Original Article

Efficacy and tolerability of lamotrigine in the treatment of focal epilepsy among children and adolescents: a meta-analysis

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Background: Epilepsy is the most common chronic neurological disease in children, and focal epileptic seizures are the most common subtype. Unlike the data supporting treatment options for adults with epilepsy, evidence regarding the most effective first-line drug therapy for focal epilepsy in children and adolescents is limited. While lamotrigine is a therapeutic option for adults, there are disagreements surrounding its efficacy and tolerability in the younger population. Therefore, we performed a meta-analysis to determine if there was sufficient evidence to support a more definitive recommendation.

Methods: We undertook electronic search strategies using Medline via Ovid SP, Embase via Ovid SP up to February 05, 2021. We also searched relevant articles through Chinese BioMedical Literature (CBM), Chinese National Knowledge Infrastructure (CNKI), WANFANG, and VIP databases up to February 05, 2021. Study selection and data extraction were performed by 2 authors independently. The randomized controlled trials on focal epilepsy in children were included, and we made risk of bias judgments based on the methods endorsed by The Cochrane Collaboration. We used fifty percent or greater reduction in seizure frequency as an indicator of efficacy, the incidence of adverse events and treatment withdrawal as indicators of tolerability. The strength of the correlation was assessed via risk ratios (RRs) and their 95% confidence intervals (95% CIs).

Results: A total of 7 randomized trials involving 757 participants fulfilled the eligibility criteria. Of the 7 trials, 3 were placebo-controlled, and 4 compared lamotrigine with carbamazepine or oxcarbazepine. Lamotrigine was significantly more effective than placebo in achieving ≥50% reduction in seizure frequency, but its efficacy was not significantly different from that of carbamazepine or oxcarbazepine (lamotrigine *vs.* placebo: RR 2.95, 95% CI, 1.88 to 4.61; lamotrigine *vs.* carbamazepine/oxcarbazepine: RR 0.95, 95% CI, 0.85 to 1.05. There was significant difference in the incidence of overall adverse events between the lamotrigine- and carbamazepine/oxcarbazepine-treated groups (RR 0.64, 95% CI, 0.45 to 0.90).

Conclusions: Lamotrigine was effective in reducing the seizure frequency when used as an add-on treatment in children with focal epilepsy, but current evidence does not suggest that lamotrigine is superior to carbamazepine/oxcarbazepine as monotherapy. For overall adverse events, lamotrigine has significantly fewer than carbamazepine/oxcarbazepine, suggesting that lamotrigine has better tolerability.

Keywords: Lamotrigine; focal epilepsy; children and adolescents; meta-analysis

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Submitted Nov 10, 2020. Accepted for publication Feb 23, 2021.
doi: 10.21037/tp-20-379
View this article at: http://dx.doi.org/10.21037/tp-20-379

Introduction

Epilepsy is the most common chronic neurological disease in children (1). Almost 10.5 million children under the age of 15 have active epilepsy, representing approximately 25% of the global population diagnosed with epilepsy (2). In all age groups, focal epileptic seizures are the most common type of epileptic seizures, and in children they account for 40–50% of total seizures (3,4). The etiology of epilepsy can be classified into hereditary, structural, metabolic, or unexplained (5,6). Focal epilepsy mostly falls into the structural or unexplained category.

Compared with adults, there is limited evidence available to guide providers in choosing the most effective first-line drug to treat focal epilepsy in children. Carbamazepine (CBZ) is recognized as the best initial treatment in adult patients. Class III open-label trials have reported that lamotrigine (LTG), a new broad-spectrum antiepileptic drug for the treatment of new or untreated focal epilepsy, has a similar curative effect as that of CBZ and is also better tolerated. In adults, LTG has also been used as the initial drug treatment (7,8). In children, only oxcarbazepine (OXC) has been proven effective as first-line monotherapy, based on class I evidence (8,9). Children who fail to respond to antiseizure drug monotherapy at adequate doses or do not tolerate effective doses should be started on a second antiseizure drug, such as a combination of valproate and ethosuximide or LTG.

Although, the U.S. Food and Drug Administration (FDA) has approved LTG as an adjunct to the treatment of focal epilepsy in adults and children aged 2 years or older, some studies suggest that LTG can also be used as the first line monotherapy in pediatric focal epilepsy (8,10-12). However, there are no clear guidelines or expert consensus to support the use of LTG as monotherapy in focal epilepsy, and clinicians rely more on their own experience than on high-level evidence-based evidence in treatment. Thus, one of the most important questions is how to choose monotherapy drug(s) among several available antiepileptic drugs (AEDs) to manage focal seizures in young patients. To address this question, we conducted a systematic review and meta-analysis to investigate the efficacy and tolerability of LTG in the treatment of children and adolescents with focal epilepsy.

We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at http://dx.doi.org/10.21037/tp-20-379) (13).

Methods

The protocol for this meta-analysis is available in INPLASY (International Platform of Registered Systematic Review and Meta-Analysis Protocols; no. INPLASY202050013).

Search strategy

We undertook electronic search strategies using Medline via Ovid SP, Embase via Ovid SP up to February 05, 2021. We also searched relevant articles through Chinese BioMedical Literature (CBM), Chinese National Knowledge Infrastructure (CNKI), WANFANG, and VIP databases up to February 05, 2021. Detailed search strategies are reported in the supporting document (Appendix 1).

Eligibility criteria

Trials were selected based on the following criteria: (I) patients younger than 18 years with a diagnosis of focal epilepsy; (II) published randomized controlled trials (RCTs) and quasi-randomized controlled trials (quasi-RCTs, methods of allocating participants are not strictly random, e.g., by hospital record number, date of birth, alternation) comparing LTG with a placebo or CBZ/OXC-treated group; (III) trials providing focal epilepsy data; (IV) full-texts available, with data eligible for extraction.

Study screening

The search results were screened by 2 reviews independently. All potentially relevant citations were requested and inspected in detail using the full-text version. Disagreements were resolved through discussion, with assistance from a third party if necessary. A PRISMA flow diagram was constructed to show the full study-selection process.

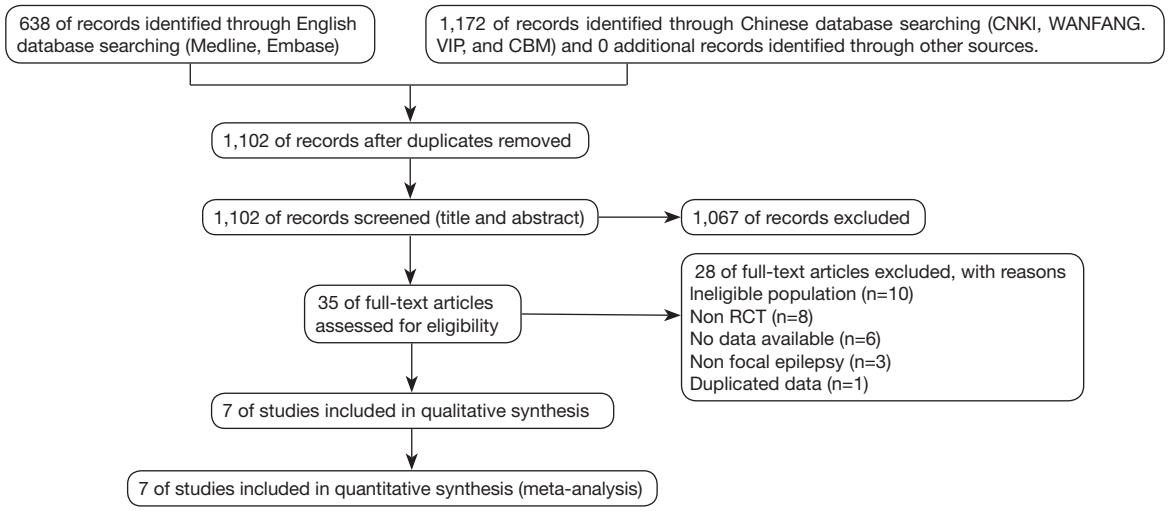

Figure 1 Study flow diagram.

Data extraction and management

Data from each study were independently extracted by 2 reviewers using a standardized data extraction form. Any disagreements were resolved by consensus with assistance from a third party if necessary. When more information relating to a potentially eligible study was lacking, we contacted and requested further information from the study authors. We extracted all relevant characteristics of included studies, including: (I) general study characteristics (first author and publication year, geographical setting of the study, trial sponsors); (II) methods (randomization, participant allocation concealment, blinding of participants and personnel, blinding of outcome assessment, measured outcomes, study attrition); (III) interventions (dosages, route of administration); (IV) participants (sample size, age, sex); (V) outcomes (measured outcomes, length of follow-up); (VI) results (all dichotomous results).

Risk of bias (quality) assessment

Risk of bias judgments were based on the methods endorsed by The Cochrane Collaboration (14). We assessed the risk of bias in the domains of randomization, patient allocation, blinding, selective reporting, attrition of study participants, and in any other detected sources of bias that may have arisen.

Statistical analysis

We summarized all dichotomous outcome data using risk ratios (RRs), risk difference (RD), and 95% confidence intervals (CIs) using the Mantel-Haenszel statistical method. When both the intervention and the control groups had 0 events, the RR was not calculated in the meta-analysis as recommended by the Cochrane Handbook (15). Subgroup analyses were performed based on treatment duration (<24, ≥24 to <48, ≥48 weeks).

We synthesized data using a fixed-effects method for all analyses. An I^2 estimate ≥50% accompanied by a statistically significant chi-square test (P<0.10) was interpreted as evidence of substantial levels of heterogeneity (16). When substantial heterogeneity was found, we explored potential sources (including clinical heterogeneity and statistical heterogeneity). When the sources of heterogeneity remained unclear, we synthesized data using a random effects model.

All meta-analyses were performed using RevMan version 5.4 (Review Manager, Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). All tests were 2-tailed, and a P value <0.05 was considered statistically significant.

Results

Search results

From the searches for RCTs and quasi-RCTs, 1,102 potentially eligible records were identified. We screened the titles and abstracts of these records for inclusion. Full texts of 30 records were read, and 7 trials met the inclusion criteria (see *Figure 1*). Of the 7 trials, 3 trials (17-19)

evaluated LTG *vs.* placebo add-on therapy for the treatment of focal epilepsy in children and adolescents. The other 4 trials (10,11,20,21) evaluated LTG versus CBZ/OXC for the treatment of focal epilepsy (we combined CBZ and OXC as a single control group because of the limited number of included studies. We consulted clinical experts to determine if this approach was reasonable and were given proper assurance).

Description of studies

The characteristics of included studies are displayed in *Table 1*.

Risk of bias in included studies

The risk of bias assessments is summarized in *Figure 2* and *Figure 3*.

A total of 4 trials reported the methods of randomization, 2 of which reported adequate methods of allocation concealment. We judged them to be at low risk of bias. When these methods were not reported, we judged these studies to be of unclear risk.

We judged blinding as low risk of bias in 1 study (Duchowny. 1999) because participants, parents, and investigators were blinded. A total of 2 trials were open-label, and we judged them as at high risk of performance and detection bias (Eun 2012; Nieto-Barrera 2001). Due to no details of the method of blinding being provided in 4 studies, we judged their blinding as unclear.

We rated all included studies except Gu 2013 as having low risk of bias for incomplete outcome data. We requested the protocols for all included studies but none were available. We rated all included studies as low risk of bias for selective reporting as there was no suspicion of selective outcome reporting bias.

We did not detect any other sources of bias across the included studies.

Effects of interventions

We included 7 studies in the final analysis. However, the outcomes chosen for this review were not reported in all studies. As planned in our review protocol, we first performed the analysis according to the reported data.

Primary outcome

A 50% greater reduction in seizure frequency

LTG vs. placebo for focal epilepsy

A chi-squared test for response to LTG indicated no significant heterogeneity between trials (chi^2=0.62, df=1, P=0.43, I^2=0%), so a fixed effects model was used to measure efficacy.

A total of 2 trials involving 262 participants (children and adolescents) contributed to this outcome analysis, the risk ratio (RR) was 2.95, the 95% confidence interval (CI) was 1.88 to 4.61, and the risk difference (RD) was 0.30, the 95% CI for any dose of lamotrigine added to regular antiepileptic drug therapy *vs.* Placebo was 0.19 to 0.40 (see *Figure 4*).

We could not calculate the reduction rate in seizure frequency for Pina-Garza (2007) because the primary end point was not reached due to treatment failure, and the reduction data were reported only in an open-label phase.

Subgroup analyses: treatment duration (<24 versus ≥48 weeks)

Treatment durations >24 and <48 weeks were not calculated because of insufficient data. The test for subgroup difference between treatment duration <24 and ≥48 weeks was not statistically significant (fixed-effect meta-analysis: P=0.43; I^2=0%; *Figure 5*). The overall pooled RR (adjusted by treatment duration for 262 participants from 2 trials) was 2.95 (fixed-effect meta-analysis: 95% CI, 1.88 to 4.61; P<0.001; *Figure 5*), indicating a statistically significant advantage for LTG over placebo in efficacy for both participants with different treatment durations. Numerical results in this analysis adjusted for treatment duration were very similar to those of the unadjusted analysis (*Figure 4*), and heterogeneity present within the analysis was equal to that in the adjusted analysis (I^2 =0%).

LTG versus CBZ/OXC for focal epilepsy

A chi-squared test for response to lamotrigine indicated no significant heterogeneity between trials [Chi^2=1.66; degrees of freedom (df)=3, P=0.65, I^2=0%], so a fixed effects model was used to measure efficacy.

For 4 studies (416 participants), the RR was 0.95, 95% CI was 0.85 to 1.05, and the RD was –0.04; for any dose of

Table 1 Characteristics of the included trials and participants

Included Trials	Treatment (maintenance)	Male/ Female	Age	Interventions	Seizure etiology	Trial sponsor	Treatment Duration
LTG *vs.* Placebo							
Duchowny 1999 (United States)	Concurrent AEDs: (LTG dose, n); enzyme-inducing AEDs: (11.6± 3.6 mg/kg/day, 53); VPA: (2.7±0.4 Mg/kg/day, 22); enzyme-inducing AEDs +VPA: (3.9±0.9 mg/kg/day, 18)	LTG: 47/51; Placebo: 56/45	USA: 2–16 years; France: 2–12 years	Add-on	LTG: Idiopathic n=37; Symptomatic n=61; Placebo: Idiopathic n=41, Symptomatic n=60	GlaxoSmithKline, the manufacturer of LTG	18 weeks (6-week titration; 12-week-maintenance)
Yang 1999 (China)	Concurrent AEDs: (LTG dose); VPA: (0.2-5 mg/kg/day and <200 mg/day); No VPA: (2–15 mg/kg/day and <600 mg/day)	35/28	2–17 years	Add-on	NA	NA	1 year
Pina-Garza 2008 (United States)	Concurrent AEDs (LTG dose); enzyme-inducing AEDs (15.6 mg/kg/day or 400 mg/day); non-enzyme-inducing AEDs or valproate (5.1 mg/kg/day or 200 mg/day)	LTG: 12/7; Placebo: 9/10	0–24 months	Add-on	LTG: Idiopathic n=3, Symptomatic n=16; Placebo: Idiopathic n=8, Symptomatic n=11	GlaxoSmithKline, the manufacturer of LTG	8 weeks
LTG *vs.* CBZ/OXC							
Nieto-Barrera 2001 (UK)	LTG: 2–15 mg/kg/day; CBZ: 5–40 mg/kg/day	NA	2–12 years	Monotherapy	NA	GlaxoSmithKline, the manufacturer of LTG	24 weeks
Eun. 2012 (Korea)	LTG: 3–6 mg/kg/day; CBZ: 10–20 mg/kg/day	LTG: 24/19; CBZ: 24/17	9.19± 2.05 years	Monotherapy	NA	NA	32 weeks (8-week: titration; 24-week-Maintenance)
Gu 2013 (China)	LTG: 2–5 mg/kg/day; OXC: 20–30 mg/kg/day	42/38	6–14 years	Monotherapy	NA	NA	1 year
Cao 2015 (China)	LTG: 2–5 mg/kg/day; OXC: 20–30 mg/kg/day	35/25	6–14 years	Monotherapy	NA	NA	1 year

LTG, lamotrigine; CBZ/OXC, carbamazepine or oxcarbazepine; VPA, valproate; AEDs, antiepileptic drugs.

LTG monotherapy *vs.* CBZ or OXC monotherapy, the 95% CI, –0.12 to 0.04 (see *Figure 6*).

Subgroup analyses: treatment duration (<48 versus ≥48 weeks)

A treatment duration of less than 24 weeks was not present in these 4 studies. The test for subgroup differences in treatment duration between <48 and ≥48 weeks was not statistically significant (P=0.21, I^2=37%, *Figure 7*). The overall pooled RR (adjusted by treatment duration for 416 participants from 4 trials) was 0.95 (fixed-effect meta-analysis: 95% CI, 0.85 to 1.05; P=0.30; *Figure 7*), indicating no statistically significant advantage for LTG over CBZ/OXC in efficacy for both participants with different treatment durations. Numerical results in this analysis adjusted for treatment duration were very similar to the unadjusted analysis.

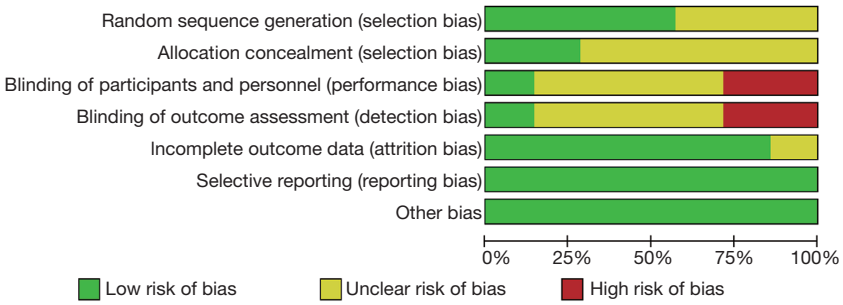

Figure 2 Risk of bias graph: review authors' judgments about risk of bias item presented as percentages across all included studies.

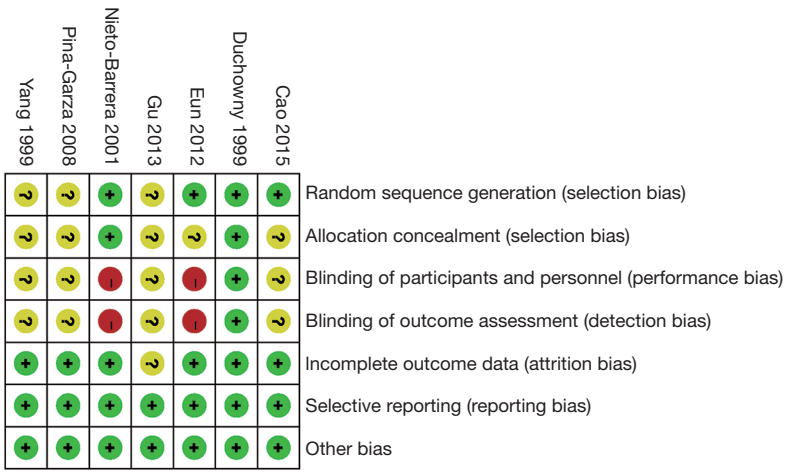

Figure 3 Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

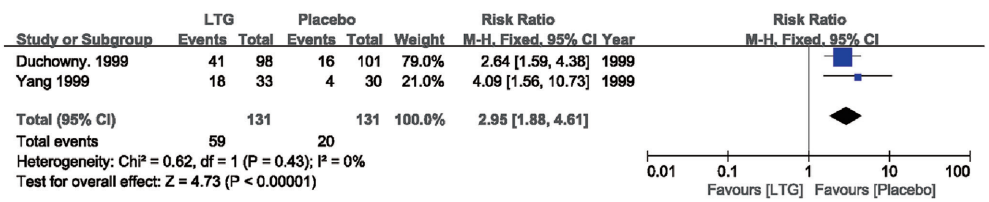

Figure 4 Lamotrigine versus placebo: fifty percent or greater reduction in seizure frequency.

Secondary outcomes

Incidence of adverse events

LTG versus placebo for focal epilepsy

A meta-analysis of all adverse events was not conducted because of high heterogeneity (I^2>50% and P<0.1), which might have been due to the different types of adverse reactions in different included studies. Therefore, we conducted a meta-analysis of specific adverse effects.

Both Duchowny (1999) and Pina-Garza (2008) reported all 3 adverse effects (2 studies, 237 participants; see *Figure 8*).

(I) fever (RR 1.17; 95% CI, 0.60 to 2.29; RD 0.02, 95% CI, −0.06 to 0.10)

(II) infection (RR 1.07; 95% CI, 0.64 to1.80; RD 0.01, 95% CI, −0.09 to 0.11)

(III) rash (RR 0.97; 95% CI, 0.54 to 1.77; RD −0.00, 95% CI, −0.09 to 0.09)

Duchowny (1999) reported that ataxia, dizziness, tremor and nausea occurred more frequently in the LTG group.

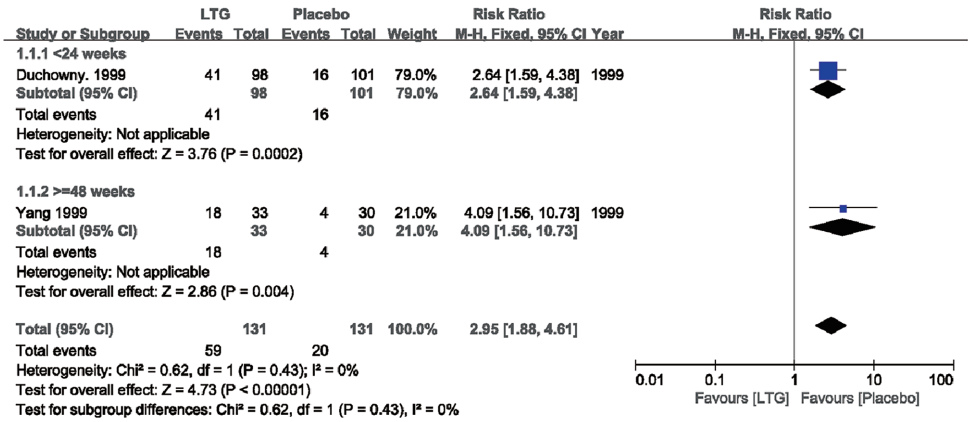

Figure 5 Lamotrigine versus placebo: fifty percent or greater reduction in seizure frequency by treatment duration.

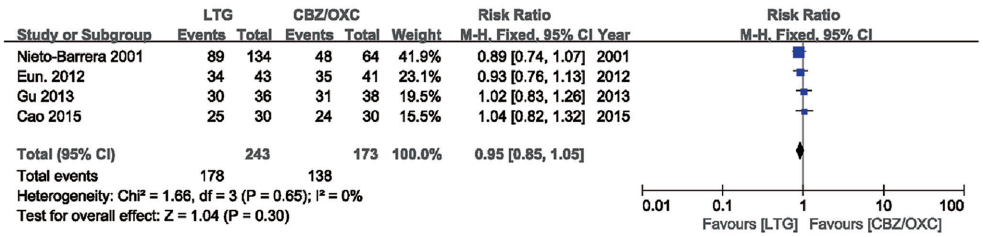

Figure 6 Lamotrigine versus carbamazepine/oxcarbazepine: fifty percent or greater reduction in seizure frequency.

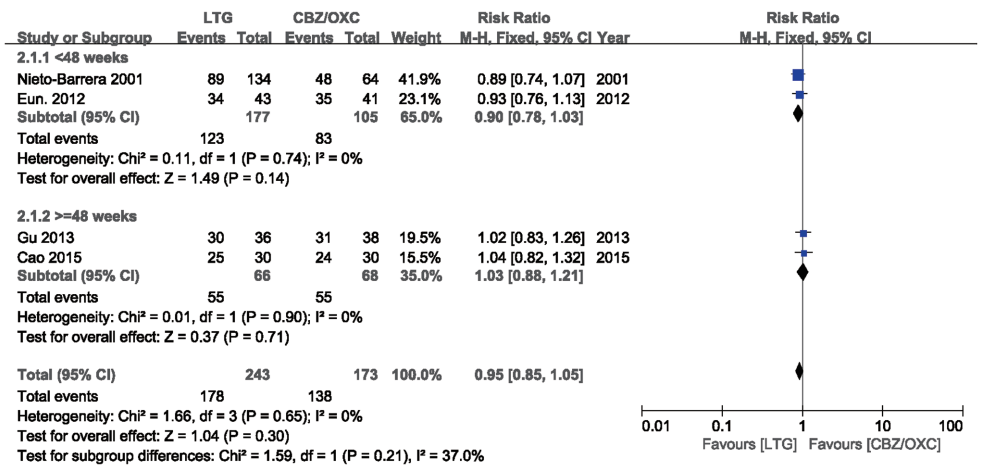

Figure 7 Lamotrigine versus carbamazepine/oxcarbazepine, fifty percent or greater reduction in seizure frequency by treatment duration.

LTG versus CBZ/OXC for focal epilepsy

Gu (2013) reported the specific number of each adverse reaction in the OXC group, but not those in the LTG group. therefore, we conducted an analysis of overall adverse effects, which included 4 studies, comprising 457 participants (RR 0.64; 95% CI, 0.45 to 0.90; RD –0.09, 95% CI: –0.17 to –0.02); see *Figure 9*).

All 3 studies (317 participants) except for Gu (2013) reported 2 adverse effects (rash and somnolence; see *Figure 9*). Two studies (Nieto-Barrera 2001 and Eun. 2012)

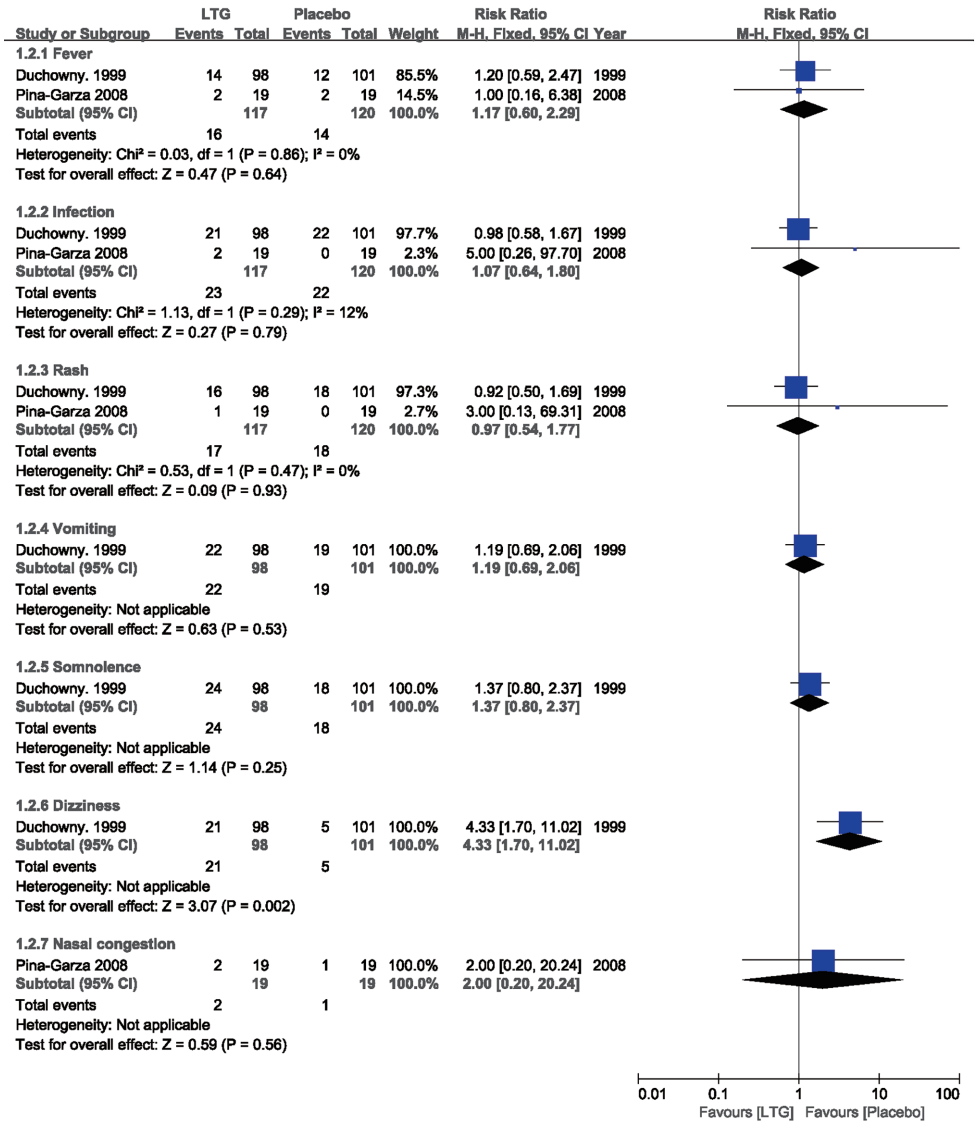

Figure 8 Lamotrigine versus placebo: adverse events.

Asthenia was reported in 2 studies (Nieto-Barrera 2001 and Eun. 2012; 317 participants; see *Figure 9*).

(I) rash (RR 0.90; 95% CI, 0.41 to 1.96); RD −0.01 (95% CI, −0.06 to 0.05)

(II) somnolence (RR 0.54; 95% CI, 0.22 to 1.31; RD −0.03, 95% CI, −0.08 to 0.02)

(III) asthenia (RR 0.72; 95% CI, 0.17 to 3.06; RD −0.01, 95% CI, −0.04 to 0.03).

Treatment withdrawal

LTG vs. placebo for focal epilepsy

All 3 studies including 300 participants reported withdrawal events. Significant differences were not observed in the total number of participants with treatment withdrawal (RR 0.78; 95% CI, 0.52 to 1.16; RD −0.05, 95% CI, −0.13 to 0.03) (see *Figure 10*). There was no evidence of significant heterogeneity (I^2=0%, P>0.1); therefore, we applied a fixed

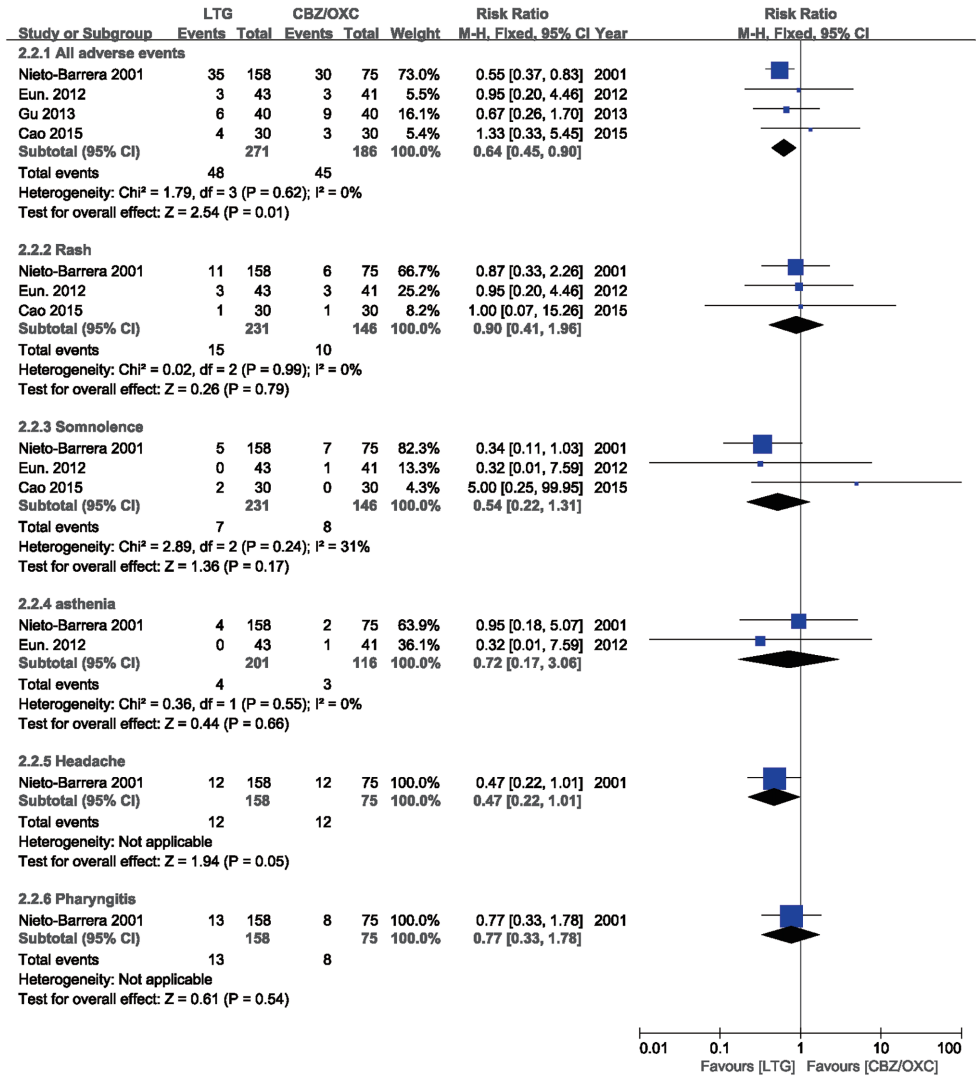

Figure 9 Lamotrigine versus carbamazepine/oxcarbazepine: adverse events.

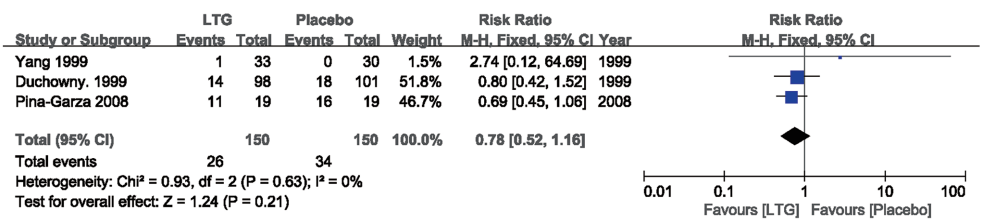

Figure 10 Lamotrigine versus placebo: treatment withdrawal.

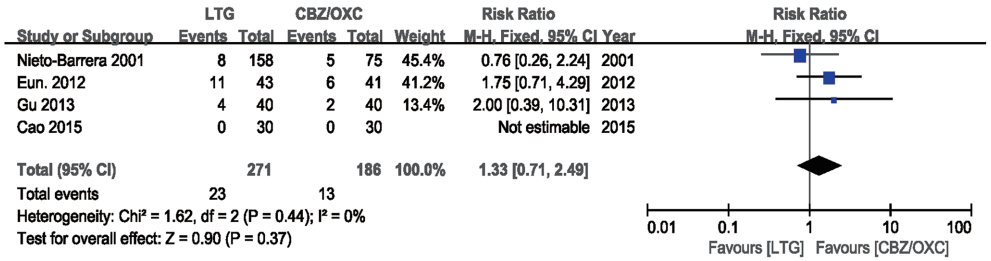

Figure 11 Lamotrigine versus carbamazepine or oxcarbazepine: treatment withdrawal.

effects model.

LTG versus CBZ or OXC for focal epilepsy

All 4 studies involving 457 participants reported treatment withdrawal. No significant differences were observed in the total number of participants (RR 1.33; 95% CI, 0.71 to 2.49; RD, 0.02, 95% CI, −0.03 to 0.07) (see *Figure 11*). There was no evidence of significant heterogeneity (I^2=0%; P>0.1); therefore, we applied a fixed effects model.

Discussion

There is limited evidence available to help practitioners decide on the most effective initial drug therapy for treating focal epilepsy in children and adolescents. While LTG is often prescribed to the adult population, there is disagreement about its efficacy and tolerability in younger age group. our meta-analysis found that LTG was more effective than placebo in treating children with focal epilepsy when used as add-on therapy. however, when used as monotherapy, there was no significant difference in efficacy between LTG and CBZ/OXC. These results were generally consistent regardless of the treatment duration. The results of the subgroup analysis also suggested that there was no difference in efficacy between different treatment durations.

We used adverse effects and treatment withdrawal as indicators of tolerability. In terms of adverse events, 2 studies reported fever, infection, and rash, and no significant difference was observed. Just 1 study reported vomiting, somnolence, and dizziness, and only dizziness was reported to be more common in the LTG than in the placebo groups. We did not analyze the total incidence of adverse effects because the heterogeneity was consistently high even when applying a random effects model. This may have in part been due to the wide variation in the types of reported adverse effects among the different included studies. A significant difference between LTG and CBZ/OXC was identified in the overall adverse reactions. However, this difference was not readily apparent when analyzing the individual adverse reactions in each study, namely rash, somnolence, asthenia, headache, and pharyngitis. Thus, overall, LTG appears to be associated with fewer adverse effects than CBZ/OXC. There was not difference in treatment withdrawal between any of the groups. Overall, LTG was well tolerated by children with focal epilepsy.

Ramaratnam *et al.* (22) concluded from a Cochrane review that LTG was significantly more effective than placebo in reducing seizure frequency. Mohd-Tahir *et al.* (23) concluded that newer AEDs (including LTG) when used as adjunct therapy for the treatment of focal epilepsy in children tended to demonstrate better efficacy compared with placebo. These results are consistent with our findings. Ramaratnam *et al.* (22) also reported a significant correlation between ataxia, dizziness, diplopia, and nausea and LTG treatment. In our review, only 1 study reported these adverse effects, and only dizziness was significantly associated with LTG. This might have been because our sample size was too small to uncover differences in the occurrence of the other side effects.

A meta-analysis by Nevitt *et al.* (24) reported that LTG was effective in the treatment of focal epilepsy in adults and children, but was not statistically significant. This is consistent with the results of our review. A meta-analysis by Rosati *et al.* (25) reported the superiority of LTG with respect to all comparators in the treatment of newly diagnosed focal epilepsy in a population of children, but this result relied on the point estimate method, which has a low power to detect significant differences. A network meta-analysis by Campos *et al.* (26) reported that LTG demonstrated neither superiority nor inferiority compared with CBZ in adults and children, which is similar to our review. Contrary to our findings, Gamble *et al.* (27) reported that LTG was significantly less likely to be withdrawn

than CBZ.

When assessing the risk of bias, we found that some included studies did not provide information about important parameters such as the method of randomization, whether or not allocation concealment was performed, the setting surrounding the blinding process, and so on. Hopefully, subsequent clinical trials will report with reference to CONSORT (Consolidated Standards of Reporting Trials). We originally intended to conduct a subgroup analysis based on the results of the risk of bias summary, but due to the small number of included studies, it was not completed.

The most notable limitation of this review was that only 7 original studies were eligible for inclusion, some of which did not even include sufficient data. Hence, additional original studies are required in this area. Second, some RCTs were of poor quality, as evidenced by those with unclear methods of randomization. Third, 3 of the included studies were sponsored by GlaxoSmithKline, a manufacturer of LTG, which could have led to sponsorship bias.

Conclusions

When used as an add-on treatment, LTG shows efficacy in reducing seizure frequency in children with focal epilepsy. However, the efficacy of lamotrigine as monotherapy has not been shown to be superior to CBZ/OXC. LTG has significantly fewer adverse events than CBZ/OXC, suggesting that LTG has better tolerability.

Acknowledgments

We sincerely thank the clinical experts at the Neurography Department at the Children's Hospital of the Capital Institute of Pediatrics for their kind help.

Funding: This work was supported by The Special Fund of the Pediatric Medical Coordinated Development Center of Beijing Hospitals Authority [no. XTCX201813]; and China Scholarship Fund [no. 201809110076].

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-379

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-379). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ji L, Chen Y, Mao Z, Chen R, Zhang J, Tan B, Meng L. Efficacy and tolerability of lamotrigine in the treatment of focal epilepsy among children and adolescents: a meta-analysis. Transl Pediatr 2021;10(4):807-818. doi: 10.21037/tp-20-379