Original Article

The efficacy and safety of antiepileptics in the prophylaxis of pediatric migraine: the meta-analysis of randomized controlled trials

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Background: Migraine is the most common primary headache among children and adolescents. The aim of this meta-analysis was to evaluate the efficacy and safety of antiepileptic drugs in the prevention of pediatric migraine.

Methods: PubMed, Cochrane Library, EMBASE and Chinese National Knowledge Infrastructure (CNKI) databases were searched for eligible published RCTs from January 1970 to June 2020. Migraine frequency and ≥50% response rate were measured as the efficacy outcomes. We used "Risk of Bias" tool for quality assessment and RevMan5.3 software for statistical analysis.

Results: Four articles containing 7 RCTs with 794 participants compared the efficacy of AEDs with placebo. Four RCTs assessed topiramate *vs.* placebo and 3 RCTs evaluated divalproex sodium extended-release (DVPX ER) *vs.* placebo. The results demonstrated that children receiving antiepileptic drugs had a significant advantage in remitting the mean monthly migraine days compared to those who received placebo, with an MD of −0.48 (n=930, 95% CI: −0.84 to −0.12, Z=2.60, P=0.009). Topiramate significantly reduced monthly migraine days (MD =−0.70, n=489, 95% CI: −1.16 to −0.25, Z=3.01, P=0.003) but failed to improve the ≥50% response rate (MD =−1.50, n=489, 95% CI: 0.70 to 3.22, Z=1.05, P=0.30). DVPX ER did not significantly reduce monthly headache frequency (n=441, 95% CI: −0.70 to 0.47, Z=0.38, P=0.70) or improve the ≥50% response rate (n=441, 95% CI: 0.59 to 1.25, Z=0.82, P=0.41) compared with placebo. Topiramate and DVPX ER were related to higher rates of side effects and adverse reactions.

Discussion: Topiramate can reduce monthly headache days in children and adolescents with migraine. However, it failed to improve the ≥50% response rate. DVPX ER showed no difference from placebo in the prophylactic treatment pediatric migraine. Side effects seemed to be more frequent in topiramate and DVPX ER treated children but generally well-tolerated.

Keywords: Antiepileptics; pediatric; migraine; prevention; meta-analysis

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Introduction

Migraine is the most common primary headache among the pediatric population (1), with the prevalence that increased from 3–5% of children to 10–20% among adolescents (2-4). Clinical symptoms of pediatric migraine are often atypical. Children and adolescents patients with migraine may present with episodic vertigo, dizzy, nausea, vomiting, and others. Headache is a disabling health condition among children and adolescents. Studies have proved that most migraine occurs between 6 AM to 6 PM in children (5), affecting their school attendance, academic performance, and social interactions with their peers and families (6,7).

Experts have advised that if patients have more than 2 migraine episodes per week or the attacks interfere with their quality of life and cause significant disability, then prophylactic migraine treatment must be initiated (8). The prophylactic treatment for pediatric migraine consists of non-pharmaceutical and pharmaceutical treatment (9). Drug interventions mainly includes acute and prophylactic medications. Acute drugs aim to relieve or stop the acute headache and the accompanying symptoms. Prophylactic treatment intends to reduce the frequency, duration, and severity of headache (10,11).

At present, preventive drugs for pediatric migraine include calcium channel blockers, tricyclic antidepressants, β-adrenergic blockers, antiepileptic drugs (AEDs) and Botulinum toxin A. In 2019, the American Academy of Neurology and the American Headache Society published practice guidelines on all the preventive medications for pediatric migraine (12) which demonstrated that the evidence for divalproex, onabotulinumtoxin-A, amitriptyline, nimodipine, and flunarizine to reduce headache frequency in children and adolescents was insufficient. Topiramate, propranolol and cinnarizine seemed to be more likely effective for pediatric migraine prevention. However, we noticed the guidelines had some limitations. Both migraine and epilepsy are episodic neurological disorders (13) and the pathogenesis of the two diseases was postulated to be related to neuronal hyperexcitability (14). AEDs such as valproate, topiramate, and levetiracetam have been proved to be effective for the prevention of episodic migraine in adults (15,16). However, there are very few studies on the efficacy and safety of antiepileptics in pediatric migraine prophylaxis and the limited trials have yielded disproportionate results. We conducted this meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy and safety of antiepileptics in the prophylaxis of episodic migraine in children and adolescents.

Methods

Search strategy

Cochrane Library, PubMed and EMBASE databases were searched to identify all eligible RCTs published from January 1970 (17) to December 2019 with no language restrictions. The search strategies included the following key words such as "pediatric migraine/headache/headache pain" or "child/children/childhood migraine/headache/headache pain" or "adolescent/adolescents migraine/headache/headache pain" or "migraine/headache/headache pain in child/children" or "migraine/headache/headache pain in adolescents" AND "antiepileptic drugs" or "antiepileptics" or "valproate" or "valproate acid" or "sodium valproate" or "divalproex sodium" or "magnesium valproate" or "topiramate" or "topamax" or "gabapentin" or "pregabalin" or "lamotrigine". Case reports, reviews, reference lists of related publications and conference abstracts were also scanned to identify relevant studies.

Selection criteria

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (available at https://dx.doi.org/10.21037/tp-20-478) (18). The inclusion criteria were as follows: (I) double-blind randomized controlled trials (RCTs) taking antiepileptics in migraine prophylaxis; (II) participants were ≤18 years old and they were diagnosed with episodic migraine according to the International Classification of Headache Disorders II (ICHD-II) or the International Classification of Headache Disorders, third edition (ICHD-3, beta version); (III) available and complete efficacy outcomes were reported. The exclusion criteria were: (I) trials other than RCTs such as cross-over designs, open-labeled studies, healthy controlled trials, and others; (II) animal trials; (III) studies evaluating the efficacy of two drugs but no placebo.

Quality assessment

The quality of the included trials was assessed independently by two experienced authors (Jia G and X Wang) using to the "Risk of Bias" tool in Review Manager Software version

5.3. Discrepancies were resolved by consultation with the corresponding author (X Wu). Seven items containing random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias were evaluated.

Data extraction

Two experienced authors independently searched the title and abstract of each study to identify all eligible trials. Disagreements between the two authors were settled by discussion or consultation with the corresponding author (X Wu). Important information including patients' characteristics, the kind, dose and duration of antiepileptic drugs and outcomes were abstracted from the suitable trials. According to the International Headache Society (IHS) recommendations (19), we regarded mean monthly headache days post-treatment and proportion of children who experienced a ≥50% reduction in monthly migraine days as the efficacy outcomes in this study. Besides, percentages of participants discontinuing for any reason and participants dropout because of adverse effects in the study were extracted for the feasibility analysis.

Statistical analysis

RevMan5.3 software (Cochrane Information Management System) was used for all of the statistical analyses. Dichotomous outcomes were analyzed with risk ratios (RRs) and 95% confidence intervals (CIs). Continuous variables were calculated with differences (MDs) and 95% CIs. The significant level was 0.10 for heterogeneity tests and 0.05 for others. I^2 was used to evaluate heterogeneity. $I^2 \leq 50\%$ indicated the heterogeneity was acceptable, then we analyzed the data with the fixed-effects model. If I^2 was >50%, the random-effects model was used.

Results

Search findings

Overall, 833 potential studies were initially identified for this analysis after searching the aforementioned databases. After searching the titles and abstracts, 60 potentially eligible full-text articles were retrieved (*Figure 1*). We ultimately screened the exclusion and inclusion criteria and identified 4 studies including 7 trials in this analysis (*Table 1*).

Characteristics of included studies

Four studies (20-23) comprised of 7 RCTs with 794 participants compared the efficacy of AEDs with placebo. Ethnic groups included Caucasian, Asian, African, and others. Three articles assessed topiramate. One of these papers included two dose treatments of topiramate (50 and 100 mg/d), so we considered it as two separate trials. One study (20) had three groups: topiramate, amitriptyline, and placebo. The amitriptyline group's data was not included in this analysis. The dose of topiramate was increased gradually in the trials and the treatment duration lasted 16–31 weeks. Another trial (23) recruited 305 patients to evaluate the efficacy of 3 different doses (250, 500, and 1,000 mg/d) of extended-release divalproex sodium (DVPX ER) *vs.* placebo. The 7 selected trials reported headache frequency per month and ≥50% response rate as efficacy index.

Quality assessment and publication bias

The methodological quality of the trials was evaluated using the Risk of Bias tool in the Cochrane Collaboration. All of the included articles with either topiramate or DVPX ER reported random sequence generation. Information on allocation concealment, and the blinding of studies and participants was described. The trials had low risk of bias (*Figure 2*).

Efficacy outcomes

All the 7 selected trials measured monthly migraine days and the ≥50% response rate. The results showed that children receiving antiepileptic drugs significantly remitted the mean migraine days per month compared to placebo (n=930, 95% CI: −0.48 to −0.12, Z=2.60, P=0.009) (*Figure 3*). The heterogeneity was low (I^2=0%; P=0.47) so that fixed-effects model was used. However, no significant difference was found between the antiepileptics and placebo groups in the percentage of patients experiencing a ≥50% reduction in headache days per month (n=930, 95% CI: 0.73 to 1.71, Z=0.51, P=0.61) (*Figure 4*). The data demonstrated significant heterogeneity (I^2=58%; P=0.03) and random-effects model was considered.

Subgroup analyses of efficacy outcomes

Since the drug types significantly contributed to the outcomes, a subgroup analysis was conducted based

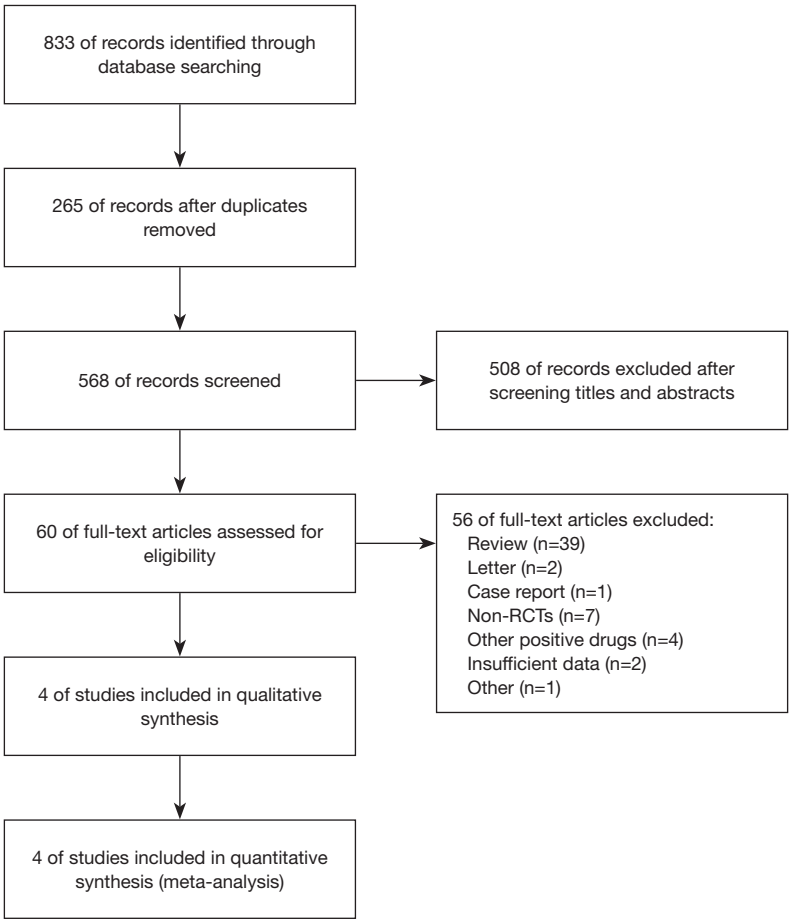

Figure 1 Study flow diagram.

on different types of antiepileptic drugs. The results demonstrated that topiramate could reduce monthly migraine frequency significantly compared with placebo (MD =–0.70, n=489, 95% CI: –1.16 to –0.25, Z=3.01, P=0.003). However, DVPX ER did not reduce monthly headache frequency compared with placebo (n=441, 95% CI: –0.70 to 0.47, Z=0.38, P=0.70) (*Figure 5*). Neither topiramate (n=489, 95% CI: 0.70 to 3.22, Z=1.05, P=0.30) nor DVPX ER (n=441, 95% CI: 0.59 to 1.25, Z=0.82, P=0.41) improved the ≥50% reduction rate in monthly headache days compared with placebo (*Figure 6*).

Adverse reactions

The trials in this study all reported side effects and adverse reactions. The percentage of withdrawals was significantly higher in the topiramate (MD =2.28, n=489, 95% CI: 1.09 to 4.78, Z=2.18, P=0.03) and DVPX ER (MD =1.87, n=450, 95% CI: 1.02 to 3.43, Z=2.03, P=0.04) groups than the placebo group (*Figure 7*). The overall incidence of common side effects was higher in the topiramate group than the placebo group (MD =1.55, 95% CI: 1.25 to 1.91, Z=4.04, *P*<0.0001) (*Table 2*). Although close to the significant level, no difference was found in the rate of side effects between the DVPX ER and placebo groups (MD =1.27, 95% CI: 0.99 to 1.64, Z=1.88, *P*=0.06) (*Table 3*). In the topiramate group, side effects such as weight loss, somnolence, paresthesia, dizziness, pharyngitis, sinusitis, abdominal pain, and other complications occurred more frequently than in the placebo group. Analysis of each common adverse reaction demonstrated weight loss (n=353, 95% CI: 1.24 to 17.51, Z=2.27, P=0.02) , paresthesia (n=489, 95% CI: 2.78 to 12.68, Z=4.61, *P*<0.01) and dizziness (95% CI: 1.20 to 24.12, Z=2.20, P=0.03) significantly increased in the topiramate group (*Table 2*). Upper respiratory tract infection, nausea, nasopharyngitis, weight gain, somnolence,

Table 1 Characteristics of included randomized controlled trials

Study	Diagnostic tool	Sample size	Mean age (years)	Treatment groups	Dose (mg/d)	Duration (week) titration maintenance	Migraine measure	Side effects
Scott W. Powers, 2017	International Classification of Headache Disorders, 2nd Edition (ICHD-II)	217	14.2±2.4	Topiramate *vs.* amitriptyline placebo	2 mg/kg	8 weeks; 16 weeks	≥50% responder rate, headache related disability (PedMIDAS), headache frequency	Fatigue, paresthesia, decreased weight, dry mouth, memory impairment, aphasia, cognitive disorder, and upper respiratory tract infection
Paul Winner, 2005	International Headache Society (IHS) classification of pediatric migraine	162	11.1±2.5	Topiramate *vs.* placebo	2–3 mg/kg	8 weeks; 20 weeks	mean headache frequency, reduction of monthly migraine days, ≥50% responder rate, ≥75% responder rate	Upper respiratory tract infection, anorexia, pharyngitis, weight decrease, abdominal pain, sinusitis, gastroenteritis, paresthesia, somnolence, influenza-like symptoms, injury, fatigue, fever nausea
Donald Lewis, 2008	ICHD-II	106	14.2±1.6	Topiramate *vs.* placebo	50, 100 mg/kg	4 weeks; 16 weeks	mean headache frequency, ≥50% responder rate, reduction in monthly migraine attacks, symptomatic medication usage	Upper respiratory tract infection, paresthesia, abdominal pain, anorexia injury, rhinitis, coughing, viral infection, pharyngitis, fatigue, nausea, dizziness, taste perversion, insomnia, back pain, conjunctivitis, sinusitis, asthma, pneumonia, fever, allergy, vomiting, nervousness, somnolence, abnormal vision, eye pain
George Apostol, 2008	IHS Guidelines for controlled trials of drugs in migraine: 2nd edition	305	14.2±1.6	Divalproex sodium extended-release (DVPX ER) *vs.* placebo	250, 500, 1,000 mg/kg	2 weeks; 10 weeks	mean headache frequency, reduction of monthly migraine days	Any adverse event, upper respiratory tract infection, nausea, nasopharyngitis, weight increased, abdominal pain upper, somnolence, gastroenteritis viral, influenza, vomiting, fatigue, ammonia increased, cough, pharyngolaryngeal pain, viral infection

Figure 2 Risk of bias graph and summary.

viral gastroenteritis, influenza, and fatigue were the most commonly reported adverse events in the DVPX ER trial. However, the meta-analysis of each side effect demonstrated no significant difference in side effects between any dose of DVPX ER and placebo, although ammonia increased (n=450, 95% CI: 0.97 to 31.73, Z=1.93, P=0.05) and weight

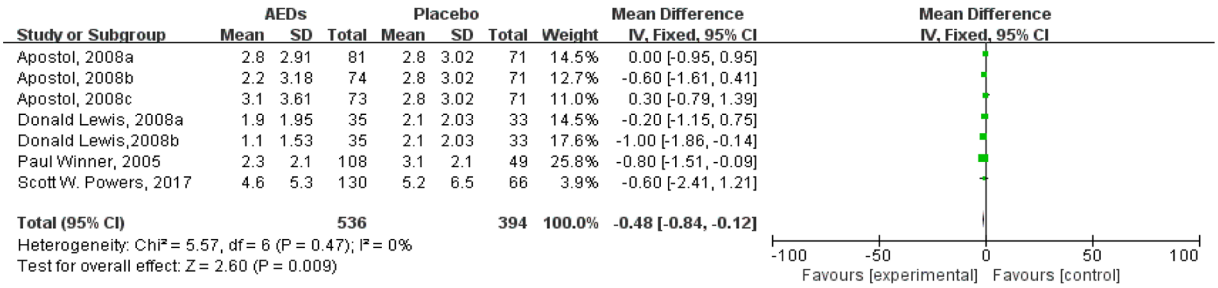

Figure 3 Comparison of the mean monthly migraine days between antiepileptics and placebo groups.

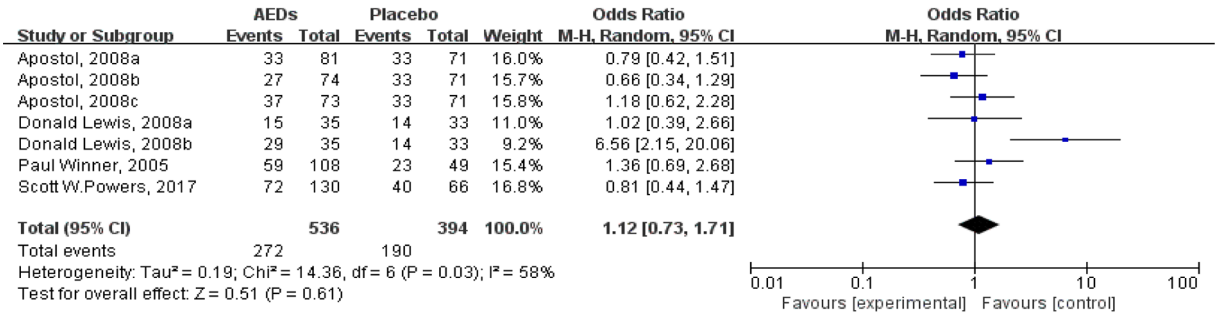

Figure 4 Comparison of ≥50% response rate between antiepileptics and placebo groups.

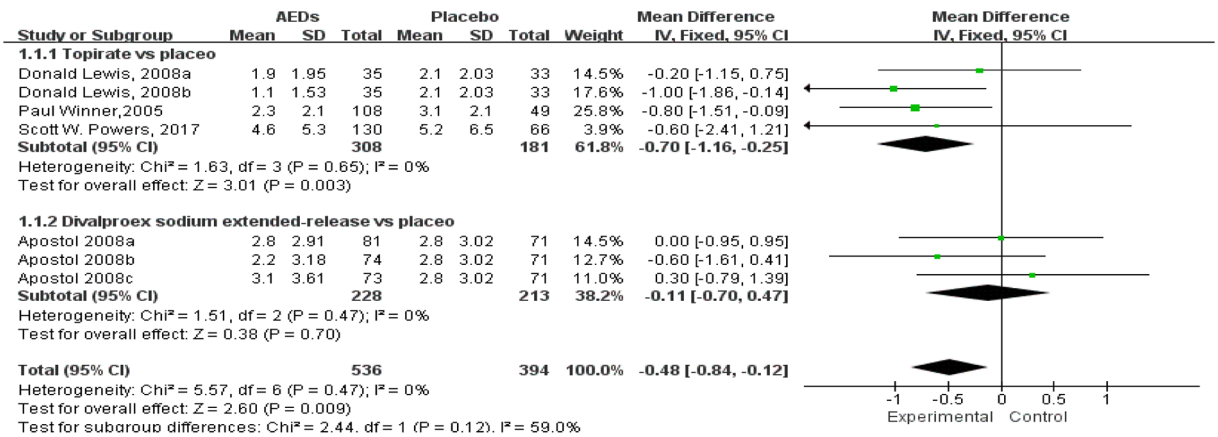

Figure 5 Subgroup analysis of monthly migraine days compared with placebo based on the type of antiepileptic drugs.

gain (n=450, 95% CI: 0.98 to 13, Z=1.94, P=0.05) were close to the significant level (*Table 3*).

Discussion

This meta-analysis assessed the clinical efficacy and safety of antiepileptic drugs in pediatric migraine prevention compared with placebo. Reduction of headache days per month and ≥50% response rate were used as meaningful end points as IHS recommended.

Based on the successful evidence of adult trials, several drugs were used commonly in the prevention of pediatric migraine. However, after searching all of the databases, we found only a few RCTs evaluating the efficacy of

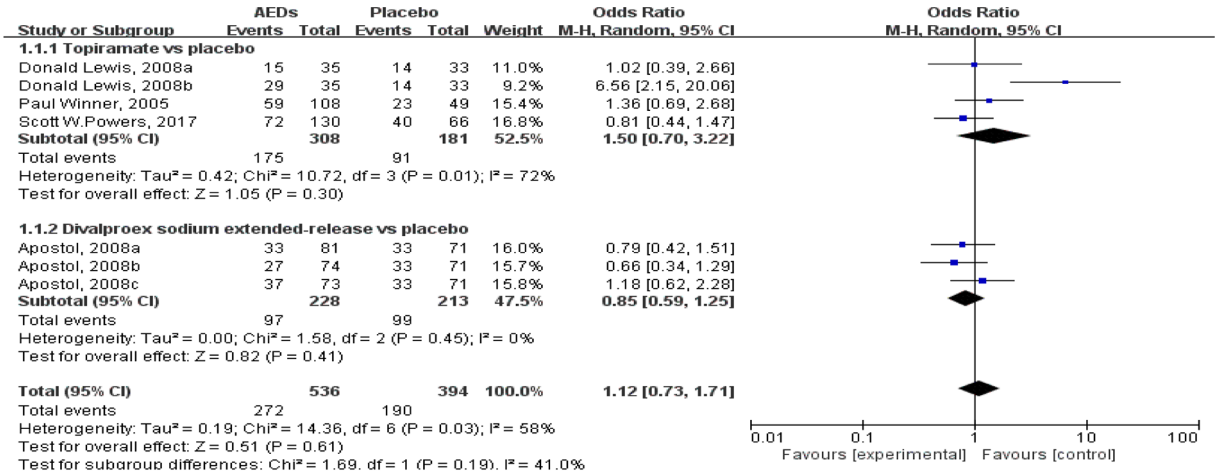

Figure 6 Subgroup analysis of ≥50% response rate compared with placebo based on the type of antiepileptic drugs.

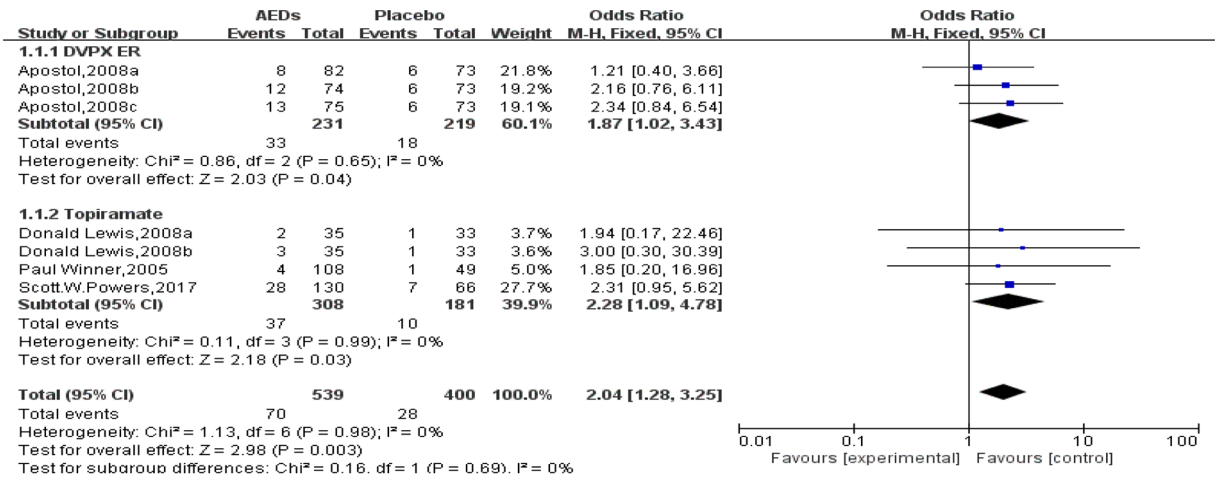

Figure 7 Comparison of withdrawals for any reason between antiepileptics and placebo groups.

antiepileptic drugs to prevent migraine in children and adolescents. Overall, 7 published RCTs with 794 participants comparing antiepileptics with placebo were identified.

As high-quality clinical trials were an essential part of the evidence base for treatment of migraine. In 2018, the IHS published guidelines for controlled trials of preventive treatment of chronic migraine in adults (24). Then in 2020, the guidelines for episodic migraine in adults were published (25). The first edition of the guidelines for preventive treatment of migraine in children and adolescents was issued in 2019 (26), which should be used in designing and conducting clinical trials of preventive treatments in pediatric migraine. Following the guidelines, we noticed one research by Lakshmi *et al.* (27) which was included in our study at first designed a baseline with medication use prior to randomization to med or placebo. The trial was excluded and all the 7 RCTs included in this study were consistent with the IHS guidelines.

The pooled analysis demonstrated that antiepileptic drugs could significantly reduce the mean migraine days per month compared with placebo. Nevertheless, no significant difference was found in the percentage of children with ≥50% response rate in headache frequency per month between antiepileptic drugs and placebo groups. The subgroup analysis of sample size reported the same pattern

Table 2 Side effects and adverse reactions of topiramate *vs.* placebo

Side effects	Topiramate, no. of events/no. of participants	Placebo, no. of events/no. of participants	Relative risk (95% CI)	Z	P	Heterogeneity		
						Z	df	I^2%
Loss of weight	22/238	2/115	4.65 (1.24–17.51)	2.27	0.02*	0.98	1	0
Paresthesia	66/308	8/181	5.94 (2.78–12.68)	4.61	<0.01**	0.45	3	0
Dizziness	14/200	1/132	5.38 (1.20–24.12)	2.20	0.03*	0.05	2	0
Pharyngitis	16/178	16/115	0.53 (0.25–1.12)	1.67	0.10	0.73	2	0
Fatigue	48/308	20/181	1.37 (0.78–2.41)	1.09	0.28	4.43	3	32
Sinusitis	14/178	8/115	0.94 (0.38–2.35)	0.13	0.90	0.41	2	0
Upper respiratory tract infection	54/308	24/181	1.37 (0.82–2.31)	1.19	0.23	2.81	3	0
Somnolence	11/178	3/115	1.80 (0.53–6.11)	0.94	0.35	0.56	2	0
Influenza-like symptoms	12/178	4/115	1.91 (0.59–6.15)	1.08	0.28	0.39	2	0
Injury	17/308	16/181	0.62 (0.31–1.26)	1.31	0.19	5.26	3	43
Abdominal pain	19/178	12/115	1.02 (0.47–2.19)	0.04	0.97	0.59	2	0
Fever	10/178	2/115	2.36 (0.65–8.51)	1.31	0.19	0.87	2	0
Anorexia	26/199	9/136	2.12 (0.94–4.75)	1.82	0.07	0.60	3	0
Nausea	11/178	7/115	1.05 (0.39–2.81)	0.09	0.93	0.17	2	0
Total			1.55 (1.25–1.91)	4.04	P<0.0001***	51.60	43	17

*P<0.05, **P<0.01, ***P<0.001.

of results. The subgroup analysis based on drug types demonstrated that topiramate rather than DVPX ER could significantly remit the monthly migraine days compared to placebo. Both topiramate and DVPX ER failed to improve the ≥50% reduction rate in monthly headache days compared with placebo.

Migraine and epilepsy both are episodic neurological disorders with episodic manifestations. They might share the similar pathologic feature of neuronal hyperexcitability. Higher concentration of extracellular glutamate (the main excitatory neurotransmitter) leads in Cortical Spreading Depression and convulsions. So that AEDs are commonly used for migraine prophylaxis in both adult and children. In 2014, topiramate, a neuromodulator, became the first medication approved by the US Food and Drug Administration (FDA) to prevent migraine in adolescents 12–18 years old (28). Divalproex sodium has been proved to be effective in both prophylactic and acute treatment of migraine in adults. One daily dose of the extended-release (ER) formulation of DVPX sodium has also been approved by the US FDA for migraine prevention in patients >18 years old.

Although our results showed that antiepileptics significantly reduced monthly migraine days, further research revealed that only topiramate could reduce migraine frequency per month, which was consistent with our previous work (29) and the practice guidelines published by American Academy of Neurology and the American Headache Society in 2019 (12). However, the practice guidelines included the trial of Lakshmi *et al.* which was without a true baseline. Although the efficacy of topiramate for preventing migraine in adults has been proved (30-32), evidence of topiramate for migraine prevention in children and adolescents was insufficient. Several randomized, double-blind trials reporting the clinical effect of topiramate for pediatric migraine prophylaxis yielded discordant results. A meta-analysis (33) demonstrated that topiramate could not reduce the headache frequency or improve the ≥50% response rate in 2017. However, after carefully screening the study, we found there were some defects in the article such as inaccurate data, inclusion of Lakshmi's trial and not all of the topiramate dosages of were included.

Table 3 Side effects and adverse reactions of Divalproex sodium extended-release (DVPX ER) *vs.* placebo

Side effects	DVPX ER, no. of events/no. of participants	Placebo, no. of events/no. of participants	Relative risk (95% CI)	Z	P	Heterogeneity		
						Z	df	I^2%
Ammonia increased	7/231	0/219	5.55 (0.97–31.73)	1.93	0.05	0.27	2	0
Weight gain	11/231	8/219a	3.58 (0.98–13.00)	1.94	0.05	0.98	2	0
Nausea	18/231	9/219	1.98 (0.87–4.50)	1.63	0.10	0.20	2	0
Abdominal pain	10/231	3/219	3.30 (0.90–12.09)	1.81	0.07	1.22	2	0
Fatigue	8/231	12/219	0.62 (0.25–1.56)	1.01	0.31	3.37	2	0
Upper respiratory tract infection	19/231	15/219	1.20 (0.59–2.43)	0.51	0.61	2.80	2	0
Nasopharyngitis	13/231	18/219	0.67 (0.32–1.39)	1.08	0.28	0.36	2	0
Somnolence	10/231	3/219	3.28 (0.89–12.06)	1.79	0.07	0.31	2	0
Gastroenteritis viral	9/231	3/219	2.90 (0.77–10.87)	1.58	0.11	0.71	2	0
Influenza	9/231	15/219	0.56 (0.24–1.30)	1.35	0.18	1.93	2	0
Vomiting	9/231	3/219	2.94 (0.79–10.98)	1.60	0.11	0.25	2	0
Cough	7/231	9/219	0.74 (0.27–2.01)	0.59	0.55	1.25	2	0
Pharyngolaryngeal pain	7/231	9/219	2.94 (0.79–10.98)	1.60	0.11	0.25	2	0
Viral infection	7/231	6/219	1.10 (0.38–3.19)	0.17	0.86	1.81	2	0
Total			1.27 (0.99–1.64)	1.88	0.06	38.30	47	30

We revised the data and proved the efficiency of topiramate to prevent pediatric migraine.

Several RCTs revealed that DVPX significantly remitted the monthly headache frequency and improved the response rate in adults (16,34-36); however, evidence for DVPX in prophylaxis of pediatric migraine is very rare. Klapper *et al.* (34) has proved that DVPX ER (1,000 mg/d) was effective for migraine without aura in adults. In this study, significant difference was found in migraine frequency and response rate in neither of the dosages of DVPX ER (250, 500 and 1,000 mg/d) compared with placebo.

DVPX ER and topiramate were well tolerated in most of the included studies; however, our study revealed that more patients withdrew from studies and experienced side effects in the DVPX and topiramate groups than in the placebo group. Studies (37-39) have reported many side effects of antiepileptics including DVPX and topiramate. Most adverse events were mild to moderate but some were serious or fatal. In 2008, the US FDA reported that all antiepileptic drugs were related to increased risks of suicidal ideation and behaviors. Furthermore, topiramate was believed to be associated with psychiatric side effects such as depression and anxiety (39). All the 4 studies with topiramate reported higher rates of side effects in the treatment group than the placebo group. Upper respiratory tract infection, weight loss, paresthesia, abdominal pain, fatigue, anorexia, somnolence, and cognitive disorders were the most common side effects in the topiramate group, which was in accordance with the previous studies in adults. Five out of 329 patients experienced serious adverse events related to topiramate (2 infections, 2 suicidal attempts, and 1 severe headache). Unlike topiramate, DVPX was related to the adverse events of weight gain and increased BMI (body mass index). Other reported most common side effects included upper respiratory tract infection, nausea, nasopharyngitis, elevated sex hormone-binding globulin (SHBG) levels and so on. Weight gain tended to increase over time but conversely, nausea relieved over time (40). The risk of suicidal behaviors of DVPX was relatively low compared with topiramate. No severe adverse events were reported in the DVPX group.

Of particular note is that neither topiramate nor DVPX ER

achieved the greater proportion of children and adolescents experiencing a ≥50% reduction in mean migraine days than placebo. One study demonstrated a ≥75% response rate (not a ≥50% response rate) favoring 2–3 mg/kg/d of topiramate compared to placebo (21). One RCT (22) showed that 100 mg/d of topiramate, not 50 mg/d, led to a significantly improved ≥50% response rate. None of the DVPX ER doses demonstrated a significant advantage in improving the ≥50% response rate. Three possible reasons may explain the results. (I) For topiramate, the ≥50% response rate may be related to the dosages, as one study reported that when patients were treated with topiramate of 100 mg/day, rather than 50 mg/day, the ≥50% response rate significantly improved (22). (II) The FDA approved topiramate for children and adolescents 12–18 years old, but age of the children in our included studies ranged from 8–17 years. It can be challenging for young patients to describe the exact times of headache attacks. Atypical symptoms of pediatric migraine such as episodic dizziness, abdominal pain, and ophthalmodynia can be easily ignored by their guardians. (III) The placebo response rate of children was higher than adults. Compared with the placebo effects approximately 35% in adult patients with migraine, the placebo effects of children with headache could reach as high as 50% or more (41). In this study, the pooled placebo response rate was 48.43%, with the ≥50% response rate of 52.42%. The placebo response rates in topiramate and DVPX ER groups were 50.50% and 46.48%, with the ≥50% response rate of 59.27% and 42.54% respectively. The differences between positive drugs and placebo were too small to illustrate the significance. The reasons for the higher placebo response rate (42) in children included that they could not take medicine on time at school; they more readily believed the efficacy of drugs when the symptoms were relieved, and "good doctor" effects.

Several RCTs appraised the efficacy of AEDs compared with other drugs. One RCT found cinnarizine significantly reduced headache frequency *vs.* topiramate (43). One included RCT (20) found there was no difference between topiramate and amitriptyline. Fallah *et al.* (44) reported that compared with propranolol, 50 mg/day of topiramate significantly decreased the mean headache days per month among children and adolescents. One RCT (45) that measured the efficacy of sodium valproate *vs.* propranolol found that propranolol significantly decreased monthly migraine days *vs.* sodium valproate.

Several limitations of this study must be addressed. First, the evidence was limited because only 4 studies containing 7 clinical trials were eligible for this meta-analysis. Second, migraine often had a long course and symptoms tended to recur. So the duration of treatment may not have been long enough in the included studies. Third, we only measured monthly migraine days and ≥50% response rates in our study. More indexes such as headache intensity, acute medication use times, and other factors should be measured for a comprehensive evaluation. The outcomes of the ≥50% response rate showed obvious heterogeneity in this analysis (I^2=71% and 59%, respectively). The heterogeneity was significant in the topiramate group. However, only 4 trials were included and none of the variables could account for the variation.

Conclusions

In conclusions, topiramate (2–3 mg/kg/d and 50, 100 mg/d) could reduce monthly headache days in children and adolescents with migraine. However, it failed to improve the ≥50% response rate. DVPX ER (250, 500 and 1,000 mg/d) showed no difference from placebo in the prophylactic treatment pediatric migraine. Side effects seemed to be more frequent in topiramate and DVPX ER treated children but generally well-tolerated. Our study could provide evidence for the prevention of pediatric migraine for pediatricians and neurologists.

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Footnote

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