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Original Article

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A meta-analysis: efficacy and safety of anti-epileptic drugs prescribed in Korea as monotherapy and adjunctive treatment for patients with focal epilepsy

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ABSTRACT

Focal epilepsy is the most common type of epilepsy in Korea, and anti-epileptic drugs (AEDs) are the main treatment option for patients. This study aimed to compare the efficacy and safety of AEDs for focal epilepsy through a meta-analysis. The AEDs prescribed in Korea as monotherapy and adjunctive treatment for patients with focal epilepsy were included for analysis. Relevant articles were searched for randomized clinical trials of AEDs and treatment outcomes were analyzed on the basis of the 50% responder rate, seizure-free rate, treatment withdrawal rate, and emergence rates of adverse events (AEs). The odds ratios (ORs) and their 95% confidence intervals (CI) of study outcome were calculated using combined data from multiple studies. A total of 47 studies were included in the meta-analysis. The seizure-free rate, treatment withdrawal rate, and AE rate were not significantly different among the AEDs recommended for monotherapy. Among the AEDs recommended for adjunctive treatment, topiramate and oxcarbazepine yielded the highest OR in comparison with placebo for each efficacy parameter: the 50% responder rate for topiramate = 6.42 (3.76–11.6) and the seizure-free rate for oxcarbazepine = 32.7 (6.05–899). The third-generation AEDs (brivaracetam and perampanel) yielded relatively better safety outcomes than other AEDs. In general, the 50% responder rate and treatment withdrawal rate tended to increase as the dose of the AEDs increased. The results from the current meta-analysis of the efficacy and safety data of various AEDs may provide insight into optimal pharmacotherapy for the treatment of focal epilepsy.

Keywords: Epilepsy; Meta-analysis; Anti-epileptic Drugs; Monotherapy; Adjunctive Treatment

INTRODUCTION

Epilepsy is the fourth most common neurologic disease in the world [1]. It affects around 50 million individuals worldwide and has an annual incidence of approximately 80 cases per 100,000 individuals [2]. Epilepsy makes patients' daily life uncomfortable, and research has also shown that it increases the risk of developing psychiatric disorders [2]. According to the operational classification of the epilepsy type by the International League Against Epilepsy,

it is classified as focal, generalized, combined, and unknown based on the occurring seizure type [3]. Among the epilepsy types, focal epilepsy accounted for the highest proportion (78.1%); conversely, only 8.0% of patients had been diagnosed with generalized epilepsy, according to an epidemiological study using a nationwide database for Korean patients with epilepsy [4]. Focal epilepsy occurs within networks limited to 1 hemisphere alone, so that when it is well-controlled, patients are expected to lead a normal life and experience an increased quality of life [3].

The treatment options for focal epilepsy are anti-epileptic drugs (AED) administration or surgical intervention [5,6]. Among these options, epilepsy surgery is not preferred in many cases owing to the limited indications and high refusal rate by patients [7,8]. For these reasons, medical treatment with AEDs to suppress seizure occurrence is the common treatment method for patients with focal epilepsy, and approximately two-thirds of the seizures are controlled by these drugs [2,5]. The type of AED to be administered is determined with consideration of its efficacy and safety as well as several other factors, such as electroencephalography findings, medical history, sex, and concomitant medication [5]. However, only a few studies have directly compared the efficacy and safety of various AEDs, which can be useful for the selection of appropriate drugs for patients.

A meta-analysis of published trials can increase the statistical power compared to a single study [9]. Although the safety and efficacy of individual AEDs were identified in clinical trials, the study results are sometimes not consistently reproducible owing to the relatively small sample size [9]. Although there are several medical treatment guidelines for epilepsy, there is limited consensus on the recommended AEDs for the treatment of focal epilepsy (**Supplementary Table 1**) [5,10-12]. Therefore, the findings of a meta-analysis that can comprehensively compare the efficacy and safety of AEDs can be useful for healthcare professionals to optimize patient care according to the best available evidence.

Based on these findings, this study aimed to compare the efficacy and safety of AEDs that are used as monotherapy and adjunctive treatment for focal epilepsy by performing a meta-analysis of existing clinical trials.

METHODS

Literature search

The AEDs prescribed in Korea as monotherapy and adjunctive treatment for patients with focal epilepsy were included for analysis (**Supplementary Table 1**) [5].

To find potentially relevant articles, PubMed, EMBASE, and the Cochrane Library were used. The function “Advanced Search” was utilized with Medical Subject Heading terms. Various drugs (“carbamazepine” or “lamotrigine” or “levetiracetam” or “oxcarbazepine” or “valproate”) and disease term (“epilepsy”) and comparator drug (“monotherapy” or “placebo”) were used to search for monotherapy study results. And various drugs (“brivaracetam” or “carbamazepine” or “clobazam” or “gabapentin” or “lacosamide” or “lamotrigine” or “levetiracetam” or “oxcarbazepine” or “perampanel" or “phenobarbital” or “phenytoin” or “pregabalin” or “rufinamide” or “topiramate” or “valproate” or “vigabatrin” or “zonisamide”) and disease term (“epilepsy”) and comparator drug (“placebo”) were used to search for adjunctive treatment study results. The database search was performed in October

2019 and March 2020. The title and abstract of all retrieved records were thoroughly screened to identify eligible studies. If there was insufficient information to make a clear judgment by reading an abstract only, the full text was reviewed at the next step. Specific eligibility criteria were applied to select the final suitable articles for the analysis.

Eligibility criteria

The inclusion criteria for selecting the eligible studies were as follows: 1) studies using AEDs prescribed in Korea as monotherapy or adjunctive treatment for patients with focal epilepsy; 2) randomized controlled trials with a comparator including placebo; 3) studies with an efficacy endpoint, i.e., seizure-free rate, defined as the proportion of participants who were free from seizure, or 50% responder rate, defined as the proportion of participants with 50% or greater reduction in seizure frequency in the treatment period, compared to that in baseline; 4) studies published in English only; 5) studies on AEDs prescribed in Korea as monotherapy or adjunctive treatment for patients with focal epilepsy. As the number of monotherapy articles for focal epilepsy is limited, the result was included if the number of patients with focal epilepsy was more than half of the total number of subjects when the study subjects included had both focal and generalized epilepsies. 6) journals published after 1990.

Conversely, the exclusion criteria were as follows: 1) studies conducted only for children (younger than 12 years); 2) non-published articles (e.g., conference proceedings and ongoing clinical trials that can be searched at ClinicalTrials.gov only; 3) *in vitro* or animal studies; 4) studies incorporating a surgical intervention or using other therapies that may affect seizure frequency; and 5) cross-over studies.

According to the abovementioned selection criteria, the title, abstract, and full text were carefully reviewed, and only eligible articles were analyzed in this study. Duplicate studies or overlapping cases were removed prior to data extraction. No restriction was imposed on the mode of treatment, such as the dose, route, and duration of administration.

Data extraction

Relevant data were extracted from the eligible studies [13-59], and statistical and non-statistical data were retrieved. The following information was considered the non-statistical data: 1) study identification (authors' name and year of publication) and 2) intervention information (drug names and duration). The following relevant information on efficacy was considered the statistical data and used as efficacy endpoints; 3) responder rate: the proportion of the number of patients with ≥ 50% reduction in seizure frequency compared with the baseline per arm; 4) seizure-free rate: the proportion of the number of patients free from seizure per arm for designated period according to each study design. The following safety relevant statistical or non-statistical data was extracted and used as safety endpoints; 5) withdrawal rate: the proportion of the number of patients who discontinued the treatment owing to adverse events (AEs); 6) AE rate: the proportion of the number of patients experiencing at least one AE per arm regardless of relevance with AEDs; and 7) common AE: AEs reported in more than 10% of subjects in total in each AED group.

For studies that reported their results as the proportion of responders only, the ratio was converted into the number of patients through calculation. When a graph or table was available to reveal the efficacy results solely, values were taken from them directly. When such data were not provided even in the table or figure, narrative information was closely reviewed

to extract the necessary data. If multiple publications were searched for the same trial, data were extracted from a single article among them.

To perform a sub-analysis for the 50% responder rate and treatment withdrawal rate owing to AEs, we separately obtained the number of responders and non-responders at each dose level when there were multiple dose levels in the same treatment arm. To calculate the odds ratios (ORs), we evenly divided the total number of patients and responders in the placebo arm against the respective dose of the treatment arm. The number of patients and the number of responders were combined according to the dose strength among the different studies to assess the total effect size at each dose level. Studies that did not reveal the efficacy by dose were excluded from the sub-analysis.

Quality assessment

The Preferred Reporting Items for Systematic Reviews and Meta-analyses were implemented in this meta-analysis [60]. The methodological quality of this study was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool, which was developed to evaluate systematic reviews of randomized trials [61,62]. The risk of bias was evaluated to ensure the quality of the selected articles.

Statistical analysis

The study used Bayesian network meta-analysis for monotherapy and indirect comparisons for adjunctive treatment to assess the efficacy and safety of each AED. For monotherapy, carbamazepine was set as a comparator drug, as it was one of the commonly prescribed first-line drugs for focal epilepsy [63]. Owing to the different scales across the studies, the ORs and their 95% confidence intervals (CI) of efficacy and safety outcome were calculated using combined data from multiple studies, based on the fixed effect model or random effect model to the standardized effect size. The 95% CI was used to gauge the clinical benefit of the treatment compared with the control. R software (Version 3.6.1) was applied, and the R commands for statistical analysis are described in **Supplementary Fig. 1**. Statistical heterogeneity was tested using the magnitude of heterogeneity quantified by calculating a point estimate of the among-study variance of true effects (τ^2) and the percentage of total variation across studies owing to heterogeneity rather than sampling error (I^2) [64]. The fixed effect model was used when heterogeneity was negative ($p \geq 0.05$) and the random effect model in the opposite case ($p < 0.05$). A publication bias test is required when more than 10 studies are involved for analysis in each treatment group; thus, the test was not applicable in this study [65].

Ethics statement

As this meta-analysis was based on existing studies, Institutional Review Board approval was not necessary.

RESULTS

Search results

A total of 1,929 relevant records were searched from the 3 databases, and 1,164 articles were identified after excluding duplicate studies. After exclusion of ineligible publications, a total of 47 studies (10 direct comparison articles for monotherapy and 37 articles for placebo control as an adjunctive treatment) were included for data analysis (**Fig. 1**). With regard to

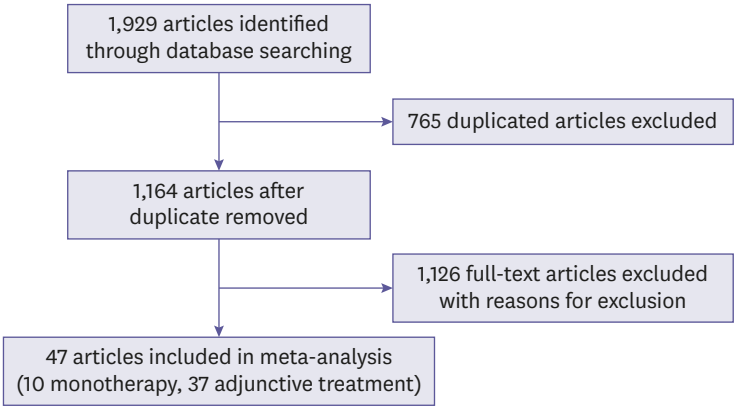

Figure 1. Flow chart showing the search strategy used in the selection of publications for this meta-analysis.

the adjunctive treatment study of clobazam, phenobarbital, and phenytoin, there were no adequate articles that satisfied the eligibility criteria; thus, they were not included in this meta-analysis. The detailed characteristics of the included studies are shown in **Table 1**.

Efficacy endpoint

Responder rate

In monotherapy, all 10 selected articles did not report the responder rate as the efficacy endpoint.

In adjunctive treatment, the 50% responder rate was significantly higher in all AED groups than in the placebo group, except for levetiracetam (**Fig. 2**). Topiramate yielded the highest responder rate among the adjunctive treatment (OR, 6.42 [95% CI, 3.76-11.6]). The responder rate for topiramate was based on 5 trials and statistically significant highest OR. The ORs for oxcarbazepine, pregabalin, zonisamide, vigabatrin, gabapentin, perampanel, brivaracetam, and rufinamide were more than 2; the results were pooled from at least 3 trials, except for oxcarbazepine, vigabatrin, and lamotrigine, which were calculated from only 1, 1, and 2 trials, respectively.

Seizure-free rate

In monotherapy, of 10 monotherapy studies, 8 studies and 7 studies assessed 6- and 12-month seizure-free events, respectively. Seizure-free rates were not statistically different (**Fig. 3**).

In adjunctive treatment, the seizure-free rates were higher for the AEDs, except for topiramate, than for the placebo (**Fig. 2**). No seizure-free rate was reported for topiramate in both arms; however, this was obtained from only 1 study performed in a small number of patients (30 patients in each treatment arm), so it was not visualized in **Fig. 2**. The OR was insignificantly higher for lacosamide, rufinamide, and zonisamide than for placebo. The highest seizure-free rate was observed for oxcarbazepine (OR, 32.7; 95% CI, 6.05–899).

Safety endpoints

Withdrawal rate

In monotherapy, the withdrawal rate owing to AEs compared to carbamazepine was not also statistically significant (**Fig. 3**).

In adjunctive treatment, the treatment withdrawal rate owing to AEs was generally higher for the AEDs (OR is greater than 1) than for the placebo, but was not significant for vigabatrin

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Table 1. Characteristics of the included studies (non-statistical data)

No.	Study	Year of publication	Monotherapy or adjunctive treatment	Comparative treatment	Study duration (weeks)	No. of subjects
1	Brodie et al. [13]	2007	Monotherapy	Levetiracetam, carbamazepine	29	472
2	Kim et al. [14]	2017	Monotherapy	Levetiracetam, oxcarbazepine	50	246
3	Brodie et al. [15]	1995	Monotherapy	Lamotrigine, carbamazepine	6	146
4	Trinka et al. [16]	2013	Monotherapy	Levetiracetam, carbamazepine	52	858
5	Heller et al. [17]	1995	Monotherapy	Carbamazepine, valproate	-	122
6	Rosenow et al. [18]	2012	Monotherapy	Lamotrigine, levetiracetam	26	409
7	Stephen et al. [19]	2007	Monotherapy	Valproate, lamotrigine	-	225
8	Werhahn et al. [20]	2015	Monotherapy	Carbamazepine, lamotrigine, levetiracetam	58	360
9	Steinhoff et al. [21]	2005	Monotherapy	Carbamazepine, lamotrigine	24	176
10	Privitera et al. [22]	2003	Monotherapy	Topiramate, carbamazepine, valproate	24	613
11	Sivenius et al. [23]	1991	Adjunctive treatment	Gabapentin, placebo	12	43
12	Yamauchi et al. [24]	2006	Adjunctive treatment	Gabapentin, placebo	12	209
13	The US Gabapentin Study Group No. 5 [25]	1993	Adjunctive treatment	Gabapentin, placebo	12	288
14	Naritoku et al. [26]	2007	Adjunctive treatment	Lamotrigine, placebo	19	243
15	Baulac et al. [27]	2010	Adjunctive treatment	Lamotrigine, pregabalin, placebo	17	434
16	Peltola et al. [28]	2009	Adjunctive treatment	Levetiracetam, placebo	12	158
17	Barcs et al. [29]	2000	Adjunctive treatment	Oxcarbazepine, placebo	28	692
18	Privitera et al. [30]	1996	Adjunctive treatment	Topiramate, placebo	18	190
19	Sharief et al. [31]	1996	Adjunctive treatment	Topiramate, placebo	11	47
20	Faught et al. [32]	1996	Adjunctive treatment	Topiramate, placebo	16	181
21	Ben-Menachem et al. [33]	1996	Adjunctive treatment	Topiramate, placebo	13	56
22	Tassinari et al. [34]	1996	Adjunctive treatment	Topiramate, placebo	12	60
23	Ben-Menachem et al. [35]	2007	Adjunctive treatment	Lacosamide, placebo	18	415
24	Halász et al. [36]	2009	Adjunctive treatment	Lacosamide, placebo	16	477
25	French et al. [37]	2014	Adjunctive treatment	Pregabalin, placebo	14	323
26	Elgar et al. [38]	2005	Adjunctive treatment	Pregabalin, placebo	12	341
27	Beydoun et al. [39]	2005	Adjunctive treatment	Pregabalin, placebo	12	312
28	French et al. [40]	2003	Adjunctive treatment	Pregabalin, placebo	12	453
29	Arroyo et al. [41]	2004	Adjunctive treatment	Pregabalin, placebo	12	287
30	Bruni et al. [42]	2000	Adjunctive treatment	Vigabatrin, placebo	36	111
31	Lu et al. [43]	2011	Adjunctive treatment	Zonisamide, placebo	16	104
32	Schmidt et al. [44]	1993	Adjunctive treatment	Zonisamide, placebo	12	139
33	Brodie et al. [45]	2005	Adjunctive treatment	Zonisamide, placebo	24	351
34	Sackellares et al. [46]	2004	Adjunctive treatment	Zonisamide, placebo	12	152
35	Kwan et al. [47]	2014	Adjunctive treatment	Zonisamide, placebo	16	480
36	Ryvlin et al. [48]	2014	Adjunctive treatment	Brivaracetam, placebo	12	399
37	Biton et al. [49]	2014	Adjunctive treatment	Brivaracetam, placebo	12	400
38	Paesschen et al. [50]	2013	Adjunctive treatment	Brivaracetam, placebo	10	157
39	Klein et al. [51]	2015	Adjunctive treatment	Brivaracetam, placebo	12	768
40	Elger et al. [52]	2010	Adjunctive treatment	Rufinamide, placebo	12	647
41	Pålhagen et al. [53]	2001	Adjunctive treatment	Rufinamide, placebo	4	42
42	Biton et al. [54]	2011	Adjunctive treatment	Rufinamide, placebo	16	357
43	Brodie et al. [55]	2009	Adjunctive treatment	Rufinamide, placebo	13	313
44	Krauss et al. [56]	2012	Adjunctive treatment	Perampanel, placebo	12 or 16	201
45	French et al. [57]	2012	Adjunctive treatment	Perampanel, placebo	19	388
46	Nishida et al. [58]	2018	Adjunctive treatment	Perampanel, placebo	19	710
47	Krauss et al. [59]	2012	Adjunctive treatment	Perampanel, placebo	13	706

and levetiracetam (**Fig. 2**). The treatment withdrawal rate owing to AEs for the third-generation AEDs was low, except for rufinamide (OR, 3.42; 95% CI, 1.96–6.08). At least 1 trial from each AED group reported a treatment withdrawal rate owing to AEs.

Total AEs

In monotherapy, emergence rate of AEs was not statistically significant (**Fig. 3**).

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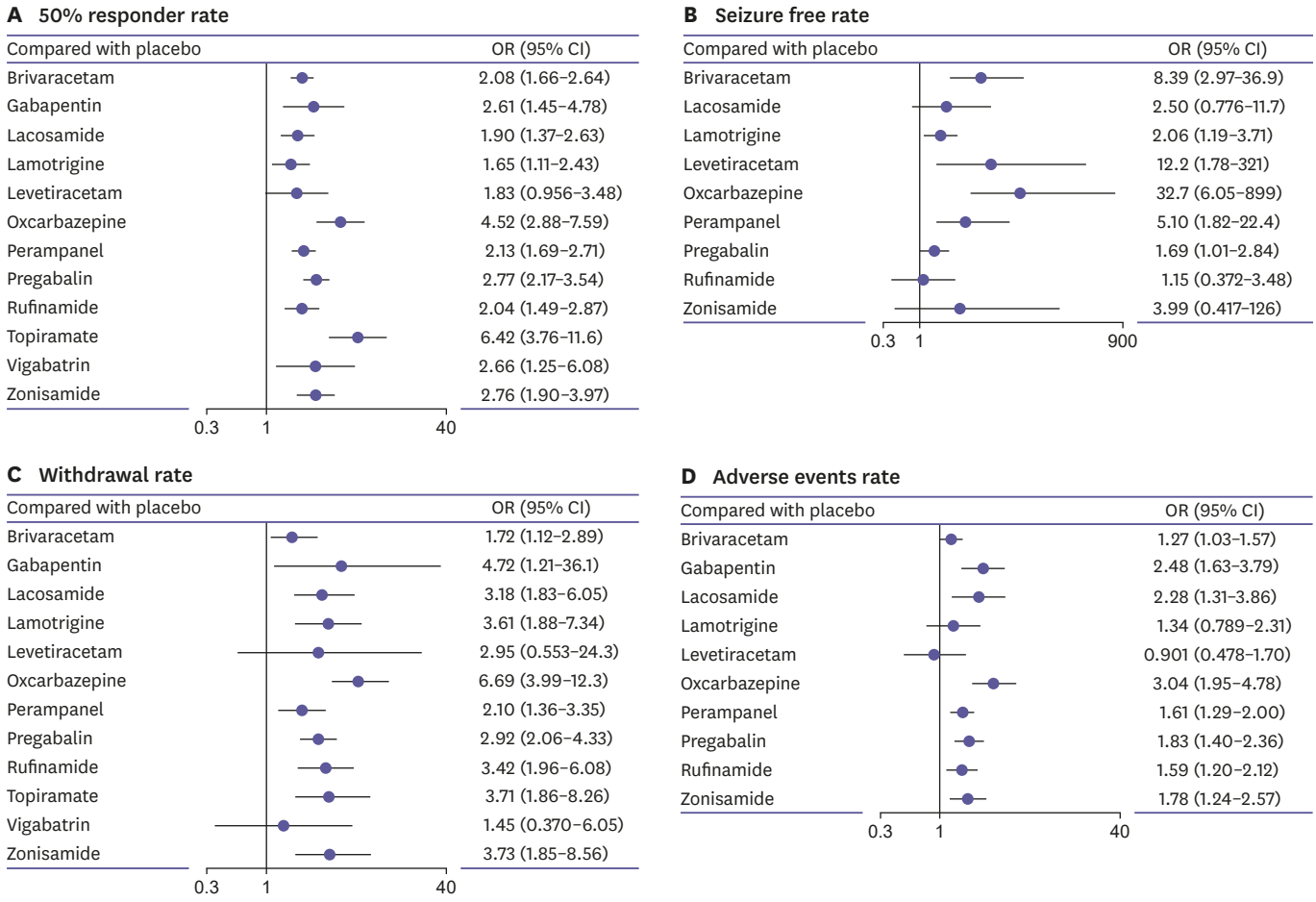

Figure 2. OR for adjunctive treatment for the 50% responder, seizure-free rate, withdrawal rate, and adverse event rates when compared with placebo.
OR, odds ratio; CI, confidence interval.

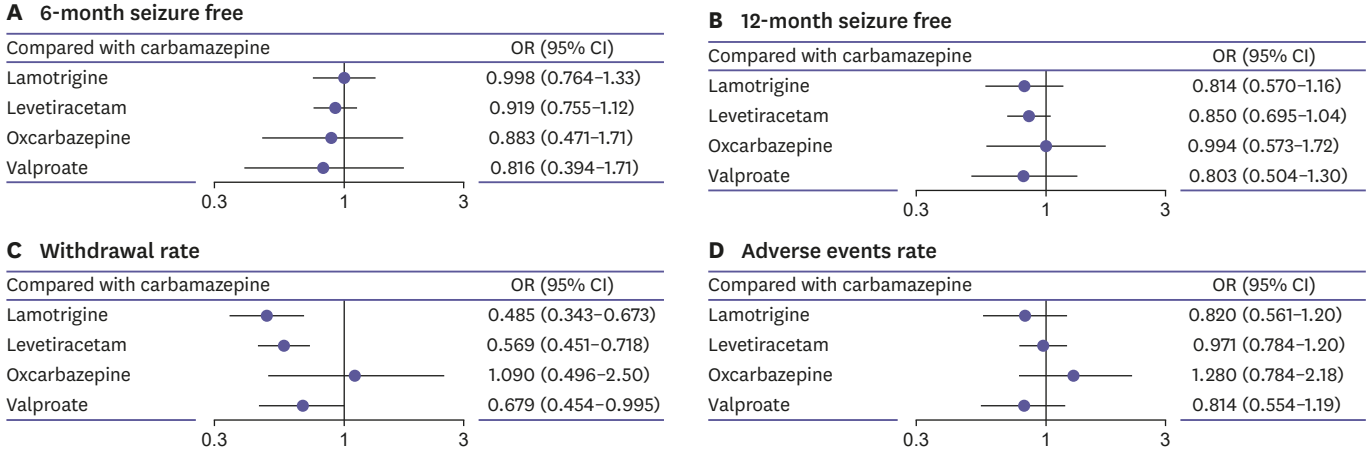

Figure 3. OR for monotherapy for the 6- and 12-month seizure-free, withdrawal rate, and adverse event rates when compared with carbamazepine.
OR, odds ratio; CI, confidence interval.

In adjunctive treatment, except for levetiracetam, the emergence rates of the AEs were generally higher for the AEDs than for the placebo; however, this finding was not significant for lamotrigine (**Fig. 2**). For levetiracetam, only one trial was analyzed, and the AE rate was

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slightly higher in the placebo arm. The emergence rates of the AEs were relatively lower for the third-generation AEDs. In general, the drugs associated with a high incidence of AEs yielded a high treatment withdrawal rate.

Frequently observed AEs

The frequently reported AEs, which were reported in more than 10% of patients, were headache, dizziness and somnolence, fatigue, and nausea (**Tables 2** and **3**). Eye-related disorders, such as diplopia, nystagmus, and blurred/abnormal vision, were observed in patients treated with oxcarbazepine, topiramate, and vigabatrin. Weight increase was a frequently reported AE in patients treated with vigabatrin and pregabalin. We could not identify the safety profile of valproate from the searched articles.

Sub-analysis results according to the dose levels of each AED

Dose-response analysis of the selected efficacy and safety item for adjunctive treatment was performed. In general, the 50% responder rate tended to increase as the dose of the AEDs increased within the same treatment group. (**Fig. 4**). In addition, the treatment withdrawal rate owing to AEs tended to increase as the dose of the AEDs increased, except for brivaracetam (**Fig. 5**).

Quality assessment

In general, the methodological quality of this meta-analysis, which was assessed using the AMSTAR tool, did not have a significant bias. In the review results, 14 items out of the

Table 2. Summary of commonly reported adverse events associated with anti-epileptic drugs recommended as monotherapy

Adverse events	Carbamazepine (n = 1,040)	Lamotrigine (n = 537)	Levetiracetam (n = 1,273)	Oxcarbazepine (n = 174)
Headache	247 (23.8)	129 (24)	263 (20.7)	20 (11.5)
Fatigue	219 (17.5)	69 (12.8)	219 (17.2)	-
Dizziness	147 (14.1)	56 (10.4)	138 (10.8)	37 (21.3)
Nausea	106 (10.2)	64 (11.9)	-	-
Somnolence	-	-	-	18 (10.3)

Data in bracket are presented as the percentage of subjects who experienced at least 1 adverse event among the total number of subjects.

Table 3. Summary of commonly reported adverse events associated with anti-epileptic drugs recommended as adjunctive treatment

Adverse events	GBP (n = 335)	TPM (n = 359)	LCM (n = 643)	VGB (n = 58)	ZSM (n = 352)	LMT (n = 118)	LEV (n = 77)	OXC (n = 519)	PGB (n = 1,391)	BRV (n = 1,204)	PER (n = 1,709)	RFA (n = 871)
Headache	38 (11.3)	143 (39.8)	83 (12.9)	19 (32.8)	-	20 (16.9)	-	142 (27.4)	-	120 (10.0)	-	191 (21.9)
Fatigue	-	113 (31.5)	-	15 (25.9)	-	-	-	72 (13.9)	-	-	-	153 (17.6)
Dizziness	72 (21.3)	168 (46.8)	112 (17.4)	13 (22.4)	-	21 (17.8)	-	172 (33.1)	367 (26.4)	128 (10.6)	494 (28.9)	183 (21.0)
Nausea	-	-	68 (10.6)	-	-	-	-	117 (22.5)	-	-	-	106 (12.2)
Somnolence	113 (33.7)	138 (38.4)	73 (11.4)	10 (17.2)	-	-	-	137 (26.4)	220 (15.8)	166 (13.8)	261 (15.3)	101 (11.6)
Diplopia	-	68 (18.9)	-	-	-	-	-	145 (27.9)	-	-	-	-
Ataxia	42 (12.5)	100 (27.9)	-	-	-	-	-	103 (19.8)	-	-	-	-
Nystagmus	-	81 (22.6)	-	-	-	-	-	88 (17)	-	-	-	-
Blurred/abnormal vision	-	-	-	8 (13.8)	-	-	-	65 (12.5)	-	-	-	-
Thinking differently	-	118 (32.9)	-	-	-	-	-	-	-	-	-	-
Increased weight	-	-	-	7 (12.1)	-	-	-	-	153 (11.0)	-	-	-
Confusion	-	41 (11.4)	-	-	-	-	-	-	-	-	-	-

Data in bracket are presented as the percentage of subjects who experienced at least 1 adverse event among the total number of subjects.
GBP, gabapentin, TPM, topiramate, LCM, lacosamide, VGB, vigabatrin, ZSM, zonisamide, LMT, lamotrigine, LEV, levetiracetam; OXC, oxcarbazepine; PGB, pregabalin; BRV, brivaracetam; PER, perampanel; RFA, rufinamide.

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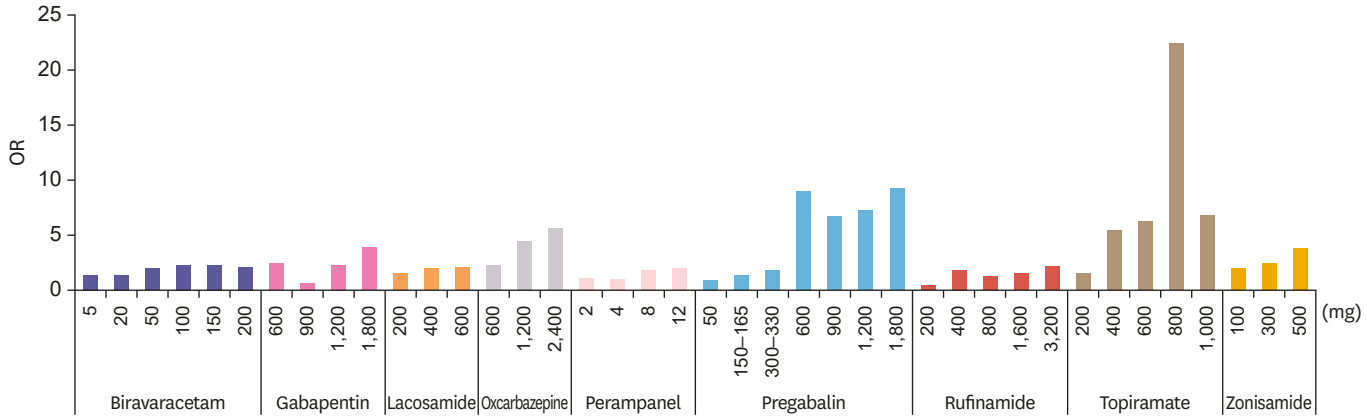

Figure 4. OR for the 50% responder rate for the efficacy outcome between each treatment and placebo at dose-specific levels.
OR, odds ratio.

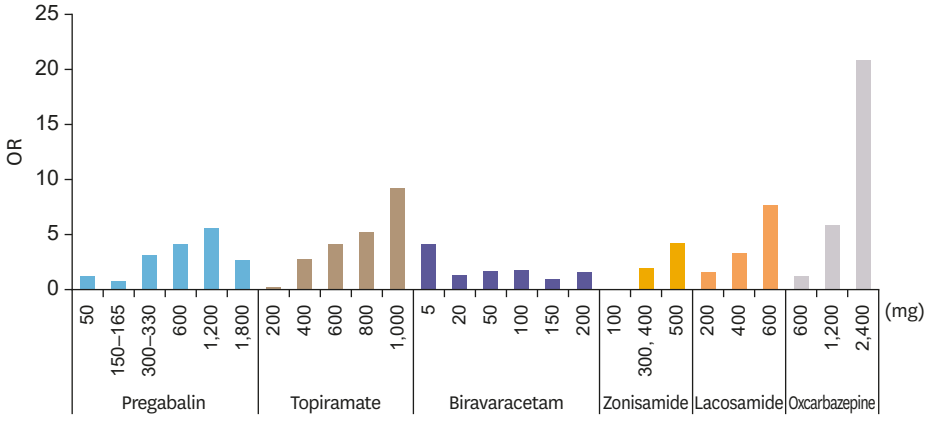

Figure 5. OR for the treatment withdrawal rate for the tolerability between each treatment and placebo at dose-specific levels.
OR, odds ratio.

16 questions were satisfied and rated as moderate at overall confidence. Although 2 items required review from the second reviewer, we selected articles according to the pre-selected inclusion and exclusion criteria to ensure fairness and verified the extracted data thrice to ensure accuracy. All of the clinical trials included in this meta-analysis could be rated as having a low risk of detection bias. Each trial had a double-blind study design, and the study results were disclosed by publishing articles to the journals. The study outcome was measured using the same methods between the intervention groups.

DISCUSSION

In this study, the total effect size for various AEDs was analyzed on the basis of efficacy and safety parameters for each drug, and the results can be useful for healthcare professionals, as the current epilepsy treatment guidelines suggest only some lists of recommended AEDs. Although the safety and efficacy profiles of each AED can be identified from individual study results, some of the individual trials lack efficacy or safety data, which limits the comprehensive understanding of specific drugs. This study obtained efficacy and safety data from several clinical trials and consolidated them based on the same endpoints to compare

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the efficacy and safety profiles of various AEDs. In addition, we provided the relative effect size weighted by the sample size to avoid bias caused by the different sample sizes of each study. Furthermore, this study focused on the AEDs prescribed in Korea for patients with focal epilepsy; therefore, our study results can provide practical information for epilepsy treatment in Korea.

In this study, a Bayesian network meta-analysis was used to compare the relative efficacy among AEDs for monotherapy. It was impossible to use a placebo as a comparator drug in the studies for AEDs recommended as monotherapy owing to ethical and safety considerations. These studies did not include common comparator drugs; therefore, it was not easy to calculate the relative efficacy among the AEDs using other meta-analysis methods. The analysis method used in this meta-analysis was appropriate to generate the relative OR for each AED based on direct comparison from individual trials.

The guidelines by the Korean Epilepsy Society suggested carbamazepine as the first choice among the suggested AEDs for monotherapy. Carbamazepine showed statistically insignificant better OR for both the 6- and 12-month seizure-free rates among the AEDs recommended as monotherapy (**Fig. 3**). Further, topiramate showed the highest OR for the 50% responder rate among the AEDs recommended as adjunctive treatment, which corresponds to a previous meta-analysis result [66]. Oxcarbazepine, perampanel, lamotrigine, and brivaracetam revealed significantly higher ORs than did placebo for both 50% responder rate and seizure-free rate.

In this study, safety and tolerability were evaluated on the basis of the treatment withdrawal rate owing to AEs and the proportion of subjects who experienced AEs. The drugs with low withdrawal rates yielded a low incidence of AEs. Among the AEDs recommended as monotherapy, the difference was not significant in terms of treatment withdrawal rate owing to AEs and AE emergence rate (**Fig. 3**). Among the AEDs recommended as adjunctive treatment, oxcarbazepine yielded the highest withdrawal rate and AE rate; therefore, careful monitoring of drug safety is needed when using oxcarbazepine (**Fig. 2**). The results of safety assessment about frequent AEs reported from over 10% of patients, headache, dizziness, somnolence, fatigue, and nausea corresponds to a previous meta-analysis result [67]. Eye-related disorders were reported as AEs when treated with oxcarbazepine, topiramate, and vigabatrin and it was aligned with the result from the previous study and guideline by Korean Epilepsy Society [5,68].

The third-generation AEDs showed a relatively better safety profile than did the other drugs (**Fig. 2**).

The sub-analysis, which was performed according to the dose levels, revealed an increasing tendency of the efficacy and safety parameters (50% responder rate and treatment withdrawal rate owing to AEs, respectively) as the dose of each AED increased (**Figs. 4** and **5**). The dose-response relationship explored in this study can add additional information that can be used for optimal pharmacotherapy for patients with focal epilepsy. This information can also be useful when adjusting the dose during pharmacotherapy of patients with focal epilepsy.

The study has some limitations. Most of the clinical trials enrolled for this analysis were conducted in non-Korean population. It appears that the studies of monotherapy for focal epilepsy also included the trails that enrolled both patient groups, focal and generalized

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epilepsies. Some of the study findings were driven from the results from a small number of clinical trials. For example, the oxcarbazepine showed highest seizure-free rate when used for adjunctive treatment. However, that result should be interpreted with some caution as that finding was driven from only one clinical trial.

Despite all of these limitations, the results of the meta-analysis would be an updated knowledge of focal epilepsy treatment in Korea. This study compared the efficacy and safety of various AEDs used for the treatment of focal epilepsy by performing a meta-analysis, and the results can be useful for optimal pharmacotherapy for patients with focal epilepsy.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Clinical guideline for anti-epileptic drugs treatment in patients with epilepsy

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Supplementary Fig. 1

R scripts and R commands using the "gemtc" package in R software, version 3.6.1 for meta-analysis, using the number of patients who responded and total number of patients who were involved for analysis in the experimental group versus control group.

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