



Oxcarbazepine versus Carbamazepine for the Treatment of Post-Stroke Epilepsy: A Systematic Review and Meta-Analysis

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ABSTRACT

AIM: To systematically evaluate the medication safety and effectiveness of Oxcarbazepine (OXC) and carbamazepine (CBZ) for the treatment of post-stroke epilepsy (PSE).

MATERIAL and METHODS: We searched Medline and other databases to identify the randomized controlled trials (RCTs) that compare the efficacies of OXC and CBZ in treating PSE. Two authors extracted and analyzed the data independently with Revman 5.3 software. The Q-test and I² were used to test the statistical heterogeneity. The fixed or random effect models were selected according to heterogeneity.

RESULTS: Eight RCTs that include 671 patients were involved in this study. The meta-analyses result showed that the overall efficiency of OXC was significantly better than that of CBZ (OR=4.55, 95% confidence interval (CI) (3.04–6.81)), the overall adverse events (OR=0.27, 95% CI (0.18–0.42)), and the incidence of vomiting (OR=0.28, 95% CI (0.09–0.85)) of OXC was significantly less than that of CBZ. No significant differences in the incidence of rash (OR=0.45, 95% CI (0.19–1.07)), lethargy (OR=0.49, 95% CI (0.16–1.45)), and dizziness (OR=0.51, 95% CI (0.20–1.35)) were detected between OXC and CBZ.

CONCLUSION: OXC seems to be superior to CBZ in the treatment of PSE, with higher efficacy, and safety than the latter. However, more research on OXC and CBZ in the treatment of PSE is required in the later stage due to the sample size limitation of our study.

KEYWORDS: Oxcarbazepine, Carbamazepine, Post stroke epilepsy, Treatment, Review

INTRODUCTION

Stroke has become a public health issue of close concern worldwide due to its associated high mortality and disability rates (8). Post-stroke epilepsy (PSE) is one of the common post-stroke complications in elderly people, which has been reported to account for 30–50% of newly diagnosed epilepsy (5,42). Previous studies have reported that patients' gender, age, stroke type, location, and number of stroke-affected lobes are associated with PSE (1,20). PSE can reduce people's quality of life significantly and increase

the cost of health treatment (18). Therefore, active and standardized drug treatment for PSE is necessary.

The treatment of PSE must consider not only the type of epilepsy but also the elderly characteristics, drug interactions (31,27). Carbamazepine (CBZ) is a traditional antiepileptic drug that is widely used in clinical practice. It is effective for many types of epilepsy and is the first-line drug for partial epilepsy and partial secondary generalized epilepsy (28). Oxcarbazepine (OXC) is a chemical homolog of CBZ that has a better effect on adults and children with partial seizure

epilepsy (23,29). However, at present, there is no reliable evidence on the drugs at home and abroad for the medical treatment of PSE (13). The treatment effect of CBZ and OXC in PSE was previously reported by some randomized controlled trials (RCTs) (9,12,14), yet the results remain conflicting. To date, there are no meta-analysis reports to study the use of CBZ and OXC in the treatment of PSE. Therefore, we have attempted to conduct this study to assess the medication safety and effectiveness of OXC and CBZ for the treatment of PSE, thereby providing insights into clinical PSE treatment.

■ MATERIAL and METHODS

This present study was conducted and reported with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (25).

Search Strategy

Foreign databases, including Medline, Cochrane Central Register of Controlled Trials, EMBASE, and Science Direct, and domestic databases, including the China Wanfang database and China National Knowledge Infrastructure, were searched from inception to February 15, 2020. The search terms were as follows: (oxcarbazepine) AND (carbamazepine) AND (post-stroke epilepsy or PSE or cerebral infarction or cerebral hemorrhage or cerebrovascular disease or epilepsy). No language limitations were used during the literature search in our study.

Study Inclusion

Two authors independently searched the related literature and selected the RCTs. Two reviewers were involved in this study. The discrepancies between them were resolved by extra discussions with a third reviewer. The studies that met the following criteria were included for data synthesis: 1) RCT design; 2) comparisons were made between oxcarbazepine versus carbamazepine; 3) the PSE diagnosis met the required diagnosis guidelines; 4) related outcomes were reported. The studies that only reported pharmacokinetic-related results or that had data that cannot be extracted were excluded. Duplicate publications were also excluded.

Data Extraction

Two authors extracted the related data of the included RCTs independently. Again, any discrepancies between reviewers were addressed by further discussions with a third reviewer. The following detailed pieces of information were extracted: study setting, sample size, patients' characteristics, the dosing regimen of CBZ and OXC, clinical outcomes, and study conclusions.

The Assessment of the Quality of Included RCTs

Two reviewers rigorously assessed the quality of RCTs independently. A comprehensive analysis of the results of the two reviewers will be carried out in the later stages. When there were conflicting results between the two reviewers, other reviewers were invited to evaluate again. Cochrane Collaboration's tool of bias risk (16) was used to evaluate potential risk and the methodological quality of bias in the

selected RCTs. Seven specific domains were involved in this tool: assignment hiding, selective result reporting, incomplete result data, blindness of outcome evaluation, sequence generation, blindness of participants and personnel, and other issues. According to the eventual judgment criteria, each separate domain is categorized as a different risk of bias (unclear, high, and low).

Statistical Analysis

Review Manager 5.3 was used as a statistical analysis tool for data processing. The odds ratio (OR) was also referred to as the dominance ratio. The 95% CI of the OR was calculated to assess the combined effect of the RCTs we included in this study. A random-effects or fixed-effect model was used to calculate the RCT-specific ORs according to the level of synthesized heterogeneity. The heterogeneity of statistics was evaluated with the Q-test and I² values. Different levels of I² represent the heterogeneity of different data; that is, 25% (lowly), 50% (moderately), and 75% (highly). In the case of I² < 50%, a fixed-effect model was conducted; in the case of the contrary, a random effect model was chosen. Subgroup analysis, which was based on intervention differences, was applied to ascertain the potential origin of the heterogeneity. Evaluating the influence of different included RCTs and neglecting one study at one time could be used as sensitivity analysis. For our present meta-analysis, all examined tests were two-sided, and p < 0.05 was considered statistically significant.

■ RESULTS

Study Selection

The selection process of articles is presented in Figure 1. Initially, our search results were derived from 89 potentially relevant articles. We first carried out duplicating exclusion, then evaluated and reviewed the titles and abstracts of the remaining 66 articles, and finally retrieved the full texts of 25 studies. Eventually, eight RCTs (9,12,14,22,34,36,39,41) were adopted in this study after careful selection according to the inclusion and exclusion criteria.

Characteristics of the Included RCTs

Eight RCTs involving 671 patients were included, with 334 and 337 patients who received OXC and CBZ, respectively. The characteristics of the included RCTs are presented in Table I. The 8 included RCTs were all carried out in China, with sample sizes that ranged from 56 to 112 patients. Also, the posologies of OXC and CBZ remained the same, with 150 mg/kg tid for OXC and 200 mg/kg bid for CBZ. The treatment duration varied from 3 months to 12 months.

Literature Quality Evaluation

The quality of the RCTs we included in this systematic review is presented in Figures 2 and 3. Although the methods used for random number generation and randomization are mentioned in every study, there is one RCT (14) in which the specific method of randomization was not stated, and there might have been pseudo-randomness. None of the eight

RCTs clearly reported the concealment and distribution or whether blinding was performed. Of the 8 included studies, five members of the control group dropped out in one RCT (14). Although the reason for their withdrawal was reported, no intention-to-treat analysis was performed, and the remaining

RCTs did not report any participants who dropped out or were lost to follow-up. Except for one study (14), the remaining 7 reported in detail the number and types of specific adverse reactions. No other significant deviations were detected in our study.

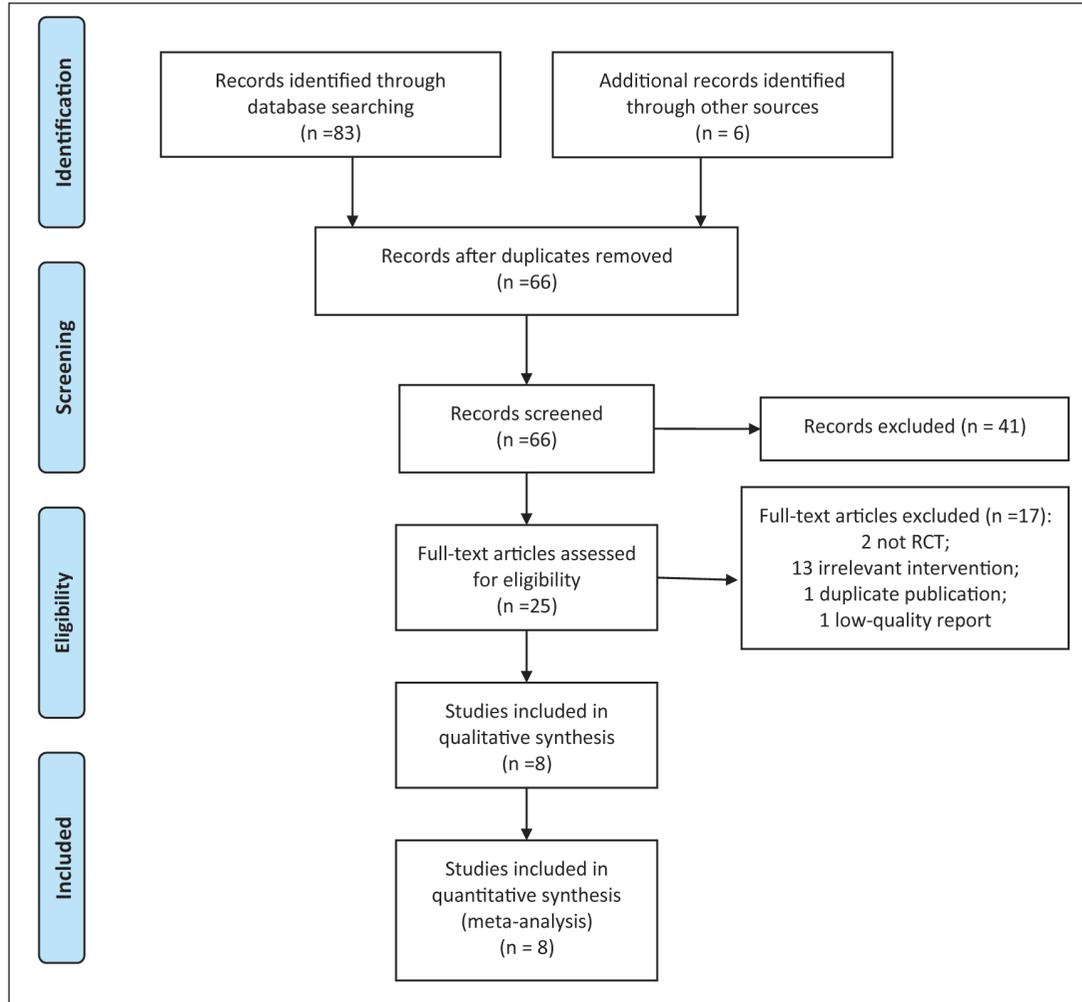


Figure 1: The flow chart of study selection.

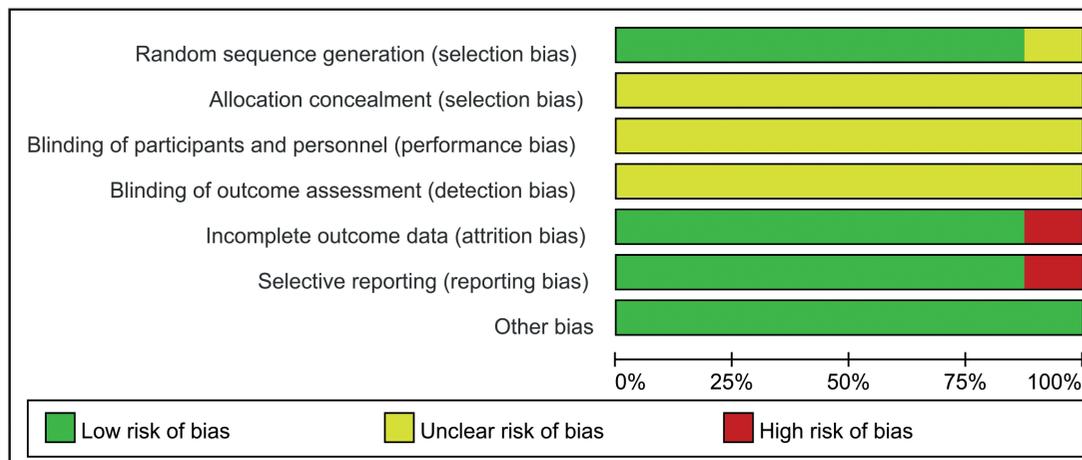


Figure 2: Risk of bias.

	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
Ding 2016	+	?	?	?	+	+	+
Feng 2019	+	?	?	?	+	+	+
Hou 2010	?	?	?	?	-	-	+
Ma 2015	+	?	?	?	+	+	+
Wang 2014	+	?	?	?	+	+	+
Wei 2016	+	?	?	?	+	+	+
Yang 2017	+	?	?	?	+	+	+
Zhang 2018	+	?	?	?	+	+	+

Figure 3: Risk of bias summary.

Table I: The Characteristics of included Randomized Controlled Trials

Studies	Sample size		Quit / lost	Gender (male/female)		Age(y)		Dose (mg/kg)		Course of treatment (mon)
	OXC	CBZ		OXC	CBZ	OXC	CBZ	OXC	CBZ	
Ding, 2016 (9)	28	28	0	15/13	16/12	58.3 ± 5.2	60.2 ± 7.3	150, tid	200, bid	3
Feng and Ma, 2019 (12)	34	34	0	20/14	17/17	58.9 ± 9.7	59.5 ± 9.5	150, tid	200, bid	3
Hou, 2010 (14)	40	40	5	N/A	N/A	N/A	N/A	150, tid	200, bid	3
Ma, 2015 (22)	56	56	0	40/16	38/18	58.9 ± 13.8	58.8 ± 13.7	150, tid	200, bid	6
Wang et al., 2014 (34)	52	52	0	38/14	40/12	62.8 ± 8.1	61.1 ± 6.2	150, tid	200, bid	3
Wei et al., 2016 (36)	41	44	0	24/17	26/18	56.2 ± 11.6	54.7 ± 12.3	150, tid	200, bid	12
Yang, 2017 (39)	40	40	0	25/15	26/14	62.23 ± 1.32	62.35 ± 1.67	150, tid	200, bid	6
Zhang et al., 2018 (41)	43	43	0	20/23	24/19	43.8 ± 6.1	44.6 ± 5.8	150, tid	200, bid	6

Notes: N/A: not available.

Overall Efficiency

All the included RCTs (9,12,14,22,34,36,39,41) reported the overall efficiency. No significant heterogeneity was found among the involved RCTs, and a fixed model was used. The final result of the analysis displayed that the overall efficiency of OXC was significantly better than that of CBZ (OR = 4.55, 95% CI (3.04–6.81), Figure 4A).

Overall Rate of Adverse Events

All the included RCTs (9,12,14,22,34,36,39,41) reported adverse events. No significant heterogeneity was found among the involved RCTs, and a fixed model was used. The final result of the analysis displayed that the overall rate of occurrence of adverse events of OXC was significantly less than that of CBZ (OR = 0.27, 95% CI (0.18–0.42), Figure 4B).

Rash

Seven RCTs (9,12,22,34,36,39,41) reported the occurrence of a rash. No significant heterogeneity was found in each of the participating RCTs, and a fixed model was used. According to the final results of the analysis, there was no significant difference in the rate of occurrence of rashes between OXC and CBZ (OR = 0.45, 95% CI (0.19–1.07), Figure 4C).

Lethargy

Five RCTs (9,22,34,39,41) reported the occurrence of lethargy. No significant heterogeneity was found in each participating RCT, and a fixed model was used. According to the final results of the analysis, there was no significant difference in the rate of occurrence of lethargy between OXC and CBZ (OR = 0.49, 95% CI (0.16–1.45), Figure 4D).

Dizziness

Seven RCTs (9,12,22,34,36,39,41) reported the occurrence of dizziness. No significant heterogeneity was found in each participating RCT, and a fixed model was used. According to the final results of the analysis, there was no significant difference in the rate of occurrence of dizziness between OXC and CBZ (OR = 0.51, 95% CI (0.20–1.35), Figure 4E).

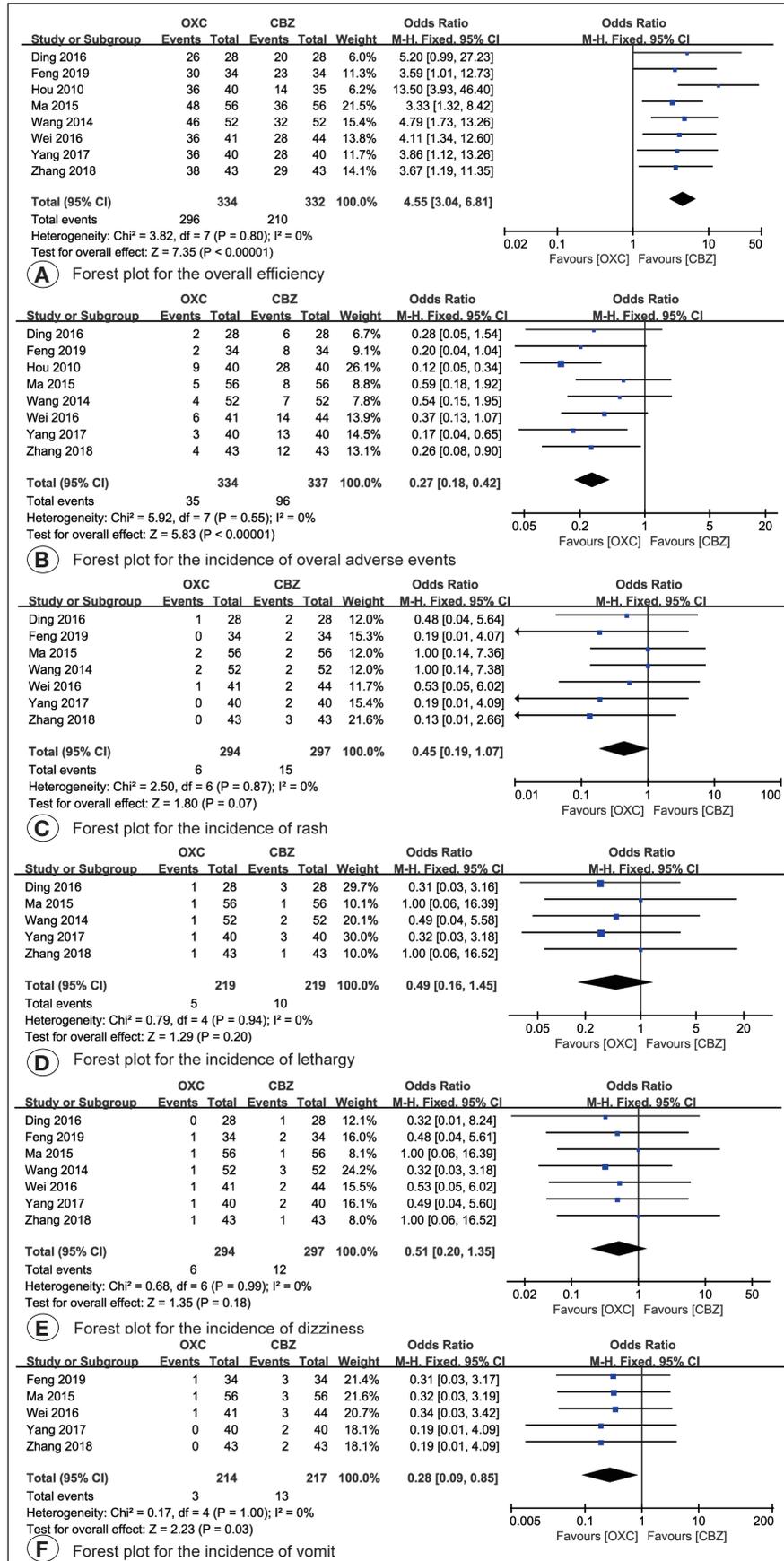


Figure 4: The forest plots for synthesized outcomes.

Vomiting

Five RCTs (9,12,22,39,41) reported the occurrence of vomiting. No significant heterogeneity was found in each participating RCT, and a fixed model was used. According to the final results of the analysis, there was no significant difference in the rate of occurrence of vomiting between OXC and CBZ (OR = 0.28, 95% CI (0.09–0.85), Figure 4F).

Sensitivity Analysis

The sensitivity analysis was performed by excluding individual RCTs one by one. The sensitivity analysis outcomes of all the results show that there was no significant change in the overall estimation results.

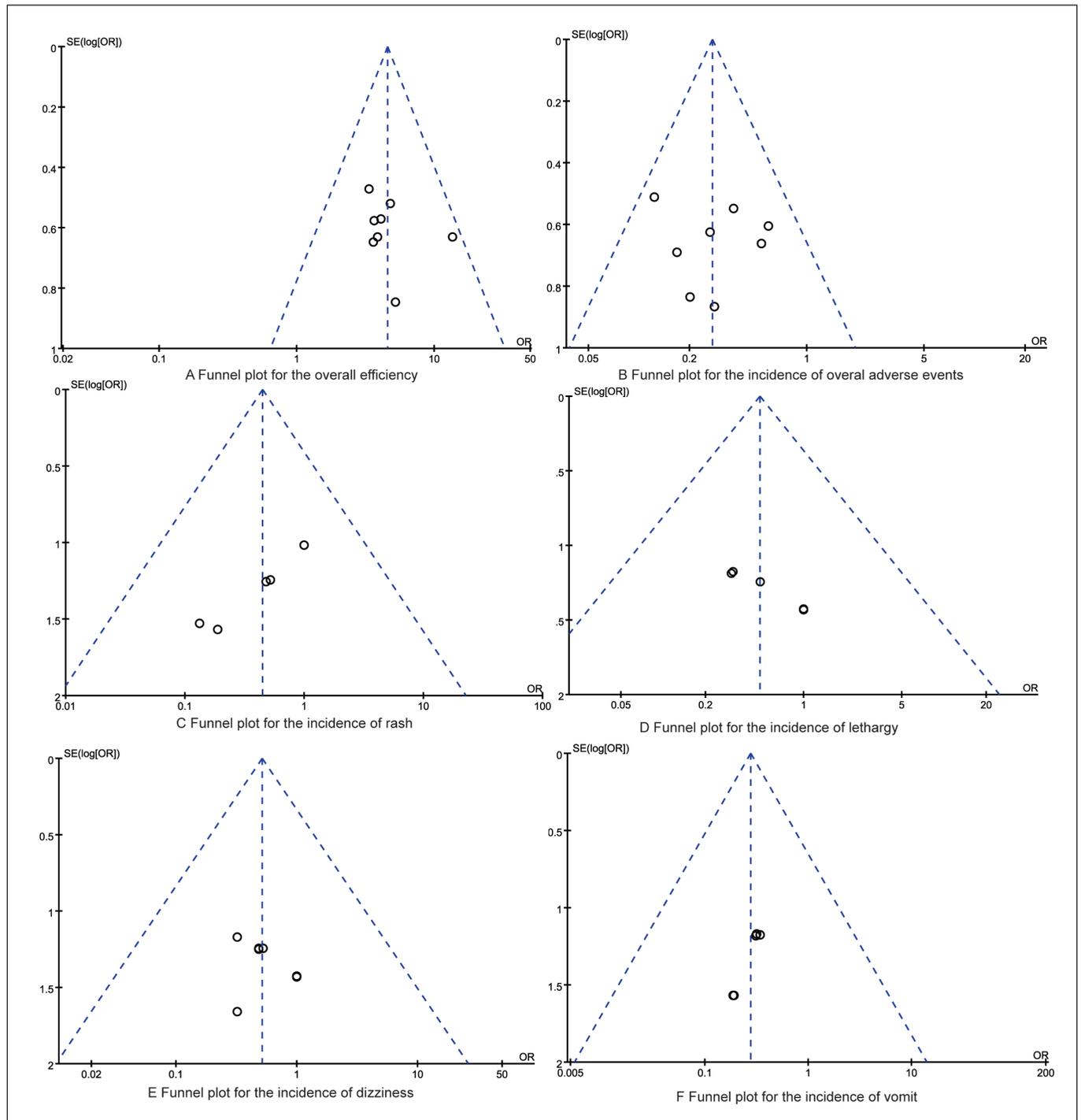


Figure 5: The funnel plots for synthesized outcomes.

Publication Bias

We used a funnel chart to judge publication bias (Figure 5), using the symmetry of the funnel chart to determine whether there was publication bias. A symmetrical funnel chart indicates that there is no publication bias, while an asymmetrical one indicates the presence of publication bias. The funnel diagram in this study remained symmetrical.

DISCUSSION

PSE is a common type of epilepsy in middle-aged and elderly patients (2,32). The treatment of PSE should consider not only the type of seizure but also the physiological and pathological characteristics, medication, and other factors of the elderly (30,38). PSE is mostly partial, and PSE patients often have several basic diseases such as hypertension, diabetes, or coronary heart disease (10). They may need to take antihypertensive drugs, anticoagulants, antiplatelet drugs, and other drugs to treat cardiovascular or cerebrovascular diseases coupled with reduced physiological function and reduced tolerance to drugs in elderly patients (26,37). Therefore, antiepileptic drugs should be selected to better control epilepsy while having fewer interactions with other drugs and better tolerance. The outcomes of our present study have demonstrated that OXC is superior to CBZ in the treatment of PSE, with consideration that OXC has better overall efficiency and fewer overall adverse events such as vomiting when compared with CBZ treatment. OXC may be a preferred drug option for the treatment of PSE.

It has been reported that CBZ has a good effect on controlling partial seizures (21). Most of the CBZ taken in is metabolized by the liver drug enzyme CYP3A4, which can induce liver drug enzymes to accelerate their own metabolism (15), and it can also speed up the metabolism of some oral anticoagulants (such as warfarin), antiepileptic drugs (such as Sodium valproate, phenytoin), oral contraceptives, and other drugs (4). Certain liver drug enzyme inhibitors (such as sodium valproate) can inhibit the metabolism of CBZ (24). Therefore, drug interactions and concentration-related adverse reactions could easily occur when taking CBZ (19). OXC is an analog of CBZ that has a good effect on partial seizures in adults. Most of them are metabolized and reduced to a monohydroxy active metabolite 10, 11-dihydro-10-hydroxy (MHD) carbamazepine in the liver (4). MHD is the chief active substance of OXC's antiepileptic effect, and most of it is metabolized and converted to O-gluconic acid form by UDP-glucuronosyltransferases (UGTs), and a small part is converted to the inactive state; therefore, it does not interact with drugs metabolized by cytochrome P450 enzymes (such as anticoagulants, etc.) (17,40). Previous studies (11,33,35) have shown that traditional antiepileptic drugs (AEDs) such as phenytoin, CBZ, and phenobarbital can affect neurological recovery and bone health and may interact with anticoagulants and antiplatelet drugs, with the related tolerance being reported to be bad. Therefore, traditional AEDs are not the preferred option for stroke patients.

The meta-analysis of this study has demonstrated that the overall effectiveness of OXC for epilepsy control in

patients with PSE was significantly higher than that of CBZ. Furthermore, the heterogeneity of the synthesized results is extremely low; thus, the results are stable and reliable. The analysis of the incidence of adverse reactions demonstrated that the overall incidence of adverse reactions in the OXC group was significantly lower than that in the CBZ group. However, the analysis of various types of adverse reactions found that there no significant differences were found in the incidence of rash, dizziness, and drowsiness between the two groups, which might be owing to the limited number of RCTs involved in our present study. Based on the above results, the effectiveness and safety of OXC for PSE are better than those of CBZ; however, considering that the number and sample sizes of the included RCTs were small, future analyses of more high-quality clinical studies with larger samples are needed to further elucidate the effect of OXC and CBZ in the treatment of PSE.

Our meta-analysis has certain limitations. First, the RCTs chosen for data synthesis are of low quality and were few. Second, the included RCTs are all from China, so it is impossible to determine whether regional and ethnic differences will affect the results. Third, stroke can be divided into ischemic stroke (cerebral infarction) and hemorrhagic stroke (intracerebral hemorrhage and subarachnoid space hemorrhage), and epilepsy can be divided into early and late-onset (6,7). The different types of stroke and epilepsy have affected the efficacy of the drug and the rate of occurrence of adverse reactions. Due to the limited data in this study, no further subgroup analyses could be performed to identify the potential influences.

CONCLUSION

In conclusion, for patients with PSE, OXC is significantly more efficient and has fewer adverse reactions than CBZ. OXC might be a better option for PSE treatment. More high-quality RCTs with larger samples and rigorous study procedures are needed in the future to provide more reliable evidence to support our findings.

AUTHORSHIP CONTRIBUTION

Study conception and design: Ying-Ju Zhang, Dong-Jun Wan

Data collection: XML

Analysis and interpretation of results: XML

Draft manuscript preparation: PWL

Critical revision of the article: CAG

Other (study supervision, fundings, materials, etc...): CAG

All authors (YJZ, XML, PWL, CAG, DJW) reviewed the results and approved the final version of the manuscript.

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