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The efficacy and safety of valproate medications for migraine in adults: a meta-analysis

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Abstract. – OBJECTIVE: Many parallel-group studies of migraine prophylaxis using valproate medications were reported in recent decades. This meta-analysis assessed the efficacy and safety of valproate medications for migraine prophylaxis in adults.

MATERIALS AND METHODS: Searches were conducted in five databases: PubMed, Wiley, ScienceDirect, Web of Science, and the Cochrane Library. The data were acquired through December 31, 2018. Two independent authors searched for controlled clinical trials involving the use of valproate medications in migraine prophylaxis. Studies that met the inclusion criteria were assessed, and their methodological quality was examined.

RESULTS: Seven placebo-controlled studies (782 participants) and seven controlled trials against active comparators (554 participants) were included in the final analysis. The active treatment of valproate medications was significantly superior to placebo (OR, 4.02; 95% CI 2.17-7.44; I^2 = 66%). Compared with the other active comparators, there were no significant differences between treatments in the proportion of responders.

CONCLUSIONS: Valproate medications were more effective than placebo in migraine prevention, with statistically significant differences. Both valproate and the other active comparators were well-tolerated, and no significant difference was noted in efficacy and safety for the prophylaxis of migraine.

Key Words:
Adverse events, Biological mechanisms, Meta-analysis, Migraine prophylaxis, Valproate.

Introduction

Migraine is a chronic neurological disorder with heterogeneous characteristics, which can result in a range of symptom profiles, burdens, and disabilities[1]. Migraine is a major social issue for public health intervention as it is the third most common neurological disorder globally, with a prevalence of nearly 15%. Migraine always leads to a lower quality of life compared with diabetes, heart disease, and depression[2], so it has been ranked as one of the topmost disabling health disorders.

Prophylactic treatment can help decrease the frequency and severity of migraines[3-5] and thereby reduce the need for health care resources and improve the quality of life[6]. However, only 3%-5% of migraine patients receive preventive therapy[7,8]. Nearly half of all migraine sufferers stop seeking care for their headaches, partly because of their dissatisfaction with therapy[7].

For prophylactic treatment of migraine, several different types of drugs have been recommended by headache treatment-related guidelines of many countries[9,10], including antiepileptics (valproate and topiramate), antidepressants (amitriptyline, fluoxetine, and venlafaxine), β-adrenergic blockers (propranolol, atenolol, and metoprolol) and a calcium channel blocker (flunarizine)[2]. Among them, valproate (sodium valproate or divalproex sodium) is the most widely prescribed in recent decades. The first study on the use of valproate for migraine prophylaxis, an open, uncontrolled trial involving 18 patients, was reported in 1988 by Sorensen et al[11]. Over subsequent decades, several parallel-group studies of the efficacy of valproate medications in migraine prophylaxis were reported. Linde et al[12] performed a Cochrane review to assess the evidence of the efficacy and tolerability of valproate medications in

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migraine prophylaxis. Ten randomized studies published before 2013 that compared valproate with placebo or other medications were included. The trials enrolled 2,296 adult patients (16 years or older) with migraines occurring on at least 15 days per month. The analysis showed that both sodium valproate and divalproex sodium more than doubled the proportion of responders relative to placebo. There was no significant difference in the proportion of responders between valproate medications *vs.* other medications (flunarizine and propranolol). Linde et al[12] identified most of the relevant trial results in the public domain. However, not all the trials were randomized, double-blind studies. Furthermore, in past years, several new epidemiological studies have been reported.

In this study, we performed a meta-analysis to evaluate the efficacy of valproate medications in migraine prophylaxis based on randomized controlled trials (RCTs) up to now. We only focused on randomized, double-blind, parallel-group studies. The main adverse events were also analyzed. We also summarized the hypotheses regarding the mechanisms of valproate medication efficacy for migraine prophylaxis.

Materials and Methods

Search Strategy

We identified procurable studies published in English up to December 2018. The literature search was performed using PubMed, Wiley, ScienceDirect, Web of Science, and Cochrane Library databases. The following combined text and Medical Subject Headings (MeSH) search strategy was used to search the databases mentioned above: (valproate or divalproex or valproic acid) AND (treat*) AND (migraine or headache). We also examined conference proceedings and the references from retrieved articles for additional relevant publications[13,14].

Inclusion Criteria

The included studies in the meta-analysis met the following criteria: (1) written in English; (2) physician-confirmed diagnosis of migraine; (3) randomized, double-blind and parallel-group studies; (4) treatment efficacy defined as a $\geq$ 50% reduction in headache frequency; (5) presentation of original data; (6) the odds ratio (OR) and its corresponding 95% confidence interval (95% CI) quantified the efficacy of valproate and controls or there were enough data to calculate these numbers. If the results of a study had been published in more than one publication, only the one with the most complete information was included[15].

Data Extraction and Assessment of the Methodological Quality

Two investigators independently extracted information from the included studies, including authors, publication years, the numbers of patients, interventions, efficacy outcomes, and adverse events. Any disagreements were resolved through discussion.

We assessed the methodological quality of individual studies using the Jadad scale (also called Jadad scoring or the Oxford quality scoring system), which was devised by Jadad et al[16]. The Jadad scale is the most widely used procedure to assess the methodological quality of a clinical independent trial and can be operationalized using Table I. Each trial can receive a score of 0 to 5 points; the trials with higher scores are assessed as being higher quality in their conduction. Two investigators scored the studies independently, and disagreements were resolved through discussion.

Table I. The Jadad score for methodological quality assessment.

Item	Score standard
Was the study described as randomized?	1 = yes; 0 = no
Was the method of randomization well described and adequate?	0 = not described; 1 = described and adequate; -1 = described, but not adequate
Was the study described as double-blind?	1 = yes; 0 = no
Was the method of double-blinding well-described and adequate?	0 = not described; 1 = described and adequate; -1 = described, but not adequate
Was the description of withdrawals and dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial?	1 = yes; 0 = no

Statistical Analysis

The odds ratio (OR) was employed to compare the efficacy of valproate *vs.* placebo or other drugs in the prophylactic treatment of migraine. Odds ratios of specific studies were weighted to obtain a pooled OR estimate and its 95% CI.

To examine the heterogeneity, we performed the Higgins I^2 test[17]. The I^2 value describes the percentage of total variation across studies due to heterogeneity rather than chance. The value of I^2 ranged from 0% (no observed heterogeneity) to 100% (maximal heterogeneity)[18]. We calculated the summary OR and its 95% CI based on the fixed-effect model if a substantial heterogeneity was not found ($I^2 \leq 50\%$). Conversely, we calculated the summary OR and its 95% CI based on the random-effect model, if the substantial heterogeneity was found ($I^2 > 50\%$). Review Manager 5.3 was used for statistical analysis. Additionally, the funnel plot test[19,20] was employed to assess the possibility of publication bias.

Results

Search Results and Study Characteristics

The flow diagram of the identification of relevant studies is shown in Figure 1. We identified 2,610 articles from the four databases and 15 from the bibliographies of relevant articles. After the exclusion of duplicates and criteria screening, fourteen studies from twelve publications between 1994 and 2015 were included in the final analysis[21-32].

Table II shows the main characteristics of the included studies in the final meta-analysis. Five trials compared valproate medications with placebo, five compared valproate medications with the other active intervention (two for cinnarizine and three for topiramate), one compared valproate with both placebo and propranolol, and one compared valproate with both placebo and levetiracetam. The placebo-controlled studies (seven trials, 782 participants) included four trials of divalproex sodium and three trials of sodium valproate. In the controlled trials against active comparators (seven trials, 554 participants), one compared divalproex with propranolol, one compared divalproex with levetiracetam, two compared sodium valproate with cinnarizine, and three compared valproate medications (one of divalproex and two of sodium valproate) with topiramate.

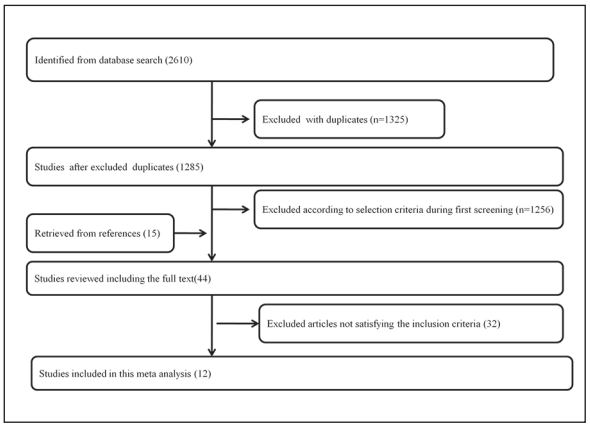

Figure 1. Selection of studies for inclusion in this meta-analysis.

We scored the methodological quality using the Jadad scale, with a maximum attainable score of 5. The mean score was 3.2 (range 1-5).

Comparison of Valproate with Placebo

As previously mentioned, seven of the included studies compared valproate medications (divalproex sodium or sodium valproate) with placebo in the prophylactic treatment of migraine. The meta-analysis of these studies is shown in Figure 2.

In a random-effect meta-analysis of the seven studies, active treatment with valproate medications was significantly superior to placebo (OR, 4.02; 95% CI 2.17-7.44; $I^2 = 66\%$) and the difference was significant ($p < 0.00001$). A funnel plot test was employed to assess the possibility of publication bias in our study. As shown in Figure 3, the logOR from each trial was plotted on the horizontal axis, and its standard error is plotted on the vertical axis. Visual inspection of the funnel plot revealed a symmetric distribution of the logORs plotted against their standard errors. This result suggests the absence of publication bias in our study.

We performed a subgroup analysis with four studies of divalproex sodium and three studies of sodium valproate, respectively. As shown in Table III, the summary OR for divalproex sodium in random-effect analysis was 3.34 (95% CI, 1.46-7.67; $I^2 = 73\%$; $p = 0.004$). The summary OR for sodium valproate in fixed-effect analysis was 5.07 (95% CI, 2.75-9.36; $I^2 = 42\%$; $p < 0.00001$).

Comparison of Valproate with Other Active Comparators

Seven trials that compared valproate medications with the other active comparators were included in this study. The subgroup analyses

Table II. Characteristics of studies included in the final analysis.

Study	Patients	Valproate		Placebo/active comparator		Jadad scale
		Form and dose	Follow-up patients and responders	Comparator and dose	Follow-up patients and responders	
Kaniecki[26]	37	Divalproex sodium, 1,500 mg/d, 2,000 mg/d	Follow-up patients 32, responders 21	Propranolol, 180 mg/d	Follow-up patients 32, responders 20	2
Sadeghian et al[24]	105	Sodium valproate, 500 mg/d	Follow-up patients 32, responders 21	Levetiraceta, 500 mg/d	Follow-up patients 27, responders 17	2
Bostani et al[21]	132	Sodium valproate, 400 mg/d	Follow-up patients 54, responders 36	Cinnarizine 50 mg/d	Follow-up patients 50, responders 16	5
Mansoureh et al[32]	125	Sodium valproate, 800 mg/d	Follow-up patients 58, responders 37	Cinnarizine 75 mg/d	Follow-up patients 67, responders 41	3
Krymchantowski et al[28]	120	Divalproex sodium, 250 mg/d, 500 mg/d	Follow-up patients 43, responders 36	Topiramate 25 mg/d, 150 mg/d	Follow-up patients 59, responders 40	2
Afshari et al[22]	76	Sodium valproate, 400 mg/d	Follow-up patients 28, responders 18	Topiramate, 50 mg/d	Follow-up patients 28, responders 20	4
Bartolini et al[29]	49	Sodium valproate, 750 mg/d	Follow-up patients 22, responders 21	Topiramate, 75 mg/d	Follow-up patients 22, responders 21	2
Mathew et al[30]	117	Divalproex sodium, 750 mg/d	Follow-up patients 69, responders 33	Placebo	Follow-up patients 36, responders 5	3
Klapper[27]	176	Divalproex sodium, 500 mg/d	Follow-up patients 129, responders 57	Placebo	Follow-up patients 42, responders 9	3
Freitag et al[23]	237	Divalproex sodium, 500, 1000 mg/d	Follow-up patients 119, responders 36	Placebo	Follow-up patients 115, responders 28	4
Sarchielli et al[31]	130	Sodium valproate, 800 mg/d	Follow-up patients 40, responders 18	Placebo	Follow-up patients 42, responders 10	4
Jensen et al[25]	43	Sodium valproate 1500, 1000 mg/d	Follow-up patients 34, responders 22	Placebo	Follow-up patients 34, responders 7	3
Kaniecki[26]	37	Divalproex sodium, 1,500 mg/d, 2000 mg/d	Follow-up patients 32, responders 21	Placebo	Follow-up patients 32, responders 6	2
Sadeghian et al[24]	105	sodium valproate, 500 mg/d	follow-up patients 32, responders 21	Placebo	Follow-up patients 26, responders 4	2

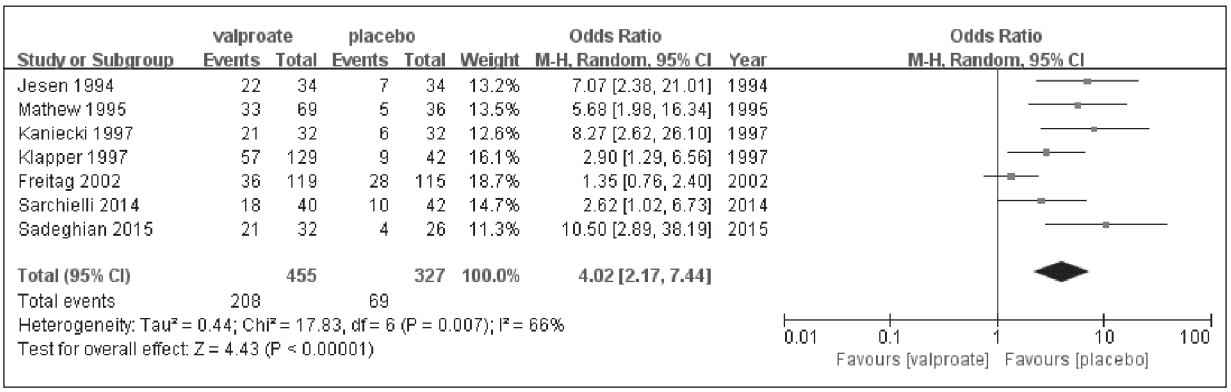

Figure 2. Odds ratio and 95% CIs from studies comparing valproate medications with placebo in prophylactic migraine treatment.

with trials of different control drugs were performed severally. The results are shown in Table III.

Three studies compared valproate medications (one of divalproex and two of sodium valproate) with topiramate. The pooled OR in fixed-effect analysis was 0.74 (95% CI, 0.39-1.40; $I^2 = 0\%$), but there was no significant difference between valproate medications and topiramate ($p = 0.35$). Two trials using an active comparator examined sodium valproate *vs.* cinnarizine. There was no significant difference between treatments in the proportion of responders (OR, 2.15; 95% CI, 0.58-7.95; $I^2 = 82\%$; $p = 0.25$). One trial compared divalproex with propranolol and another with levetiracetam. There was no significant difference when comparing valproate with propranolol (OR, 1.15; 95% CI 0.41-3.18; $p = 0.79$) or levetiracetam (OR, 1.12; 95% CI 0.39-3.27; $p = 0.83$).

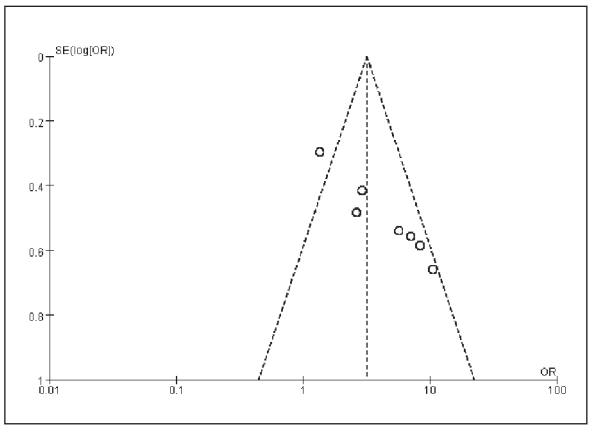

Figure 3. Funnel plot of studies that compared valproate medications with placebo in the prophylactic treatment of migraine. The log OR from each study is plotted on the horizontal axis, and its standard error is plotted on the vertical axis.

Summary of Treatment-Emergent Adverse Events

Among the studies comparing valproate medications with placebo, five reported adverse events were registered in the valproate and the placebo arms during the trials. The adverse events are summarized in **Supplementary Tables S1** and **S2**. The most frequent adverse events associated with valproate were nausea, asthenia, somnolence, vomiting, tremor, alopecia, weight gain, and pain (neck and shoulders, especially). Additionally, there were several uncommon side effects, including restless legs, dry mouth, dyspnea, tinnitus, declines in sexual desire, depression, pruritus, flu-like syndrome, gastritis, pre-syncope, and others.

Discussion

Efficacy of Valproate Medications for the Prophylactic Treatment of Migraines

All the studies included in this systematic analysis reported the clinical efficacy of valproate medications in the prophylactic treatment of migraines. The pooled analysis of seven placebo-controlled trials showed that valproate medications were more effective than placebo in migraine prevention, with statistically significant differences. Most of the studies reported a significantly higher efficacy of valproate medications than placebo. However, Freitag et al[23] reported that the proportion of subjects achieving at least a 50% reduction in migraine headache rate was

Table III. Pooled odds ratios and 95% confidence intervals of valproate for migraine.

Comparison	No. of studies	OR	95% CI	I2 (%)	Analysis model	*p*-value
Valproate *vs.* placebo	7	4.02	2.17-7.44	66	Random effect	0.00001
Divalproex sodium *vs.* placebo	4	3.34	1.46-7.67	73	Random effect	0.004
Sodium valproate *vs.* placebo	3	5.07	2.75-9.36	42	Fixed effect	0.00001
Valproate *vs.* topiramate	3	0.74	0.39-1.40	0	Fixed effect	0.35
Sodium valproate vs. cinnarizine	2	2.15	0.58-7.95	82	Random effect	0.25
Divalproex *vs.* propranolol	1	1.15	0.41-3.18	NA	Fixed effect	0.79
Divalproex *vs.* levetiracetam	1	1.12	0.39-3.27	NA	Fixed effect	0.83

higher in the divalproex sodium group than in the placebo group, but this difference was not significant ($p = 0.251$)[23].

In the subgroup analysis, both divalproex sodium and sodium valproate showed significant preventive effects of migraine compared with placebo. The results showed that the protective effects of sodium valproate were greater than those of placebo (OR 5.07 *vs.* 3.34).

The pooled analysis of trials comparing valproate medications with active comparators showed no significant differences between the efficacies of different treatment groups. The responder rate for patients treated with valproate was lower than those with topiramate and higher than those with cinnarizine, but the differences were not statistically significant. In Sadeghian et al[24], the difference was statistically different for both levetiracetam and sodium valproate compared with placebo, while the difference was not significant between levetiracetam and sodium valproate themselves. Likewise, Kaniecki[26] showed no significant difference between divalproex and propranolol for migraine prophylaxis.

Safety and Tolerability

The reported number of side effects varies considerably between different studies of the same drug in migraine prophylaxis. This observation probably reflects the manner of recording rather than actual differences[25]. In Freitag et al[23], no significant differences were detected between treatment groups in either the overall incidence or in the incidence of any specific treatment-emergent adverse events[23]. In the other placebo-controlled studies, the occurrence of nausea, dizziness, asthenia, vomiting, drowsiness (also reported as sleepiness or somnolence), and tremors were significantly higher in the valproate group than in the placebo group. However, these adverse reactions are tolerable for most patients.

In the studies comparing valproate with active comparators (topiramate, cinnarizine, propranolol), no significant differences were noted in the adverse events for the prophylaxis of migraine, and all experimental medications were well tolerated by most patients.

Hypotheses of Biological Mechanisms

The results of this meta-analysis indicated the efficacy and safety of valproate for migraine prevention. However, the mechanism underlying the protective effect of valproate remains poorly elucidated. At present, several mechanisms explaining the protective effects of valproate against migraines have been proposed.

Migraine is a systemic disorder associated with both peripheral and central dysfunction. The protective activity of valproate should be also the result of comprehensive action in different ways[33-36]. It is generally believed that the preventive effect of valproate against migraine mainly results from several aspects, including the modulation of neurotransmitter release, the regulation of cell membrane ion channels, effects on glycogen synthase kinase-3 and the Wnt/β-catenin pathway, the effects on brain lipids and their metabolism, and effects at the genomic level.

Limitations of This Study

Some limitations of this meta-analysis should be mentioned here. First, the number of studies that included the necessary data is too small; thus, more trials are required because of the paucity of data published on this issue. Second, the definitions of valproate medications used in each study were heterogeneous. The doses and durations of valproate medications used varied according to the definitions of each study. This discrepancy could lead to heterogeneity across the included studies. Third, only studies in English were considered. This limitation may result in the omission of relevant studies published in

other languages. Finally, there is heterogeneity and a possibility of publication bias across some subgroup analyses.

Conclusions

We performed a meta-analysis of valproate medications for the prophylactic treatment of migraines in adults. Three vital perspectives were obtained from this study. Firstly, valproate medications were more effective than placebo in migraine prevention, with statistically significant differences. Secondly, both valproate and the other active comparators were well tolerated, and no significant difference was noted in the efficacy for the prophylaxis of migraine. Thirdly, several mechanisms for the protective effects of valproate for migraine have been proposed. The findings from these observational studies should be confirmed in future research, such as in more prospective cohort studies or RCTs providing the highest level of evidence.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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