSK) GW610 (GSK) lchim et al ³⁶ Goldsmith et al ⁵

Notes: SCAA2008, SCAA2009, SCA100223, SCA30924, SCA40910, SCAA2010, SCAB2005, SCAB2001, GW609, and GW610 are raw data sets conducted by GSK.

Abbreviations: RCT, randomized controlled trials; GSK, GlaxoSmithKline.

In another RCT conducted with either unipolar or bipolar patients, LTG monotherapy was compared to gabapentin (GBP) monotherapy or PLC over the course of 6 weeks, with two subsequent crossover trials.²⁴ Overall response rates as a primary outcome, with response defined as “much improved” or “very much improved” in the CGI-Bipolar scale, were LTG 52%, GBP 26%, and PLC 23% (Cochrane’s $Q [n = 31, df = 2] = 6.952, P = 0.031$). A positive trend for the superiority of LTG monotherapy in the treatment of patients with refractory mood disorder could be shown (post hoc Q differences: LTG versus GBP, $Q_{diff} = 5.33, P = 0.011$; LTG versus PLC, $Q_{diff} = 4.76, P = 0.022$; and GBP versus PLC, $Q_{diff} = 0.08, P = 0.700$).²⁴

In 2006, Brown et al²⁵ compared LTG with the combination of olanzapine/fluoxetine (OFC) in the acute treatment of bipolar I depression. Primary outcome measure was defined as change in the CGI-S score from baseline. A significantly greater improvement in the OFC group compared to the LTG group could be shown ($P = 0.002$, overall mixed model repeated measures [MMRM]). Also in MADRS ($P = 0.002$) and Young Mania Rating Scale scores, a greater improvement among the OFC group was found ($P = 0.001$). The response rates of both treatment groups did not differ significantly (response defined as $\geq 50\%$ reduction in MADRS total score, OFC: 68.8% versus LTG: 59.7%, $P = 0.073$). These results could be confirmed in the follow-up trial, which was conducted over 25 weeks. Patients receiving OFC showed greater improvements in week 25 in CGI-S ($P = 0.008$ overall MMRM, overall effect size = 0.22) and MADRS total scores ($P = 0.005$ overall MMRM, overall effect size = 0.23). Time to response was shorter for the OFC group than for the LTG group, and response and remission rates were similar in both treatment groups.²⁶

LTG was compared to citalopram in a RCT by Schaffer et al in 2006.²⁷ The authors examined patients with BD1 or BD2 disorder who were in a current depressive episode, and in this small sample size ($n = 20$), both treatment groups had a significant reduction in MADRS score from baseline (LTG $\Delta -13.3$, $SD = 8.0$; $P = 0.001$; citalopram $\Delta -14.2$, $SD = 10.2$, $P = 0.002$), but no differences between these groups could be shown ($F = 0.55$, $df = 7$, $P = 0.78$). Therefore, the obtained responses, remission rates, and levels of reduction did not differ between the two groups.

Nolen et al²⁸ also compared LTG with an antidepressant. Patients with refractory bipolar depression who were already on mood stabilizers were treated either with supplementary LTG or tranylcypromine. This trial was underpowered because of a small sample size and could not show statistically significant differences in terms of changes in depressive symptoms between the two agents, but the authors found a positive trend for tranylcypromine. Both drugs exhibited positive trends, but evidence for an acute antidepressant effect of LTG is sparse.

The role of LTG in the maintenance treatment and prevention of depressive episodes is more convincing. Bowden et al²⁹ and Calabrese et al³⁰ published the results of two randomized, PLC-controlled trials in which patients with BD1 who had recently undergone either manic/hypomanic or depressive episode were treated with LTG, lithium, or PLC. Calabrese et al³⁰ found that both agents were significantly

superior to PLC for the time to intervention for any mood episode (LTG versus PLC: $P = 0.029$; lithium versus PLC: $P = 0.029$); however, both agents did not differ on this measure ($P = 0.915$). The authors found evidence that LTG is superior to PLC for prolonging time to relapse for depressive episodes ($P = 0.047$); lithium showed an effect on prolonging time for manic episodes ($P = 0.026$). Similar results were published by Bowden et al,²⁹ and time for intervention for any mood episode was extended with both agents (LTG versus PLC: $P = 0.02$; lithium versus PLC: $P = 0.003$).

These results were confirmed in a pooled analysis of these two RCT. It was concluded that lithium and LTG prevent the relapse of any mood episode, which is superior to PLC (LTG versus PLC: $P < 0.001$; lithium versus PLC: $P < 0.001$), and that LTG showed greater effectiveness in prolonging time to intervention for depressive episodes compared to lithium (LTG versus PLC: $P = 0.009$; lithium versus PLC: $P = 0.120$).³¹

In the trial of van der Loos et al,³² LTG was used as an add-on treatment compared to PLC in patients with bipolar 1 or 2 depression already on lithium monotherapy. First, they analyzed acute treatment effects within the first 8 weeks and there was a significant reduction in the MADRS total score in the LTG group compared to the PLC group (LTG -15.38 versus PLC -11.03 , $P = 0.024$, primary outcome). Response, which was defined as a reduction $\geq 50\%$ in the MADRS total score, was also significantly distinct between the two groups ($P = 0.03$).³² When analyzing the follow-up data after 68 weeks, positive effects of LTG add-on treatment could be confirmed.³³ The percentage of responders and time to relapse after response was higher in the LTG algorithm group (median time LTG group 10.0 months [95% CI: 1.1–18.8] versus PLC group, 3.5 months [95% CI: 0.7–7.0]).³³

Chang et al³⁴ conducted a prospective study dealing mainly with the long-term effects of adjunctive use of LTG over a 52-week period in BD2 patients with therapy refractory depression, treated previously with different mood stabilizers, atypical antipsychotics, and antidepressants. The effect size for changes in the CGI-Bipolar Version-Severity for depression was large (Cohen's $d > 0.8$), and the reduction in the CGI-Bipolar Version-Severity scores from baseline to endpoint was significant ($t = 13.6$, $df = 108$, $P < 0.001$). Use of LTG in treatment-resistant bipolar depression was also examined by Nierenberg et al.³⁵ LTG as an add-on treatment showed no difference compared to inositol or risperidone in the primary outcome measure, "rate of recovery;" however, the rate of recovery for LTG was 23%, in contrast to 17.4%

and 6.4% for inositol or risperidone, respectively, and a modest positive trend for LTG was revealed, supporting the findings from previous cited studies.^{21,22,24,27,30,32,33}

LTG and treatment of mania/mixed states

Reliable evidence was not found for LTG for either acute or maintenance treatment of mania. All of the guidelines mentioned in this article do not recommend LTG as an option for therapy.^{9–12,15–17} Two recent meta-analyses compared different drugs approved for acute mania treatment. Yildiz et al²⁰ could not show significant antimanic effects of LTG after meta-analytic calculation (Hedges' $g = -0.02$; 95% CI -0.43 to 0.39 , $P = 0.927$). They included the trial by Ichim et al,³⁶ and one review of two trials conducted by GSK (GW609, GW610). In addition, Cipriani et al¹⁹ recently published one meta-analysis of antimanic drugs, including three RCTs dealing with LTG in antimanic therapy, two protocols published by GSK (SCAA2008, SCAA2009), and the trial of Ichim et al.³⁶ The authors concluded that there is less efficacy of LTG in the acute treatment of mania compared to haloperidol, and this treatment is not superior to PLC (standardized mean difference [SDM] [95% CI]: LTG versus haloperidol: -0.48 [-0.77 to -0.19], LTG versus PLC: 0.01 [-0.21 to 0.22]). When compared to lithium, the authors found a greater effectiveness of LTG (SDM [95% CI] LTG versus lithium: 0.21 [-0.02 to 0.50]).¹⁹ Ichim et al³⁶ found, in their RCT, significant effectiveness of LTG in treating mania, compared with lithium. But both drugs did not differ in terms of response rates across the different psychopathological rating scales (manic rating scale [MRS] score difference from baseline to week 4: LTG group improved from 34.4 to 14.3 [$P = 0.002$], lithium group improved from 31.6 to 13.2 [$P = 0.005$]; CGI scale difference from baseline to week 4: LTG group improved from 4.93 to 2.77 [$P = 0.002$], lithium group improved from 4.67 to 2.83 [$P = 0.005$]). Some limits of this publication include the absence of a PLC control group, the small number of included patients ($n = 30$), and a low mean plasma level for lithium (0.743 mmol/L). There is also less evidence for the efficacy of LTG in maintenance treatment and prevention of manic episodes. Both Calabrese et al³⁰ and Bowden et al²⁹ showed that LTG is not superior to PLC in preventing manic relapse over an 18-month period (LTG versus PLC, $P = 0.28$).

Another meta-analysis dealing with LTG actions in the treatment of BD was published by Amann et al,¹⁸ who asserted that LTG is inferior to lithium in preventing or improving manic symptoms or episodes. Amann et al¹⁸ analyzed the

results of the previous studies by Calabrese et al³⁰ and Bowden et al,²⁹ and they also included the RCT by GSK (study protocols SCAA2008 and SCAA2009). In the first of these two trials, both LTG and lithium showed no difference in terms of change in MRS score from baseline to day 22 compared to PLC. In the second study, lithium met the primary endpoint criteria. LTG was not superior to PLC in terms of changes in MRS score in manic patients.

In 2000, Calabrese et al³⁷ published a double-blind, PLC-controlled study including 324 patients meeting the criteria for rapid cycling BD, and patients received LTG first as an add-on therapy or as a monotherapy in a randomized phase. For the primary endpoint, this study did not show a significant difference in the time to additional pharmacotherapy (median survival time for LTG: 18 weeks; PLC: 12 weeks; $P=0.177$). One year earlier, Bowden et al³⁸ had shown that, in 75 patients with BD, whether rapid cycling or not, there was a significant change in MRS or HAM-D scores from baseline across both groups (rapid-cycling and non-rapid-cycling patients, $P < 0.05$). However, rapid-cycling patients showed less improvement in MRS scores after the last observation carried forward in week 48 than did non-rapid-cycling patients. This was not found in initially depressed patients when the HAM-D score differences were compared.

Discussion

In this review, we discussed the role of LTG in recent guidelines based on findings from literature indices and databases. First, studies dealing with therapeutic options of LTG published promising results.^{21,24} These two RCT provided reasoning to recommend LTG as a first-line agent in the acute treatment and prophylaxis of bipolar depression in accordance with the guidelines from the British Association of Psychopharmacology in 2009; the meta-analysis by Geddes et al²² supported this decision (Table 3). The Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorder, in 2009, also proposed LTG for the treatment and prevention of acute depressive episodes.⁹ In contrast, NICE Guidelines (2006)¹⁰ do not advise using LTG as first-line monotherapy in acute depression, and suggest LTG as a second mood stabilizer when the combination of an antidepressant and mood stabilizer has failed. For BD2 patients and patients with chronic or recurrent depressive episodes, LTG as monotherapy is advised.¹⁰ Grunze et al^{11–15} discussed the role of LTG in their recommendations in the World Federation of Societies of Biological Psychiatry guideline for depressive episodes, and based on a more differentiated data set, LTG was rated

as Category of Evidence “B” (limited positive evidence from controlled studies) or Recommendation Grade “3” (based on Category of Evidence “B”); this was not changed in the 2010 update.¹⁴ In the recently published S3 guidelines on the diagnosis and therapy of BDs, Pfennig et al¹⁷ ranked LTG in the acute treatment and prevention of BD as “0,” with the recommendation defined as “open.” The authors criticized studies by Calabrese et al²¹ and Geddes et al²² for not meeting primary endpoints, or for only showing slight effects in pooled data. They argued that downgrading LTG in the use of acute depressive episode results from trials and reviews that showed more modest results.^{5,18,22,23,39} Mok et al¹⁶ also referred to the publications by Calabrese et al²¹ and van der Loos et al,³² and advised that LTG be used as an add-on treatment for patients already on lithium, but not as monotherapy in bipolar depression; this received a Recommendation Grade “A.” One reason that these studies showed only slightly positive effects could be due to the need for slow titration over 5 to 6 weeks for a daily dosage of 200 mg/day. Here the first antidepressant effects occur.³⁰ Because most trials last only up to 8 weeks, possible antidepressant effects can be diminished. Another reason for the modest effects could also be found in high PLC response rates, so small antidepressant effects of LTG were not represented adequately.⁴⁰ For the treatment of mania, neither in acute states nor in prophylaxis was an antimanic effect confirmed;^{19,20,29} therefore, LTG is not recommended in any guideline for the treatment of mania in BD.^{9,10,12,15–17}

In the long-term treatment of bipolar depression, LTG plays a more convincing role. Results have consistently shown that LTG extends the time to relapse for depression, not only in a head-to-head comparison with PLC, but also with well-established comparators like lithium.^{29,32,36} In the World Federation of Societies of Biological Psychiatry guidelines, LTG is ranked as recommendation grade “A.”¹³ The Canadian guidelines⁹ and the British guidelines⁸ also recommend LTG in maintenance treatment (Table 3). As promoted in the NICE guidelines,¹⁰ LTG does show positive effects as an add-on therapy.^{33,34} Mok et al¹⁶ even state in their 2011 guideline that LTG should only be used for maintenance treatment when effects occurred previously in acute use (Recommendation Grade “A”).^{37,40} One advantage of long-term treatment is the good tolerability of LTG. Severe side effects were reported only in a small number of patients. Mostly mild side effects occurred and included headache, nausea, or dizziness.^{5,6,41} No metabolic side effects or weight gain were reported during LTG therapy, and no evidence of inducing shifts into mania was found.^{5,42}

We did not perform a systematic search of articles dealing with the use of LTG in BD because we wanted to discuss the role and position of LTG in recent therapy guidelines on BD, and to recapitulate its changing position throughout time based on newer publications used in the development of treatment guidelines. Results of our study emphasize the changing position of LTG in international therapy guidelines. Therefore, the findings of our review article may stimulate a meta-analysis of all studies, including unpublished data.

Conclusion

LTG, as a maintenance therapy and as an add-on drug, is a well-tolerated option, even in therapy-refractory patients; however, further studies are required.

Disclosure

The authors report no conflicts of interests in this work.

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