Epilepsy Research 153 (2019) 40–48

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Review article

Efficacy and safety of Levetiracetam as adjunctive treatment in children with focal onset seizures: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Antiepileptic drugs
Pediatric
Epilepsy
Dverse effects
Prospective studies

ABSTRACT

Objective: To assess the efficacy and safety of levetiracetam (LEV) as adjunctive treatment in children (0–18 years) with focal-onset seizures (FOS) with a larger dataset.
Methods: A pooled analysis would be performed for prospective clinical trials and a meta-analysis for controlled studies. Retrospectives studies were also summarized using descriptive statistics.
Results: Thirty-one articles (1763 patients) were identified, eighteen prospective self-controlled studies and thirteen retrospective studies. LEV was more effective than placebo, the pooled risk ratios (RRs) and 95% confidence intervals (CIs) for the 50% responder rate, seizure freedom rate and the median percentage reduction rate were 1.98 (1.49–2.63), 5.12 (2.09–12.51) and 3.19 (2.37–4.30), respectively. The overall response rates (ORRs) and 95% CIs were 56% (52%–60%), 14% (9%–19%) and 55% (31%–79%), respectively. For safety assessment, the pooled RRs and 95% CIs for the at least one treatment-emergent adverse events (TEAE) rate and at least one adverse drug reactions related (ADR-related) TEAE rate were 1.03 (0.94–1.13) and 1.45 (1.13–1.86) between two group. The ORRs and 95% CIs were 74% (54%–94%) and 48% (40%–55%). The adverse events significantly associated with LEV were somnolence 2.26 (95% CI 1.30–3.93) and hostility 2.33 (95% CI 1.15–4.70). The most frequency adverse events were pyrexia, headache, nervousness, upper respiratory tract and somnolence. The RRs for withdrawal rate or the ADR-related withdrawal rate were 0.77 (95% CI 0.44–1.38) and 0.91 (0.42–1.98), the ORRs were 17% (5%–28%) and 6% (4%–8%).
Conclusion: The meta-analysis suggested that add-on LEV can significantly reduce seizure frequency and fairly tolerated compared to placebo.

1. Introduction

Epilepsy is one of the most common neurological disorders globally, affecting approximately 50 million people around the world (Ngugi et al., 2010). More than 10.5 million children aged younger than 15 years have active epilepsy (Guerrini, 2006). Epileptic seizures are generally described in two major categories: generalized onset seizures and focal-onset seizures (FOS), while FOS are frequently occurred in children (Sillanpaa et al., 1999). According to World Health Organization (WHO) Global Burden of Disease 2010 study, neurological disorders present 3.0% of global DALYs (disability-adjusted life years), of which a quarter were caused by epilepsy (Murray et al., 2014). FOS contribute the bulk of seizure burden in pediatric epilepsy (1989). There is widespread discrimination against epilepsy patients, which can cause serious psychological barriers to pediatric patients and their families. Moreover, Almost 25% of pediatric patients experience refractory seizures or intolerable adverse events (Park et al., 2007), which can increase the possibility of learning difficulties, mental disorders and sudden unexpected death in epilepsy (Donner et al., 2017). Given that there are many challenges inherent in conducting clinical trials in children, children are often treated with off-label or unlicensed products. Choosing the appropriate antiepileptic drugs (AEDs) for children

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https://doi.org/10.1016/j.eplepsyres.2019.04.001
Received 10 January 2019; Received in revised form 16 February 2019; Accepted 1 April 2019
Available online 03 April 2019
0920-1211/

is still challenging.

As an important add-on therapy for both adult and pediatric use, levetiracetam (LEV) is one of the most commonly prescribed new generation AEDs. Previous studies proved the efficacy of LEV on pediatric epilepsy. A Cochrane Review (Mbizvo et al., 2012) reported better responders of children with adjunctive LEV treatment in partial seizures than adults. Arya et al. (Arya and Glauser, 2013) suggested that LEV have Class I efficacy evidence for treatment of pediatric FOS according to two randomized controlled trials (RCTs), however no quantitative synthesis of LEV efficacy data was included in this systematic review. Abbaskhanian et al. (Abbaskhanian and Shahmohammadi, 2016) reviewed the efficacy and safety of add-on LEV in children with refractory epilepsy, indicating that LEV is effective when treating childhood refractory epilepsy. So far, no meta-analysis was conducted to explore the efficacy and safety of LEV as adjunctive treatment of pediatric epilepsy combined multiple studies with convincing quantitative evidence. Even the most updated network meta-analysis (Rosati et al., 2018) included only two RCTs about LEV.

Due to the increasing utilization of LEV as add-on therapy in pediatric epilepsy, a meta-analysis with larger dataset and appropriate study design is required. Here, we conducted a meta-analysis to synthesis evidence from available publications for the efficacy and safety of LEV as adjunctive treatment of pediatric epilepsy, including data from RCTs, controlled cohort studies and self-controlled prospective studies.

2. Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Liberati et al., 2009; Zeng et al., 2015).

2.1. Eligibility criteria

Researches were eligible for entry the meta-analysis if met the following criteria.

(1) Types of studies: RCTs, controlled cohort studies and self-controlled studies.
(2) Types of participants: Children (0–18 years) with partial epilepsy, of any gender, ethnicity, and seizure severity. If involves both children and adults or children with mixed seizure type, only studies with specific report of children with partial seizures were included.
(3) Types of interventions: The treatment group receives LEV in additional to conventional AEDs treatment (LEV group), and the control group receives placebo in addition to conventional AEDs treatment (placebo group).

2.2. Search strategy

Databases PubMed (Medline), Web of Science, the Cochrane Central Register of Controlled Trials and the US NIH Clinical Trials Registry (http://www.clinicaltrials.gov) were searched for articles (using search strategy outlined in Supplementary material 1). References of included studies were hand-searched for additional reports, and we consulted experts in the field to ensure no unpublished or ongoing researches were missed. There were no restrictions for time or language. The last search was performed in January 2018.

2.3. Study selection and data extraction

Two authors independently reviewed studies and extracted data using a standardized data extraction form. Any discrepancies were resolved by discussion with a third review author. The data extracted included authors, publication year, trial design, the number of patients, baseline period, evaluation phase, initial dose and final dose. Age and seizure type of participants were also collected. Outcomes data including the 50% responder rate, seizure freedom rate, and the median percentage reduction were summarized. Number of patients experienced at least one treatment-emergent adverse events (TEAE), at least one adverse drug reactions related (ADR-related) TEAE, withdrawal and frequencies of each adverse event were also extracted.

2.4. Outcome measures

The efficacy outcomes were measured by the 50% responder rate (the proportion of patients experiencing a $\geq$50% reduction in partial seizure frequency during the treatment period comprared with baseline), seizure freedom rate (the proportion of seizure-free patients over the entire treatment period) and the median percentage reduction rate (the proportion of patients with a median percentage reducction from baseline in seizure frequency).

The safety and tolerability outcomes were measured by at least one TEAE rate (the proportion of patients who experienced at least one treatment-emergent adverse event) and at least one ADR-related TEAE rate (the proportion of participants with at least one treatment-emergent adverse event related to LEV). We also assessed withdrawal rate (the proportion of patients who withdrew from treatment for any reasons) and the ADR-related withdrawal rate (the proportion of patients who withdrew from treatment due to adverse events).

2.5. Quality evaluation

Two authors independently evaluated the quality of the included studies, using the Cochrane Collaboration's tool and Methodological index for non-randomized studies (MINORS) (Slim et al., 2003). The Cochrane Collaboration's tool was introduced for assessing the quality of RCTs and MINORS for prospective non-randomized studies. Quality analysis was not performed for retrospective studies. Non-randomized studies scored no less than 10 points and controlled studies scored no less than 14 points were rated as high quality. Any conflicting results were resolved through discussion with a third review author.

2.6. Statistical analysis

A pooled analysis would be performed for all prospective clinical trials and a meta-analysis for controlled studies. Overall response rate (ORR) and 95% confidence intervals (CIs) were used to describe outcomes (efficacy and safety) in self-controlled studies. Mantel-Haenszel risk ratios (RRs) with 95% CIs were used to describe outcomes in controlled studies. Besides, if both core randomized controlled studies and extension studies adopted in the same trial, the efficacy and safety data were collected from extension studies, while TEAEs data were collected from either core study or the extension studies.

The meta-analysis was performed using Stata14. Heterogeneity among trials was examined by the x^2 test and the I^2 statistics. Significance was set with p value $\leq$ 0.05 or an I^2 value $\geq$ 40%. The random-effects model would be employed to pooled trials if statistical heterogeneity were significant ($p \leq 0.05$, $I^2 \geq 40\%$), otherwise, the fixed-effect model would be used ($p > 0.05$, $I^2 < 40\%$).

If heterogeneity was noted ($p \leq 0.05$, $I^2 \geq 40\%$), a sensitivity analysis was performed to identify the source of the heterogeneity and assess the effect of selected study quality on the efficacy and safety results. Forest and leave-one-out were generated by Stata14 to visualize the results of meta-analysis and sensitivity analysis. All tests were two-sided and a $p < 0.05$ was considered statistically significant.

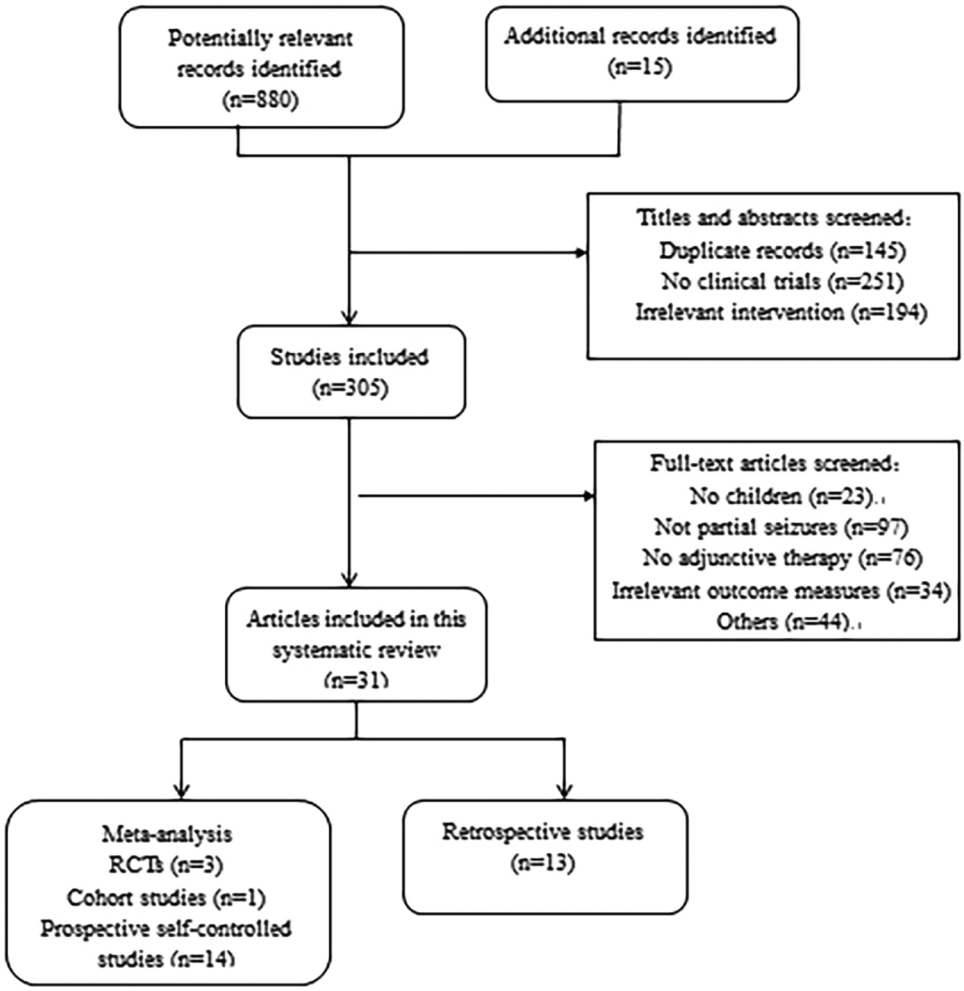

Fig. 1. Flow diagram of study selection process.

3. Results

3.1. Study selection and characteristics

Fig. 1 depicted the study selection process. A total of 880 records were identified by the search of PubMed (Medline), Web of Science and the Cochrane Central Register of Controlled Trials. Eighteen prospective studies (Callenbach et al., 2008; Chhun et al., 2011; Fountain et al., 2007; Glauser et al., 2006, 2002b; Grosso et al., 2005; Iwasaki et al., 2015; Kanemura et al., 2013; Lagae et al., 2005, 2003; Levisohn et al., 2009; Nakamura et al., 2013; Pina-Garza et al., 2009, 2010; Posar et al., 2014; Schiemann-Delgado et al., 2012; Tonekaboni et al., 2010; Wheless and Ng, 2002) and thirteen retrospective studies (Dureau-Pournin et al., 2014; Enoki et al., 2015; Gallentine et al., 2009; Giroux et al., 2009; Grosso et al., 2007; Incecik et al., 2012; Krief et al., 2008; Lee et al., 2010; Obeid and Pong, 2010; Opp et al., 2005; Perry and Benatar, 2007; Tan and Appleton, 2004; von Stulpnagel et al., 2010) were screened. All three RCTs (Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009) were considered low risk (Supplementary 1), and no trial was excluded by MINORS (Supplementary 2). As a result, all eighteen prospective trials (1131 patients) were finally included in the meta-analysis and thirteen retrospective studies (632 patients) were included in descriptive analysis (Supplementary 1). In most studies, patients received LEV at an initial dose of 10 mg/kg/day or 20 mg/kg/day, gradually increased to a final target dose of 60 mg/kg/day. The median period of baseline was 4 weeks [2days-24weeks] and the median evaluation phase was 16 weeks [5days-2years]. More characteristics of the included studies were summarized in Supplementary 1.

3.2. Results of efficacy

3.2.1. The 50% responder rate

Fourteen prospective studies (621 patients) were included in the pooled analysis(Callenbach et al., 2008; Chhun et al., 2011; Fountain et al., 2007; Glauser et al., 2002b; Grosso et al., 2005; Lagae et al., 2005, 2003; Levisohn et al., 2009; Pina-Garza et al., 2010; Schiemann-Delgado et al., 2012; Tonekaboni et al., 2010; Wheless and Ng, 2002). The chi^2 test indicated no statistically significant heterogeneity (chi^2 = 19.29, I^2 = 32.6%, p = 0.114). And the fixed-effect model was adopted, showing the ORR was 56% (95% CI: 52%–60%) for the 50% responder rate (Fig. 2A).

412 patients (LEV, n = 225; placebo, n = 187) from three RCTs were included in the meta-analysis(Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009). The chi^2 test for heterogeneity indicated no statistically significant heterogeneity (chi^2 = 1.85, I^2 = 0.0%, p = 0.398). Fixed-effect model was adopted, and the overall RR showed significant difference (RR = 1.98, 95% CI: 1.49–2.63) between these two groups, favoring LEV group were more effective than placebo group (Fig. 2B).

3.2.2. Seizure freedom rate

Eleven prospective studies (536 patients) evaluated the efficacy of LEV based on seizure freedom rate were included in the pool analysis

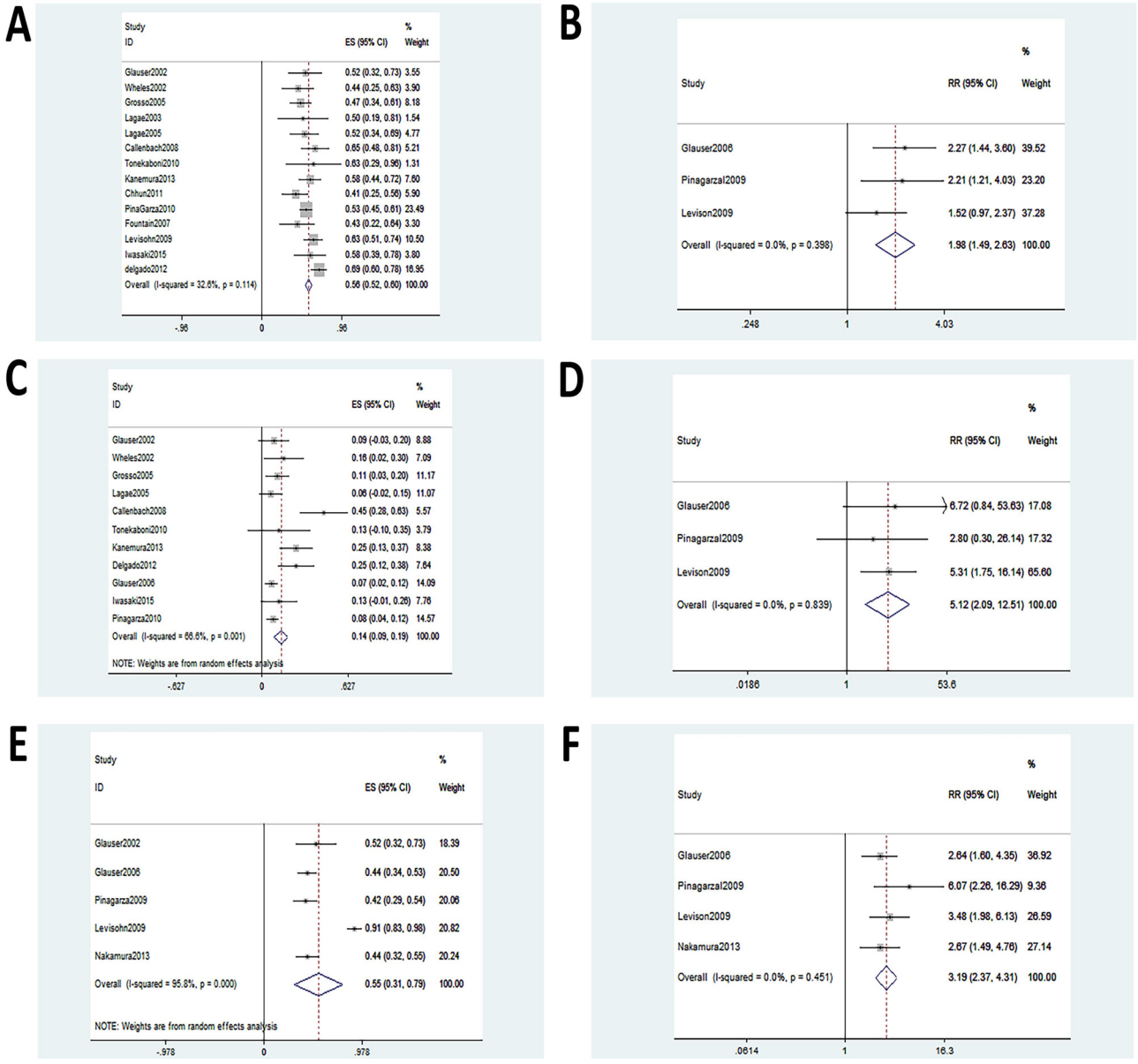

Fig. 2. Meta-analysis of the efficacy of add-on levetiracetam (LEV) in children with focal-onset seizures (FOS): (A) Overall response rate of the 50% responder for LEV group; (B) Risk ratio of the 50% responder for LEV group vs. placebo group;(C) Overall response rate of seizure freedom rate for LEV group; (D) Risk ratio of seizure freedom rate for LEV group vs. placebo group;(E) Overall response rate of the median percentage reduction rate for LEV group; (F) Risk ratio of the median percentage reduction rate for LEV group vs. placebo group.

(Callenbach et al., 2008; Glauser et al., 2006, 2002b; Grosso et al., 2005; Iwasaki et al., 2015; Kanemura et al., 2013; Lagae et al., 2005; Schiemann-Delgado et al., 2012; Tonekaboni et al., 2010; Wheless and Ng, 2002). The chi^2 test indicated statistically significant heterogeneity between trials, (chi^2 = 29.97, I^2 = 66.6%, p = 0.004), thus random-effects model was adopted. The ORR was 14% (95% CI: 9%–19%) for seizure freedom rate (Fig. 2C). A sensitivity analysis was performed, no studies were removed.

Three RCTs (LEV, n = 250; placebo, n = 212) were included in the meta-anlysis(Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009). A chi^2 test for heterogeneity indicated no statistically significant heterogeneity (chi^2 = 0.35, I^2 = 0.0%, p = 0.839), and a fixed-effect model was adopted. The overall RR showed significant difference between these two groups (RR = 5.12, 95% CI: 2.09–12.51), favoring LEV group were more effective than placebo group (Fig. 2D).

3.2.3. The median percentage reduction rate

Five prospective studies (321 patients) evaluated the efficacy of LEV based on the median percentage reduction rate were included in the pooled analysis(Glauser et al., 2006, 2002b; Levisohn et al., 2009; Nakamura et al., 2013; Pina-Garza et al., 2009). The chi^2 test indicated statistically significant heterogeneity between trials (chi^2 = 96.16, I^2 = 95.8%, p = 0.000), and a random-effects model was adopted. The ORR was 55% (95% CI: 31%–79%) in the pooled analysis for overall median percentage reduction rate (Fig. 2E). A sensitivity analysis was performed, one prospective self-controlled study was removed, and indicated a slight decrease in the rate of the median percentage reduction rate with a pooled ORR of 55% (95% CI: 31%–79%).

A total of 568 patients (LEV = 298; placebo = 260) from head-to-head trials were included in meta-analysis (Glauser et al., 2006; Levisohn et al., 2009; Nakamura et al., 2013; Pina-Garza et al., 2009). The chi^2 test showed no statistically significant heterogeneity between trials, (chi^2 = 2.64, I^2 = 0.0%, p = 0.451), and the fixed-effect model

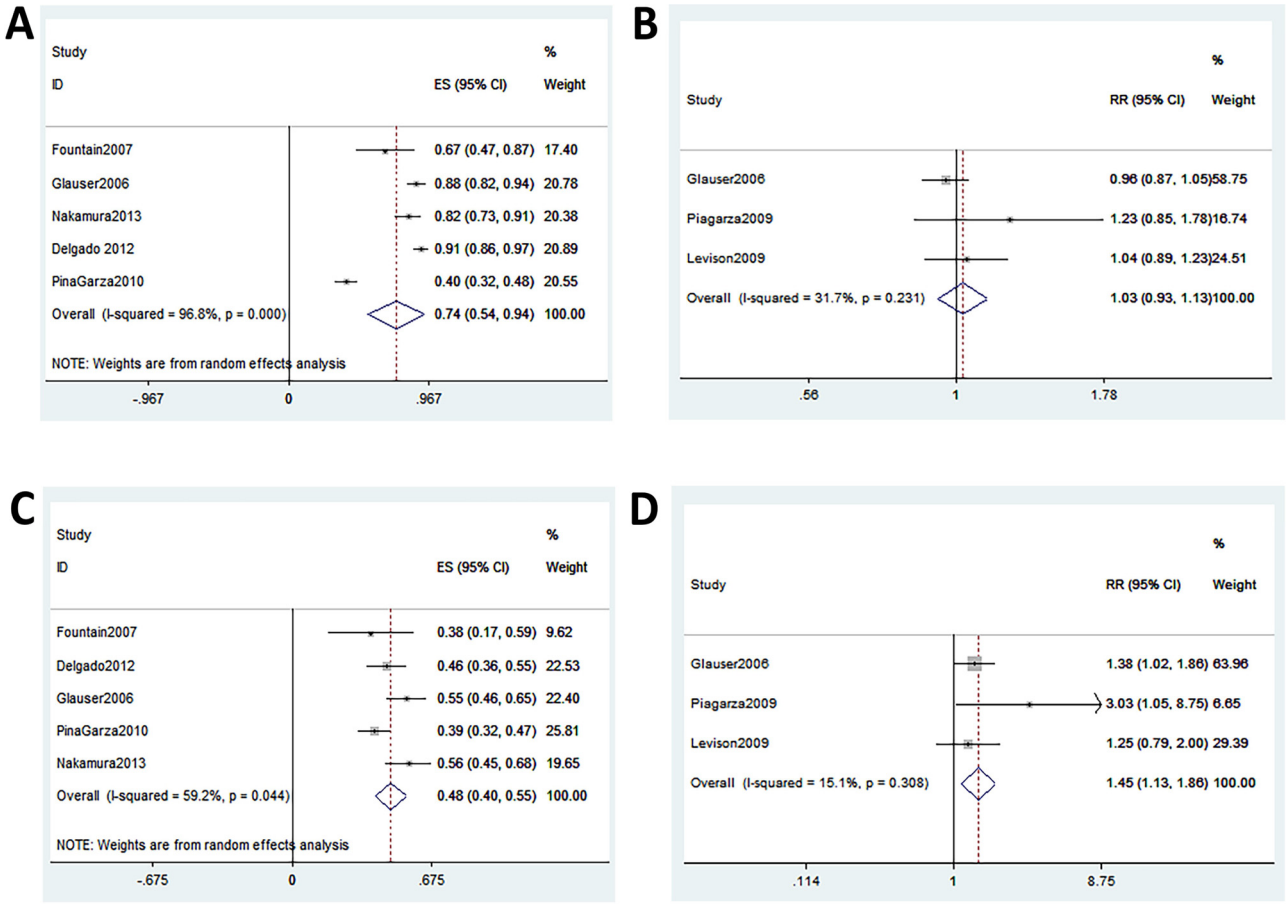

Fig. 3. Meta-analysis of the safety of add-on levetiracetam (LEV) in children with focal-onset seizures (FOS): (A) Overall response rate of at least one treatment-emergent adverse events (TEAEs) rate for LEV group; (B) Risk ratio of at least one TEAEs rate for LEV group vs. placebo group; (C) Overall response rate at least one adverse drug reactions related (ADR-related) TEAEs rate for LEV group; (D) Risk ratio at least one ADR-related TEAEs rate for LEV group vs. placebo group.

was chosen. The overall RR was 3.19 (95% CI: 2.37–4.31) between these two groups (Fig. 2F).

3.3. Results of safety

3.3.1. At least one TEAE rate

The pooled analyses were conducted to evaluated the safety of LEV based on at least one TEAE rate (449 patients) (Fountain et al., 2007; Glauser et al., 2006; Nakamura et al., 2013; Pina-Garza et al., 2010; Schiemann-Delgado et al., 2012)and on at least one ADR-related TEAE rate (450 patients) (Fountain et al., 2007; Glauser et al., 2006; Nakamura et al., 2013; Pina-Garza et al., 2010; Schiemann-Delgado et al., 2012). The chi^2 test indicated statistically significant heterogeneity for at least one TEAE rate ($chi^2 = 126.60$, $I^2 = 96.8\%$, $p = 0.0482$) or at least one ADR-related TEAE rate ($chi^2 = 9.79$, $I^2 = 59.2\%$, $p = 0.000$), and the random-effects model was chosen. The ORRs for at least one TEAE rate and at least one ADR-related TEAE rate were 74% (95% CI: 54%–94%) (Fig. 3A) and 48% (95% CI: 40%–55%), respectively (Fig. 3C). Sensitivity analysis was performed for at least one TEAE rate, one prospective study was removed, and indicated a slight increase with a pooled ORR of 86% (80%–92%). No studies were removed for the sensitivity analysis of at least one ADR-related TEAE rate.

For meta-analysis of at least one TEAE rate and at least one ADR-related TEAE rate compared LEV group and placebo group (Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009), The chi^2 test presented no statistically significant heterogeneity for at least on TEAE rate ($chi^2 = 2.93$, $I^2 = 31.7\%$, $p = 0.231$) or at least one ADR-related TEAE rate ($chi^2 = 2.36$, $I^2 = 15.1\%$, $p = 0.308$), and the fixed-effect model was chosen. The overall RRs for at least on TEAE rate and at least one ADR-related TEAE rate were 1.03 (95% CI: 0.93–1.13) and1.45 (95% CI: 1.13–1.86), favoring LEV treatment associated with a significant higher incidence of TEAEs (Fig. 3B, D).

3.3.2. Withdrawal rate

The pooled analyses were performed to analyze withdrawal rate in six prospective trials (408 patients) (Fountain et al., 2007; Glauser et al., 2006, 2002b; Pina-Garza et al., 2010; Posar et al., 2014; Schiemann-Delgado et al., 2012) and ADR-related withdrawal rate in four prospective trials (377 patients) (Fountain et al., 2007; Glauser et al., 2006; Pina-Garza et al., 2010; Schiemann-Delgado et al., 2012). The chi^2 test indicated significant heterogeneity between trials ($chi^2 = 55.35$, $I^2 = 91.0\%$, $p = 0.000$) for withdrawal rate, and the random-effects model was adopted. The chi^2 test showed no statistically significant heterogeneity ($chi^2 = 1.86$, $I^2 = 0.0\%$, $p = 0.601$), and the fixed-effect model was chosen. The ORRs for withdrawal rate and ADR-related withdrawal rate were 17% (95% CI: 5%–28%) (Fig. 4A) and 6% (95% CI: 4%–8%), respectively (Fig. 4C).

For meta-analysis of withdrawal rate and ADR-related withdrawal rate compared LEV group and placebo group (Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009), The chi^2 test presented no statistically significant heterogeneity for withdrawal rate ($chi^2 = 3.12$, $I^2 = 35.9\%$, $p = 0.210$) or ADR-related withdrawal rate ($chi^2 = 2.19$, $I^2 = 8.5\%$, $p = 0.814$), thus the fixed-effect model was adopted. The overall RRs for withdrawal rate and ADR-related withdrawal rate were 0.77 (95% CI: 0.44–1.38) and 0.91 (95% CI: 0.42–1.98), respectively. (Fig. 4B, D).

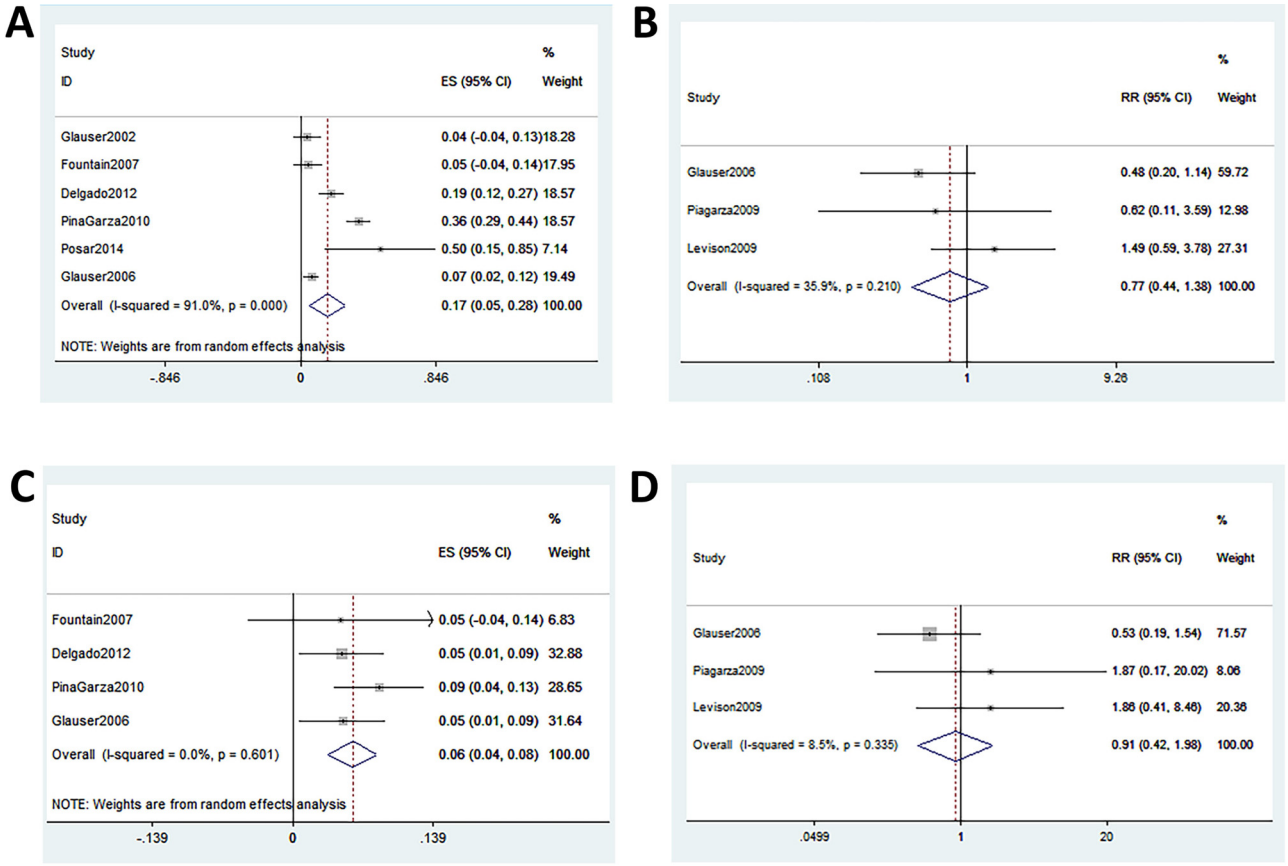

Fig. 4. Meta-analysis of the safety of add-on levetiracetam (LEV) in children with focal-onset seizures (FOS): (A) Overall response rate of withdrawal rate for LEV group; (B) Risk ratio of withdrawal rate for LEV group vs. placebo group; (C) Overall response rate the adverse drug reactions related (ADR-related) withdrawal rate for LEV group; (D) Risk ratio the ADR-related withdrawal rate for LEV group vs. placebo group.

3.3.3. Adverse events

412 patients (225 LEV, 187 placebo) from three RCTs were included in the meta-analysis of the AEs (Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009). And a pooled analysis was conducted for AEs in eight prospective trials (511 patients) (Fountain et al., 2007; Glauser et al., 2006, 2002b; Lagae et al., 2003; Levisohn et al., 2009; Pina-Garza et al., 2009; Schiemann-Delgado et al., 2012). No significant difference was reported between LEV group and placebo group regarding all AEs except somnolence (RR = 2.26, 95% CI: 1.30–3.93) and hostility (RR = 2.33, 95% CI: 1.15–4.70). The most frequent adverse events were pyrexia, headache, nervousness, upper respiratory tract, accidental injury and upper abdominal pain. RRs and the corresponding AE incidence rates for all selected TEAEs are shown in Table 1.

3.4. Brief summary of retrospective studies

Thirteen retrospective studies (632 participants.) included in systematic review were published between 2004–2015 (Dureau-Pournin et al., 2014; Enoki et al., 2015; Gallentine et al., 2009; Giroux et al., 2009; Grosso et al., 2007; Incecik et al., 2012; Krief et al., 2008; Lee et al., 2010; Obeid and Pong, 2010; Opp et al., 2005; Perry and Benatar, 2007; Tan and Appleton, 2004; von Stulpnagel et al., 2010). Three studies evaluated only pediatric patients (≤4 years old). In most studies, efficacy of LEV add-on therapy was reported to be efficacious. The median seizure freedom rate was 19.5% [10%–63%], the median the 50% responder rate was 46.6% [20%–72.7%]. The seizure freedom rate of pediatric patients (≤4 years) was significantly higher than other studies (4–18 years) in Perry at al.(Perry and Benatar, 2007), indicate that the adjunctive LEV treatment may be more effcective in pediatric patients than children (4–18 years). Tolerability was not reported in those researches. For details see Supplementary 1.

3.5. Brief summary of prospective studies

In consideration of no control arm in some prospective trials, pooled analysis for all prospective self-controlled studies and meta-analysis of controlled studies were conducted separately. As add-on therapy to conventional AEDs in young participants with partial epilepsy, LEV group can significantly reduce seizure frequency and not appear to increase adverse events compare to placebo group except at least one ADR-related TEAE rate. Results of prospective studies were summarized in Table 2.

3.6. Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of individual study on the overall risk of results. By omitting one study at a time, it was found that there was no substantial impact on the results. We also performed both fixed-effect model and random-effects model analysis for each result. There was no significant difference in results between the two models.

4. Discussions

4.1. Current Evidence for efficacy and safety of LEV

An integration of clinical data can help with the AED selection during the pediatric epilepsy treatment. Some existing meta-analysis and systematic review studies had explored the efficacy and safety of LEV therapy, however no synthesis of sufficient statistical evidence

Table 1
Meta-analysis and Pooled-analysis of AEs.

Adverse events	Events	ORR(95%CI)(%)	RR (95%CI)
Nervous			
headache	34/167	23.6(16.5–30.6)	1.80(0.73–4.47)
somnolence	51/301	17.9(10.4–25.5)	2.26(1.30–3.93)*
fatigue	16/167	9.6(2.6–16.5)	1.20(0.40–3.60)
dizziness	15/186	7.9(4.0–11.8)	1.63(0.79–3.39)
insomnia	8/147	3.1(0.4–5.9)	
asthenia	9/101	8.9(3.4–14.5)	1.77(0.81–3.85)
Behavioural			
personality disorder	8/101	7.9(2.7–13.2)	
anxiety	4/64	6.3(0.3–12.2)	
aggression	8/103	7.8(2.6–12.9)	
psychomotor hyperactivity	4/64	6.3(0.3–12.2)	
irritability	27/356	10.1(6.4–13.8)	
altered mood	4/64	6.3(0.3–162.2)	
agitation	6/101	5.9(1.3–10.6)	
hostility	27/225	12.0(7.7–16.2)	2.33(1.15–4.70)*
incr.alterlness	3/101	3.0(1.6–5.84)	
behavior abnormal	7/113	6.1(1.7–10.5)	
emotional lability	9/124	6.7(2.3–11.0)	
nervousness	5/23	21.7(4.9–38.6)	
Gastrointestinal			
vomiting	56/356	10.3(7.2–13.3)	1.13(0.64–1.99)
anorexia	26/209	11.1(6.9–15.4)	
diarrhea	34/225	12.5(5.0–20.1)	
nausea	33/255	11.8(1.7–21.9)	
gastroenteritis	6/103	5.8(1.3–10.3)	
constipation	20/163	10.1(−3.7–23.9)	
Respiratory			
cough	42/377	9.4(6.7–12.1)	1.59(0.72–3.52)
pyrexia	87/278	26.1(11.5–40.6)	0.79(0.29–2.14)
upper respiratory tract infection	22/103	21.4(13.4–29.3)	
nasopharyngitis	13/107	12 . 6(6.2–19.0)	
nasal congestion	6/64	9.4(2.2–16.5)	
epistaxis	3/64	4.7(−0.005–0.1)	
rhinitis	13/101	12.9(6.3–19.4)	1.56(0.67–3.60)
pharyngitis	23/227	9.4(5.6–13.1)	
Pain			
upper abdominal pain	54/276	15.9(3.0–28.9)	
back pain	6/103	5.8(1.3–10.3)	
otitis meida	19/175	10.8(6.2–15.4)	
accidental injury	22/124	17.6(10.9–24.3)	1.70(0.82–3.53)
other pain	6/101	5.9(1.3–10.6)	
Skin			
rash	10/163	4.8(−2.0–11.7)	
Other			
convulsion	35/278	10.2(6.7–13.6)	

* means significant difference significant between LEV group and placebo group.

Table 2
Summary of efficacy and safety outcomes from our stuides.

	Prospective studies ORR (95% CI)	RCT RR (95% CI)
Efficacy outcomes		
50%responder rate	56% (52%–60%)	1.98(1.49–2.63)
seizure freedom rate	14% (9%–19%)	5.12 (2.09–12.51)
the median percentage reduction rate	55% (31%–79%)	3.19(2.37–4.30)
Safety outcomes		
at least one TEAE rate	74% (54%–94%)	1.03(0.94–1.13)
at least one ADR-related TEAE rate	48% (40%–55%)	1.45(1.13–1.86)
Withdrawal rate	17% (5%–28%)	0.77 (0.44–1.38)
The ADR-related withdrawal rate	6% (4%–8%)	0.91(0.42–1.98)

about LEV treating pediatric partial seizure was provided.

The meta-analysis of Fang et al.(Fang et al., 2014) did not show statistically siginificant difference of AE incidence for all seizure types at any age between LEV and placebo group.The result was not supported in our study since the RRs of somnolence and hostility were 2.26 (95% CI: 1.30–3.93) and 2.33 (95% CI: 1.15–4.70). Moreover, Fang et al. showed a better effect of add-on LEV therapy on partial seizures, with a much higher the 50% responder rate (OR: 3.23, 95% CI: 1.95–5.37) and seizure freedom rate (OR: 7.15, 95% CI: 0.86–59.23) than our study. However, only two RCTs were included in Fang's study, implying the research result may be feeble.

A Cochrane Review conducted by Mbizvo et al.(Mbizvo et al., 2012) showed only somnolence retained statistically significant risk over placebo, while hostility did not show significant difference with RR = 1.92 (99% CI: 0.56–6.60). In Mbizvo's analysis, the overall RR for the 50% responder rate and withdrawal rate were 1.91 (95% CI: 1.38–2.63) and 0.8 (95% CI: 0.43–1.46) respectively, and the corresponding RR in this study were consistent with 1.96 (95% CI: 1.51–2.55) and 0.77 (95% CI: 0.44–1.38).

A Verrotti et al.(Verrotti et al., 2015) analyze the adverse events (AEs) significantly associated with LEV therapy on children and adults, convincing results with large data set from 26 RCTs were provided, indicating that nasopharyngitis, somnolence, dizziness, nervousness/irritability and asthenia/fatigue were caused by LEV therapy. Although significantly higher AE-related withdrawal rate was observed in this research, the difference may be caused by the different sampling population.

Hostility is a significant adverse event in our research. From a medical perspective, the prevalence of psychiatric comorbidities in patients with epilepsy is high and medically-refractory. From a social perspective, hostility is a potential threat to family and treating physician. Therefore, we should also be pay high attention to it.

Compared with previous publication, this systematic review provided more reliable findings based on a large study size, appropriate study design and the most updated clinical evicence of LEV therapy. After a strict quality evaluation, thirty-one studies with 1763 patients were included, both pooled and meta analysis were conducted to investigate outcome measures and the withdrawal rate. The results strongly support LEV a good efficacy and fairly well-tolerated, and furtherly verified the better efficacy of adjunctive LEV in pediatric partial seizures than placebo.

4.2. The best adjunctive AEDs for pediatric partial seizures

A cross-trial comparative analysis was performed to determine the best AED option for add-on therapy in children with FOS. Efficacy and safety of AEDs were ranked by clinical evidence from RCTs(Appleton et al., 2001; Duchowny et al., 1999; Elterman et al., 1999; Glauser et al., 2002a; Guerrini et al., 2013; Mann et al., 2014; Meador et al., 2016; Rosenfeld et al., 2015), and seven AEDs were evaluated.

LEV was proved with higher the 50% responder rate and the median percentage reduction rate, while lamotrigine maybe superior to LEV in seizure freedom rate, with a median increase of 28%. Nevertheless, patients receiving lamotrigine reported the highest incidence of adverse events. Based on the above, LEV could be the optimal solution as add-on AEDs for pediatric partial seizures, with best efficacy and relatively lower AE rate, see Supplementary.

Lattanzi et al. (Lattanzi et al., 2018a,b; Lattanzi et al., 2018c) found that adjunctive eslicarbazepine acetate could significantly reduce baseline seizure frequency and well-tolerated in children and adolescents with focal-onset seizures uncontrolled by concomitant stable antiepileptic drug regimens, and cannabidiol had a greater reduction in seizure frequency and higher rate of AEs as adjunctive treatment in patients with epilepsy (didn't distinguish between Lennox–Gastaut syndrome and Dravet syndrome) and Lennox–Gastaut syndrome in their analyses. Network meta-analysis is needed to compare efficacy of these treatments and provide more valuable reference for clinical practice.

Brivaracetam (BRV) is aracetam derivative of LEV, which binds synaptic vesicle protein 2A with 20 times higher affinity than LEV and is used in the treatment of partial-onset seizures for patients since the age of 16 years (Lattanzi et al., 2016). Since there are many higher

frequency adverse events, such as pyrexia, headache, nervousness, upper respiratory tract and somnolence, a switch to BRV can be considered in patients with LEV-induced adverse events (Schubert-Bast et al., 2018).

4.3. Limitations and future research

This systematic review has several limitations. First, few RCTs were included in the meta-analysis and the heterogeneity among pooled analysis may weaken the strength of evidence. Second, this study cannot provide the efficacy and safety information for neonatals (≤2 years old), infants (≤4 years old) and children (≤18 years old) separately. Third, because the duration of the evaluation phase varies widely, the meaning of change in seizure frequency, and the number and even types of adverse effects seen by medications may impact on results. According to the present available evidence mentioned above, we speculated that the longer the duration of the evaluation phase is, the more number and types of adverse events may occur. Further researches are needed to achieve a definite answer. Finally, the results of the cross-trial comparison may be confounded by differences in study design and sampling.

To provide accurate and specific evidence for clinical decision-making, further head-to-head studies are necessary. And RCTs with larger scale and higher quality are still required to verify the efficacy of adjunctive LEV therapy in treating pediatric partial-seizure.

5. Conclusion

All relevant published studies to date were included in this review, indicating that LEV may be superior option as add-on treatment in children with partial seizures, as its favorable efficacy and insignificant toxicity. However, further studies are still needed to draw definitive conclusions about LEV when used in children younger than two years old, and to evaluate the long-term efficacy and safety.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Study design, literature research, manuscript editing, Yaohua Cao and Xin He; data acquisition: Lina Zhao; statistical analysis: Sen Wang; revised and polished the manuscript: Yuwen He; manuscript final version approval: Jie Jiang and Tian-tian Zhang.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (grant No. 71704064), the Natural Science Foundation of Guangdong Province, China (grant No. 2017A030310174) and the Fundamental Research Funds for the Central Universities (grant No. 21616324).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.04.001.

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