

Efficacy and safety of oxcarbazepine in the treatment of children with epilepsy: a meta-analysis of randomized controlled trials

Hua Geng
Chengzhong Wang

Department of Pediatrics, Maternal and Child Health Hospital of Yancheng, Yancheng City, People's Republic of China

Background: To assess the efficacy and safety of oxcarbazepine (OXC) in the treatment of children with epilepsy.

Methods: Randomized controlled trials (RCTs) published in PubMed, Embase, Web of Science, Cochrane Library, Scopus, SinoMed (Chinese BioMedical Literature Service System, China), and Chinese National Knowledge Infrastructure (China) database were systematically reviewed. Eligible studies were those that compared the efficacy and safety of OXC with other antiepileptic drugs in epilepsy. Risk ratio (RR) with 95% confidence intervals (95% CIs) was calculated using fixed-effects or random-effects model.

Results: Eleven RCTs with a total of 1,241 patients met the inclusion criteria and were included in this meta-analysis. Compared with other antiepileptic drugs (sodium valproate, levetiracetam, phenytoin, and placebo), OXC was associated with similar seizure-free rate (RR =1.06, 95% CI: 0.94, 1.20; $P=0.366$) and percentage reduction from baseline in seizure frequency (for $\geq 75\%$ reduction: RR =1.15, 95% CI: 0.88, 1.49; $P=0.310$; for 50%–75% reduction: RR =1.12, 95% CI: 0.90, 1.39; $P=0.301$; for $<50\%$ reduction: RR =0.79, 95% CI: 0.56, 1.12; $P=0.179$). Moreover, patients treated with OXC had a comparable incidence of adverse events compared with those treated with other antiepileptic drugs (RR =1.01, 95% CI: 0.92, 1.11; $P=0.760$).

Conclusion: OXC showed similar effects and safety as other antiepileptic drugs in the treatment of children with epilepsy. Further well-conducted, large-scale RCTs are needed to validate these findings.

Keywords: epilepsy, children, oxcarbazepine, meta-analysis

Introduction

Epilepsy is a disease characterized by a wide range of symptoms resulting from a variety of cerebral disorders.¹ Semiologically, it is classified as partial or generalized.² The clinical manifestations can occur through sensitive, sensory, psychological, vegetative, and motor signs and symptoms of simple or complex nature depending on the neural system involved in the genesis of the disease.^{2–4} It has been estimated that 50 million patients around the world suffer from epilepsy.¹ Treatment approaches for pediatric population with epilepsy still face unique challenges. Despite seizures being effectively controlled by the antiepileptic drugs (AEDs) in most of children, more than 25% of pediatric patients who were treated with AEDs still developed intractable seizures or troublesome adverse events.⁵ In the past decade, new AEDs have been introduced, and these have proved to be effective and well-tolerated in patients.

Oxcarbazepine (OXC) is a new AED that is used for epilepsy treatment, both in adults and in pediatric patients.^{6–8} It was developed in an attempt to improve the

Correspondence: Chengzhong Wang
Department of Pediatrics, Maternal and Child Health Hospital of Yancheng, Yancheng City, Jiangsu Province, 224002, People's Republic of China
Email wangmengzh@sohu.com

tolerability of carbamazepine without affecting its anti-convulsant potency.⁹ Having been registered in more than 50 countries around the world, OXC is widely used as first-line and add-on treatment for generalized tonic-clonic seizures (GTCS) and partial seizures with or without secondarily generalized seizures.¹⁰ Because OXC did not have the extensive oxidative metabolism, it had a lower potential for induction of hepatic enzymes than other AEDs.¹¹ Moreover, owing to the low protein binding (40%), OXC induced markedly fewer pharmacokinetic drug interactions and treatment-related adverse events than standard AEDs.^{10–12}

The effects and safety of OXC have been evaluated in several clinical trials; however, their results remained controversial. Therefore, we conducted this meta-analysis based on eligible randomized controlled trials (RCTs) to compare the efficacy and safety of OXC with other AEDs in children with epilepsy.

Methods and materials

Search strategy

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.¹³ We conducted a systematic electronic search in PubMed, Embase, Web of Science, Cochrane Library, Scopus, SinoMed (Chinese BioMedical Literature Service System, China), and China National Knowledge Infrastructure (China) from inception to October 12, 2016, and the literature search was updated on January 12, 2017. The following search items were used: ((“pediatrics” [MeSH Terms] OR “pediatrics” [All Fields] OR “pediatric” [All Fields]) OR (“Childhood” [Journal] OR “childhood” [All Fields])) AND (“epilepsy” [MeSH Terms] OR “epilepsy” [All Fields]) AND (“oxcarbazepine” [Supplementary Concept] OR “oxcarbazepine” [All Fields]). There was no language restriction, but participant ages were restricted to children aged between 3 and 17 years. We also manually searched the reference lists of relevant reviews and all included studies until no potentially eligible studies were found.

Study selection

Two investigators (Hua Geng and Chengzhong Wang) independently conducted the initial search, deleted duplicate records, reviewed the abstract/title and full-text information, and identified the records as included or excluded. The disagreement between two investigators was resolved by discussion and consensus. Studies included in this meta-analysis must meet the following selection criteria: 1) study design: RCTs; 2) population: involving children

with epilepsy; 3) intervention: OXC; 4) comparison: other AEDs or placebo; and 5) outcomes: providing at least one of the following outcomes: seizure-free rate, reduction from baseline in seizure frequency, and adverse events.

Data collection

Data collection was performed by two independent investigators (Hua Geng and Chengzhong Wang). A standardized Excel form file was used to extract the following information from the included studies: first author's name, year of publication, country, number of patients in each group, patients' demographic characteristics, duration of the follow-up, dosage of OXC, and outcome data. We also contacted the corresponding authors for missing data.

Risk of bias assessment and grading quality of evidence assessment

We assessed the risk of bias in included studies, using the Cochrane risk of bias tool.¹⁴ Each trial was regarded as at being high, low, or unclear risk of bias according to the following criteria: random sequence generation, allocation concealment, blinding of outcome participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

The quality of evidence for outcomes was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology¹⁵ and was classified as very low, low, moderate, or high. A summary table was prepared using the GRADE profiler (GRADE pro, version 3.6).

Statistical analysis

We calculated risk ratio (RR) with 95% confidence intervals (95% CIs) for dichotomous outcomes. Heterogeneity across the included studies was assessed by using I^2 statistic and Cochran's Q χ^2 test.¹⁶ An I^2 value $>50\%$, or the value of $P < 0.10$ indicated significant heterogeneity.¹⁶ When significant heterogeneity was identified, a random-effects model (DerSimonian–Laird method)¹⁷ was used to pool the estimates; otherwise, a fixed-effects model (Mantel–Haenszel method)¹⁸ was applied. We also conducted subgroup analysis based on comparators, study quality, and sample size to check the influence of various factors on the outcomes. Publication bias was assessed using Begg's¹⁹ and Egger's²⁰ tests. A P -value of <0.05 was considered as statistically significant, except where otherwise specified. All analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search

The initial search yielded 2,911 records. Of these, 1,924 were removed as they were duplicate records and 966 were excluded after a review of titles/abstracts. Then, 21 potential studies were identified for further analysis. However, 10 of them were excluded for the following reasons: eight studies involved adults rather than children; one study did not provide outcome of our interest; and one study was a single-arm trial (Figure 1). Finally, 11 RCTs^{21–31} met the inclusion criteria and were included in this meta-analysis.

Study characteristics

The main characteristics of the included studies are presented in Table 1. These RCTs were published from 1997 to 2016. The sample size in these studies ranged from 39 to 267. Among these RCTs, one was conducted in Brazil,²¹ one in the USA,²² one in Italy,²³ and eight in China.^{24–31} Six studies compared OXC with levetiracetam;^{23,25,28–31} three studies compared OXC with sodium valproate;^{24,26,27} each study compared OXC with phenytoin²¹ or placebo.²² The dosage and schedule of OXC among these studies varied greatly. In these studies, OXC was initiated at a dosage of

5–20 mg/kg/day and was increased up to a maximum dosage of 35 mg/kg/day.

Risk of bias assessment and quality of evidence

The details of risk of bias assessment are presented in Figure 2. Of the 11 included RCTs, two^{21,22} were considered to be at low risk of bias, six^{23–25,28,30,31} at unclear risk of bias, and three^{26,27,29} at high risk of bias. Randomized sequence was adequately generated in four trials,^{21–23,25} and allocation concealment was reported in detail in two trials.^{21,23} The blinding of participants and personnel was described in three trials.^{21–23} There was no incomplete outcome data, selective reporting, or other bias in all the included studies.

The GRADE evidence profiles for these outcomes are shown in Table 2. The quality of evidence was moderate for seizure-free rate, reduction from baseline in seizure frequency, and adverse events.

Seizure-free rate

All the trials reported the data of seizure-free rate.^{21–31} The seizure-free rate in the OXC and other AED group was 39.0% and 37.7%, respectively. Pooled estimates suggested that patients treated with OXC had a comparable seizure-free rate with those treated with other AEDs (RR = 1.06, 95% CI: 0.94, 1.20; $P=0.366$) (Figure 3). The test for heterogeneity was not significantly different ($P=0.290$, $I^2=16.1\%$).

We also conducted subgroup analysis based on the comparators, study quality, and sample size. The aggregated results showed that OXC had similar effect with phenytoin (RR = 1.01, 95% CI: 0.79, 1.31; $P=0.923$), levetiracetam (RR = 0.98, 95% CI: 0.84, 1.14; $P=0.786$), sodium valproate (RR = 1.27, 95% CI: 0.92, 1.77; $P=0.150$), and placebo (RR = 4.67, 95% CI: 0.55, 39.47; $P=0.157$) in terms of seizure-free rate (Figure 3; Tables 3 and 4).

Subgroup analysis based on sample size showed that patients treated with OXC had a comparable seizure-free rate than those treated with other AEDs regardless of the sample size (for sample size < 100, RR = 1.04, 95% CI: 0.86, 1.26; $P=0.413$; for sample size > 100, RR = 1.07, 95% CI: 0.91, 1.26; $P=0.685$) (Tables 3 and 4).

Subgroup analysis based on study quality showed that OXC had a similar seizure-free rate with other AEDs among the studies with low or unclear risk of bias (for studies with low risk of bias: RR = 1.09, 95% CI: 0.84, 1.41; $P=0.507$; for studies with unclear risk of bias: RR = 0.93, 95% CI: 0.80, 1.09; $P=0.374$), whereas for the studies with high risk of

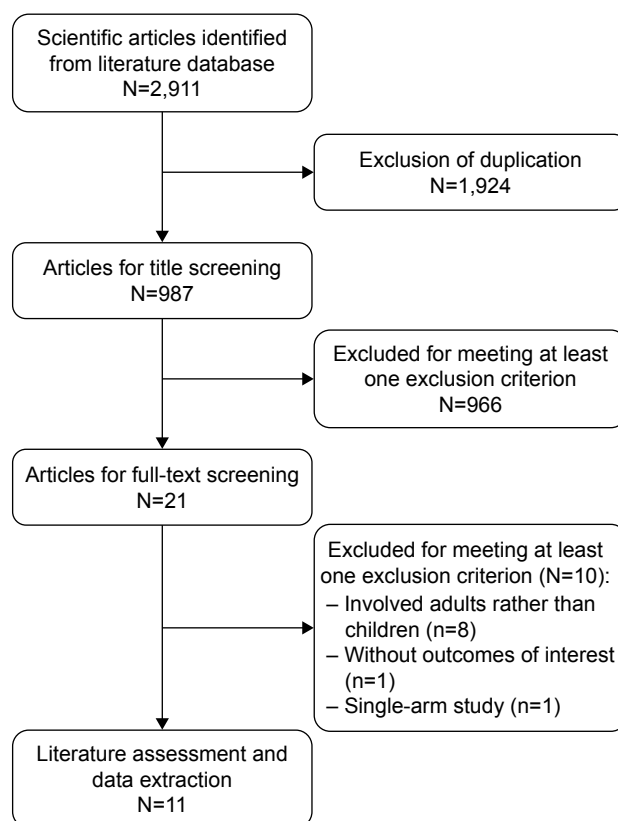


Figure 1 Eligibility of studies for inclusion in meta-analysis.

Table 1 Baseline characteristics of patients in the trials included in the meta-analysis

Study	Year	Country	Intervention	Number of patients	Male/female	Age (mean \pm SD, y)	Mean duration of epilepsy (m)
Guerreiro et al ²¹	1997	Brazil	150 mg OXC	97	46/51	10.22 (5–17)	NR
Glauser et al ²²	2000	USA	50 mg phenytoin	96	50/46	10.85 (6–17)	NR
			30–46 mg/kg/d OXC	138	51/49	11 (3–17)	NR
Coppola et al ²³	2007	Italy	30–46 mg/kg/d placebo	129	55/45	11 (3–17)	NR
			5–20 mg/kg/d OXC	18	10/8	3.3–14	8.52
Ma ²⁴	2016	People's Republic of China	5–20 mg/kg/d levetiracetam	21	11/10	3.3–14	3.7
			8–10 mg/kg/d OXC	72	42/30	9 \pm 1.3	NR
Tan ²⁵	2016	People's Republic of China	15 mg/d sodium valproate	72	42/30	10 \pm 1.1	NR
			OXC	54	NR	NR	NR
Wang and Yu ²⁶	2014	People's Republic of China	Levetiracetam	54	NR	NR	NR
			5–10 mg/kg/d OXC	21	NR	6.9 \pm 1.2	NR
Ding ²⁷	2016	People's Republic of China	10–40 mg/kg sodium valproate	21	NR	6.9 \pm 3.5	NR
			5–10 mg/kg/d OXC	75	39/36	7.3 \pm 1.1	6.0 \pm 0.9
Hou et al ²⁸	2015	People's Republic of China	10–40 mg/kg sodium valproate	75	38/37	7.5 \pm 1.2	5.8 \pm 0.7
			10 mg/kg OXC	38	21/17	6.13 \pm 2.62	7.34 \pm 4.22
Zhang et al ²⁹	2015	People's Republic of China	Levetiracetam	37	19/18	6.82 \pm 3.12	8.23 \pm 3.89
			5–10 mg/kg/d OXC	48	NR	NR	NR
Zhang ³⁰	2014	People's Republic of China	10 mg/kg/d levetiracetam	41	NR	NR	NR
			10 mg/kg/d OXC	32	NR	6.8 \pm 2.6	5.8 \pm 2.2
Chen et al ³¹	2013	People's Republic of China	10 mg/kg/d levetiracetam	34	NR	6.8 \pm 2.6	5.8 \pm 2.2
			5–10 mg/kg/d OXC	48	NR	9.8 \pm 3.5	NR
			10 mg/kg/d levetiracetam	55	NR	9.8 \pm 3.5	NR

Abbreviations: OXC, oxcarbazepine; SD, standard deviation; NR, not reported.

bias, OXC was associated with a significantly higher seizure-free rate than other AEDs (RR =1.45, 95% CI: 1.06, 1.99; $P=0.019$) (Tables 3 and 4).

Reduction from baseline in seizure frequency

Nine studies reported the data of percentage reduction from baseline in seizure frequency.^{22,24–31} Compared with patients treated with other AEDs, patients who had OXC experienced a comparable effect in $\geq 75\%$, 50%–75%, or $<50\%$ reduction from baseline in seizure frequency (for $\geq 75\%$ reduction: RR =1.15, 95% CI: 0.88, 1.49; $P=0.310$; for 50%–75% reduction: RR =1.12, 95% CI: 0.90, 1.39; $P=0.301$; for $<50\%$ reduction: RR =0.79, 95% CI: 0.56, 1.12; $P=0.179$) (Figures 4–6).

We conducted subgroup analysis based on the comparators. The pooled results showed that OXC resulted in a similar effect with sodium valproate (RR =1.16, 95% CI: 0.85, 1.58; $P=0.349$) and levetiracetam (RR =1.12, 95% CI: 0.69, 1.81; $P=0.650$) in $\geq 75\%$ reduction from baseline in seizure frequency (Figure 4).

OXC resulted in a similar effect with sodium valproate (RR =0.85, 95% CI: 0.59, 1.22; $P=0.372$) and levetiracetam (RR =0.90, 95% CI: 0.61, 1.34; $P=0.617$), but a better effect than placebo (RR =1.86, 95% CI: 1.27,

2.74; $P=0.002$) in 50%–75% reduction from baseline in seizure frequency (Figure 5).

OXC resulted in a similar effect with levetiracetam (RR =1.00, 95% CI: 0.65, 1.56; $P=0.985$), but an inferior effect than sodium valproate (RR =0.54, 95% CI: 0.30, 0.96; $P=0.0035$) in $<50\%$ reduction from baseline in seizure frequency (Figure 6).

Subgroup analysis based on the study quality showed that in the studies with low risk of bias, OXC was associated with a significantly better effect in 50%–75% reduction from baseline in seizure frequency (RR =1.86, 95% CI: 1.27–2.74; $P=0.002$) (Tables 3 and 4). For studies with high risk of bias, OXC was associated with a prior effect in $<50\%$ reduction from baseline in seizure frequency (RR =0.42, 95% CI: 0.22–0.79; $P=0.007$) (Tables 3 and 4).

Subgroup analysis based on the sample size showed that sample size did not affect the pooled results of OXC for $\geq 75\%$, 50%–75%, or $<50\%$ reduction from baseline in seizure frequency (Tables 3 and 4).

Adverse events

Ten RCTs reported the data of adverse events.^{21–23,25–31} The incidence of adverse events in the OXC and other AED groups was 49.2% and 47.1%, respectively. The pooled estimates demonstrated that patients treated with OXC had

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen et al ³¹	?	?	?	?	+	+	+
Coppola et al ²³	+	?	+	+	+	+	+
Ding ²⁷	−	?	?	?	+	+	+
Glauser et al ²²	+	+	+	+	+	+	+
Guerreiro et al ²¹	+	+	+	+	+	+	+
Hou et al ²⁸	?	?	?	?	+	+	+
Ma ²⁴	?	?	?	?	+	+	+
Tan ²⁵	+	?	?	?	+	+	+
Wang and Yu ²⁶	−	?	?	?	+	+	+
Zhang ³⁰	?	?	?	?	+	+	+
Zhang et al ²⁹	−	?	?	?	+	+	+

Figure 2 Risk of bias summary.

Notes: Red, high risk; blue, low risk; orange, unclear risk.

similar incidence of adverse events with those treated with other AEDs (RR =1.01, 95% CI: 0.92, 1.11; $P=0.760$).

Publication bias

The assessment of publication bias showed that there was no potential publication bias among the included studies (Egger's test, $P=0.27$; Begg's test, $P=0.43$).

Discussion

The objective of this meta-analysis was to compare the efficacy and safety of OXC with other AEDs (sodium valproate, levetiracetam, phenytoin, and placebo) in the treatment of children with epilepsy. Based on the 11 RCTs, our results showed that OXC had similar efficacy and safety as other

AEDs when treating children with epilepsy. There was no significant difference between OXC and other AEDs in terms of seizure-free rate and percentage reduction from baseline in seizure frequency. Furthermore, no significant difference in the incidence of adverse events was observed between these treatments.

There have been two published meta-analysis that compared the efficacy and safety of OXC with phenytoin/OXC in patients with epilepsy.^{32,33} The study conducted by Muller et al³² included two RCTs in children or adults with epilepsy.³² Based on these included studies, they found that OXC was associated with a significantly better effect than phenytoin in time to treatment withdrawal (hazard ratio [HR] =1.64, 95% CI: 1.09–2.47), but similar effects in time to 12-month remission (HR =0.92, 95% CI: 0.62–1.37) and time to first seizure (HR =1.07, 95% CI: 0.83–1.39).³² However, in another meta-analysis conducted by Koch et al,³³ different results were observed. In that study, three RCTs that compared the efficacy and safety of OXC with carbamazepine for partial onset seizures were included.³³ They observed that OXC was associated with comparable effects with carbamazepine in time to treatment withdrawal (HR =1.04, 95% CI: 0.78–1.39), and treatment withdrawal for inadequate seizure control (HR =1.33, 95% CI: 0.82–2.15).³³ Moreover, there was no significant difference in treatment withdrawal for unacceptable side effects between the two groups (HR =0.85, 95% CI: 0.59–1.24).

Our meta-analysis expands on these two early meta-analyses to explore better characterization of evidence for OXC in children with epilepsy. 1) The present meta-analysis had a larger sample size than the previous meta-analyses, and this enhanced the statistical power to evaluate the effects of OXC. In this meta-analysis, the number of included RCTs was 11, while for the previous ones, they were two or three, and the number of available studies for analysis was only one. 2) In this meta-analysis, we restricted study subjects to children, whereas in the previous meta-analyses, studies with both adults and children were included. The authors did not provide the data for children and adults, respectively. Thus, we are still uncertain whether OXC is effective in children or adults. 3) In the present meta-analysis, we conducted subgroup analysis based on several important factors, including comparators, study quality, and sample size. The subgroup analysis based on these factors did not significantly change the overall estimates, which added robustness to our results.

In this meta-analysis, we found that OXC had a similar effect on seizure-free rate compared with other AEDs (sodium valproate, levetiracetam, phenytoin, and placebo).

Table 2 GRADE evidence profile

Quality assessment		Number of patients		Effect		Quality	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Absolute
Seizure-free rate							
11	Randomized trials	Very serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association ^b	244/625 (39%) 232/616 (37.7%) 41.4%
							1.06 (0.94 to 1.20) 23 more per 1,000 (from 23 fewer to 75 more) 25 more per 1,000 (from 25 fewer to 83 more)
							⊕⊕⊕⊕O Moderate Critical
≥75% reduction from baseline in seizure frequency							
7	Randomized trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	87/334 (26%) 76/335 (22.7%) 23.5%
							1.15 (0.88 to 1.49) 34 more per 1,000 (from 27 fewer to 111 more) 35 more per 1,000 (from 28 fewer to 115 more)
							⊕⊕⊕⊕O Moderate Important
50%–75% reduction from baseline in seizure frequency							
9	Randomized trials	Serious ^c	No serious inconsistency	No serious indirectness	No serious imprecision	None	131/523 (25%) 115/517 (22.2%) 16.7%
							1.12 (0.90 to 1.39) 27 more per 1,000 (from 22 fewer to 87 more) 20 more per 1,000 (from 17 fewer to 65 more)
							⊕⊕⊕⊕O Moderate Important
<50% reduction from baseline in seizure frequency							
8	Randomized trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	48/388 (12.4%) 60/389 (15.4%) 13.0%
							0.79 (0.56 to 1.12) 32 fewer per 1,000 (from 68 fewer to 19 more) 27 fewer per 1,000 (from 57 fewer to 16 more)
							⊕⊕⊕⊕O Moderate Important
Adverse events							
9	Randomized trials	Serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	None	256/520 (49.2%) 245/520 (47.1%) 24.1%
							1.01 (0.92 to 1.11) 5 more per 1,000 (from 38 fewer to 52 more) 2 more per 1,000 (from 19 fewer to 27 more)
							⊕⊕⊕⊕O Moderate Important

Notes: ^aOnly two trials were judged to be at low risk of bias. ^bA total of 1,241 patients were enrolled. ^cOnly one trial was judged to be at low risk of bias.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, risk ratio; CI, confidence interval.

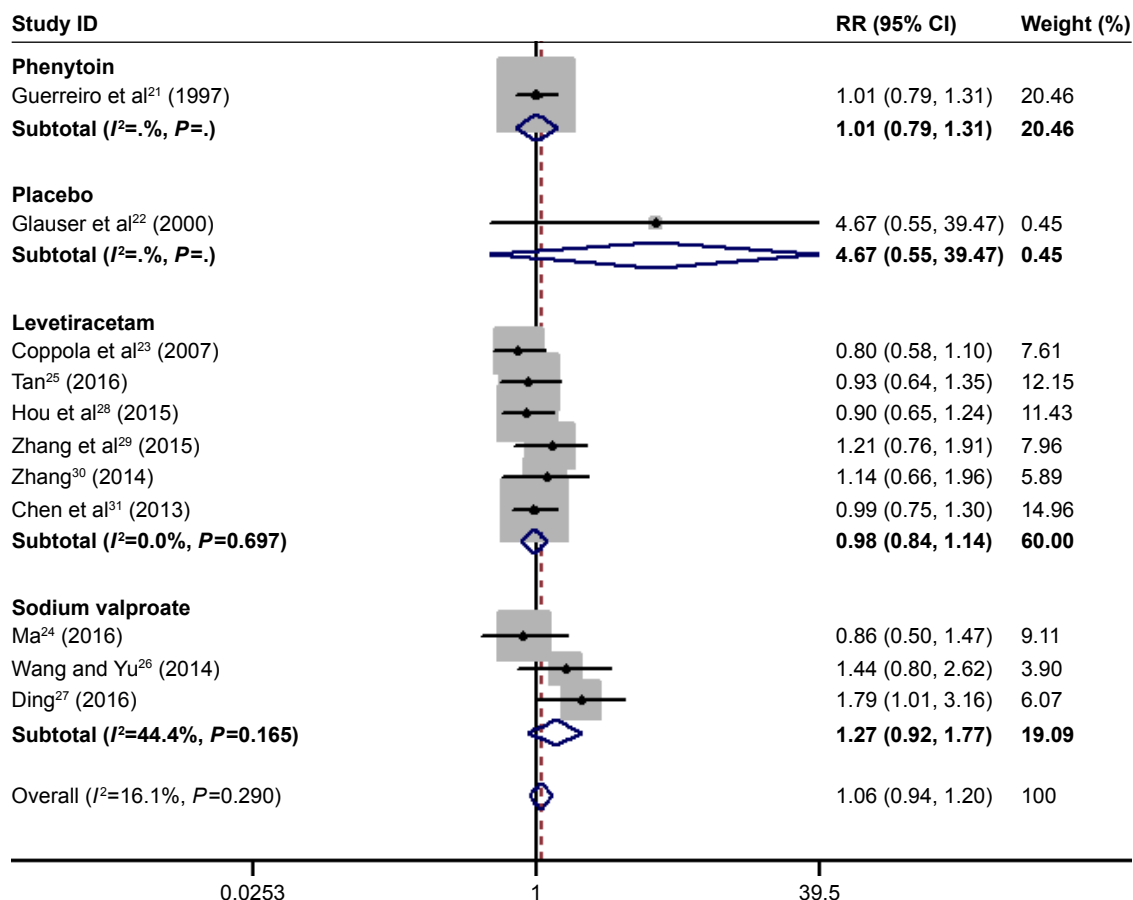


Figure 3 Forest plot showing the effects of OXC on seizure-free rate.

Abbreviations: CI, confidence interval; RR, risk ratio; OXC, oxcarbazepine.

Our result is comparable to data from some other studies. In the trial of Coppola et al,²³ children with newly diagnosed benign epilepsy with centrottemporal spike were randomized to receive OXC or levetiracetam.²³ At a mean follow-up period of 18.5 months, 13 out of 18 (72.2%) children in the OXC group and 19 out of 21 (90.5%) in the levetiracetam group had no further seizures.²³ Although the seizure-free rate in levetiracetam group seemed to be higher than that in OXC group, the difference between them was not statistically significant ($P=0.41$).²³ Similarly, in another double-blind, randomized trial, no significant difference in seizure-free rate was observed between OXC and phenytoin.²¹ In that study,

193 children with either secondarily generalized seizures or GTCS without partial onset were enrolled.²¹ During the maintenance period, 61% of children in the OXC group and 60% of children in phenytoin group were seizure free,²¹ which indicated that OXC had a similar effect with phenytoin in making patients seizure free.

Assessment of the percentage reduction from baseline in seizure frequency also suggested a similar effect with OXC compared with other antiepileptic drugs (sodium valproate, levetiracetam, and placebo). Seventeen percentage of patients treated with OXC experienced a $\geq 75\%$ reduction from baseline in seizure frequency compared with 16.0% of patients

Table 3 Summary of the risk ratios with 95% confidence intervals of outcomes in the subgroup analysis

Outcomes	Comparators			
	Phenytoin	Levetiracetam	Sodium valproate	Placebo
Seizure-free rate	1.01 (0.79–1.31)	0.98 (0.84–1.14)	1.27 (0.92–1.77)	4.67 (0.55–39.47)
$\geq 75\%$ reduction from baseline in seizure frequency	–	1.12 (0.69–1.81)	1.16 (0.85–1.58)	–
50%–75% reduction from baseline in seizure frequency	–	0.90 (0.61–1.34)	0.85 (0.59–1.22)	1.86 (1.27–2.74)
<50% reduction from baseline in seizure frequency	–	1.00 (0.65–1.56)	0.54 (0.30–0.96)	–

Table 4 Summary of the risk ratios with 95% confidence intervals of outcomes in the subgroup analysis based on study design and sample size

Outcomes	Study quality			Sample size	
	Low risk of bias	Unclear risk of bias	High risk of bias	≥ 100	< 100
Seizure-free rate	1.09 (0.84–1.41)	0.93 (0.80–1.09)	1.45 (1.06–1.99)	1.07 (0.91–1.26)	1.04 (0.86–1.26)
≥75% reduction from baseline in seizure frequency	–	1.12 (0.79–1.59)	1.18 (0.79–1.76)	1.22 (0.89–1.65)	1.01 (0.61–1.65)
50%–75% reduction from baseline in seizure frequency	1.86 (1.27–2.74)	0.96 (0.67–1.37)	0.77 (0.52–1.15)	1.05 (0.67–1.64)	0.97 (0.53–1.77)
<50% reduction from baseline in seizure frequency	–	1.09 (0.70–1.67)	0.42 (0.22–0.79)	0.82 (0.52–1.29)	0.74 (0.43–1.27)

treated with levetiracetam (RR = 1.12, 95% CI: 0.69, 1.81; $P=0.650$). Similarly, in comparison with sodium valproate, OXC also resulted in a comparable effect. The percentage of patients who had a $\geq 75\%$ reduction from baseline in seizure frequency in the OXC and sodium valproate groups was 34.5% and 29.8%, respectively. However, OXC showed a statistically significant improvement in reduction from baseline in seizure frequency as compared with placebo. In the trial of Glauser et al,²² 41% of patients in the OXC group developed a $>50\%$ reduction from baseline in partial seizure frequency per 28 days compared with 22% of patients in the placebo group.²² These results demonstrated that OXC did not have superior effects than sodium valproate or levetiracetam in the reduction of seizure frequency.

Regarding the safety profile, the incidence of adverse events was almost similar between the OXC and other

AED groups. The most common adverse events for OXC included nausea, vomiting, and rash, which would lead to discontinuation of therapy. Hyponatremia has been reported to be associated with OXC use.^{31–34} Children treated with OXC were less likely to develop hyponatremia than adults.³⁵ This finding was confirmed in the multicenter, randomized, placebo-controlled trial conducted by Glauser et al.²² In that trial, no hyponatremia was observed in the pediatric patients.²² According to the previous report, hyponatremia usually appears in the first 3 months of treatment;³⁴ thus the 4-month phase in the Glauser's study was long enough to assess the emergence of hyponatremia.

There have been several potential limitations in this meta-analysis that should be considered. 1) Our study included 11 RCTs, and some of the included studies had a

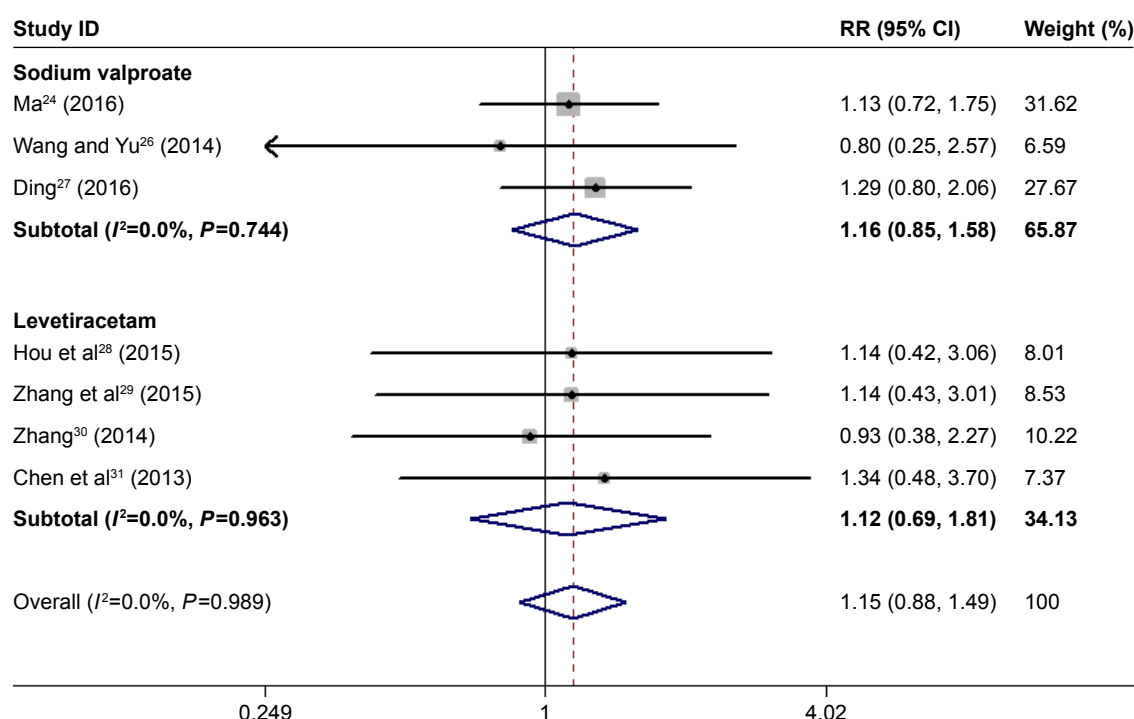


Figure 4 Forest plot showing the effects of OXC on $\geq 75\%$ reduction from baseline in seizure frequency. Abbreviations: CI, confidence interval; RR, risk ratio; OXC, oxcarbazepine.

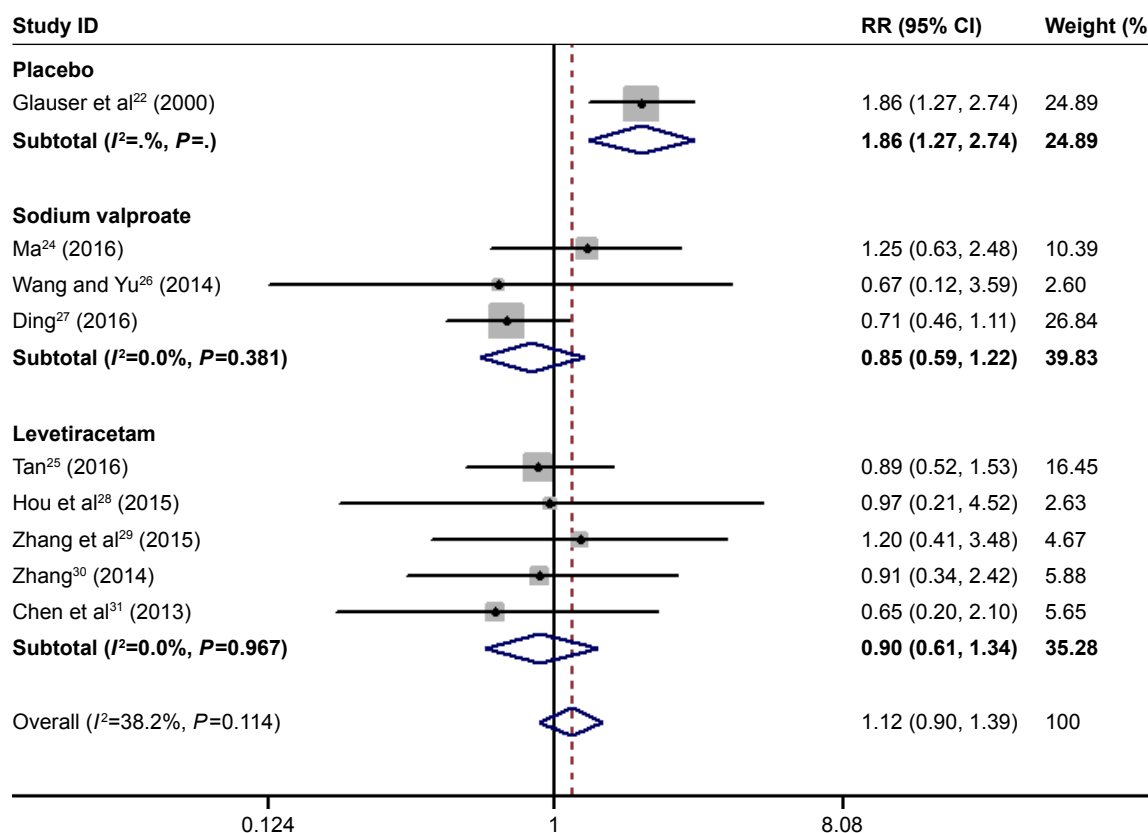


Figure 5 Forest plot showing the effects of OXC on 50%–75% reduction from baseline in seizure frequency.
Abbreviations: CI, confidence interval; RR, risk ratio; OXC, oxcarbazepine.

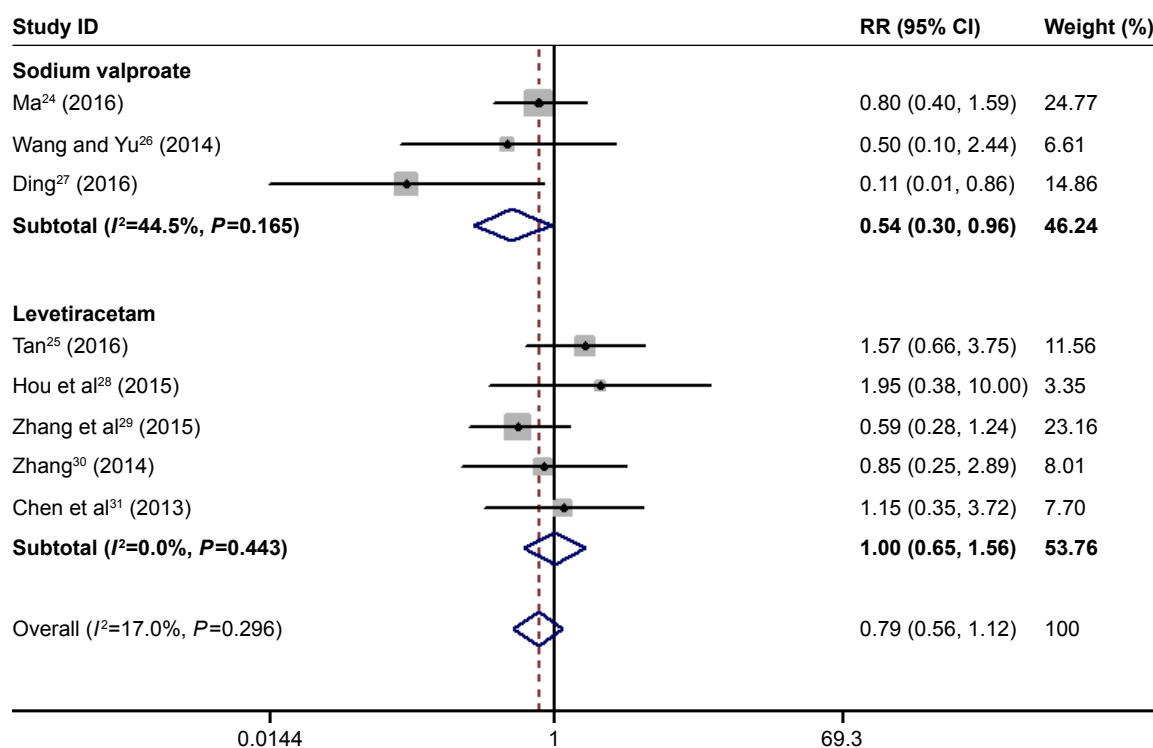


Figure 6 Forest plot showing the effects of OXC on <50% reduction from baseline in seizure frequency.
Abbreviations: CI, confidence interval; RR, risk ratio; OXC, oxcarbazepine.

relatively small sample size. Small trials are more likely to result in an overestimate of the treatment effects compared with larger trials. 2) There was substantial heterogeneity among the included studies. However, one should not be surprised when considering the differences in dosage of OXC, treatment schedule, treatment controls, the types of epilepsy, and study quality. These factors have a potential impact on the pooled estimates. 3) Due to the sparse reporting among the included studies, we did not assess the effects and safety of OXC in different types of epilepsy. Further large-scale RCTs are needed to investigate the effects of OXC in different types of epilepsy. 4) Most of the included studies were from Chinese publications. Although no potential publication bias was identified among the included studies, we could not exclude the possibility that our results were biased by these Chinese studies. Thus, physicians should be with caution when applying these findings into clinical practices.

Conclusion

In conclusion, this meta-analysis suggested that OXC had similar seizure-free rate and percentage reduction from baseline in seizure frequency as other AEDs in children with epilepsy. Moreover, OXC also induced a similar incidence of adverse events with other AEDs. However, considering the limitations of this meta-analysis, large-scale RCTs are needed to verify our findings and investigate the effects of OXC in children with different types of epilepsy.

Disclosure

The authors report no conflicts of interest in this work.

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