Review Article

Efficacy of prophylactic sodium valproate in pediatric migraines: a systematic review of randomized clinical studies

Ghida Askar[1], Omar Askar[2], Maryam Altuhafy[1], Ravleen Nagi[1,2], Junad Khan[1]

[1]Eastman Institute for Oral Health, Center of Orofacial Pain and Temporomandibular Joint Disorders, Rochester, NY, USA; [2]Beirut Arab University – Beirut Campus, Tarik El Jadida, Beirut, Lebanon

Contributions: (I) Conception and design: G Askar; (II) Administrative support: O Askar; (III) Provision of study materials or patients: G Askar; (IV) Collection and assembly of data: R Nagi; (V) Data analysis and interpretation: J Khan, M Altuhafy; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Junad Khan, DDS, MSD, MPH, PhD. Assistant Professor, Program Director, Eastman Institute for Oral Health, Center of Orofacial Pain and Temporomandibular Joint Disorders, 625 Elmwood Ave., Rochester, NY 14620, USA. Email: Junad_khan@urmc.rochester.edu.

Background: Migraine is a neurological disorder that is chronic and presents with episodes of paroxysmal features consisting of multiphase attacks of head pain, along with other symptoms related to neurological dysfunction such as sensitivity to movement, photophobia, phonophobia, nausea, and vomiting. Antiseizure medications are frequently used for the treatment of migraine. Of the antiseizure medications, sodium valproate and topiramate have received approval from the Food and Drug Administration (FDA) to prevent adult migraine. More recently, topiramate gained approval for pediatric migraine, whereas sodium valproate did not. Nevertheless, the off-label utilization of these drugs for pediatric migraine is widespread. The objective of this review is to assess the prophylactic efficacy of sodium valproate in the management of pediatric migraines.

Methods: The protocol of this study was registered with PROSPERO (CRD42023454491). Therefore, this systematic review aims to assess the efficacy of sodium valproate as a prophylaxis treatment for pediatric migraine. A comprehensive unrestricted search of indexed databases, including PubMed, Embase, Web of Science, and Cochrane, was conducted without any restrictions until May 2024.

Results: The review included five randomized controlled trials (RCTs). Among these, two exhibited a generally low risk of bias (RoB), while the remaining RCTs demonstrated a high risk for bias.

Conclusions: The findings from the current evidence suggest no significant differences in the effectiveness of sodium valproate compared to other frequently used medications in preventing pediatric migraine. Subsequent studies should maintain uniformity in their protocol design and introduce blinding methodologies across outcome assessment, participants, and researchers. These strategies hold significant importance in mitigating potential sources of bias.

Keywords: Pediatric; migraine; prophylactic; headaches; pain

Submitted Jul 18, 2024. Accepted for publication Nov 05, 2024. Published online Dec 27, 2024.
doi: 10.21037/tp-24-279
View this article at: https://dx.doi.org/10.21037/tp-24-279

Introduction

Migraine is a prevalent neurological issue that is frequently encountered in primary healthcare. Recent data from the Global Burden Disease study reveal that migraine remains the second most common cause of disability globally and is the primary cause among young women (1). Migraine is a common disorder that affects approximately 18% of women and 6% of men. Chronic migraine, a more severe form of the condition, affects around 2% of the worldwide population. This condition is associated with a significant burden for patients, their families, and society (2).

Migraine is a neurological disorder that is chronic and presents with episodes of paroxysmal features consisting of multiphase attacks of head pain, along with other symptoms related to neurological dysfunction such as sensitivity to movement, photophobia, phonophobia, nausea, and vomiting. The migraine attack is divided into three distinct phases: the premonitory (prodrome) phase, the headache phase, and the postdrome phase, each with unique and often disabling symptoms. Additionally, about 20–25% of individuals with migraine experience a fourth phase known as aura (3).

Migraine is a prevalent condition in the pediatric population, with an estimated overall prevalence of 7.7% (4). The incidence of migraine increases during childhood and adolescence, with rates ranging from 5% among children aged 5 to 10 years to approximately 15% among teenagers (5). Chronic migraine, which is defined as experiencing headaches at least 15 days per month, affects 0.8% to 1.8% of children aged 12 to 17 years (5,6). While both boys and girls are equally affected by migraine in childhood and early adolescence, the prevalence of migraine is higher in girls during late adolescence, with a ratio similar to that seen in adults (4). Migraine can cause significant disability in children and adolescents, leading to school absenteeism, impaired academic performance, and missed extracurricular activities (7).

Primary headaches are diagnosed based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) diagnostic criteria (8). While migraines in adults typically last between 4 to 72 hours, pediatric patients may experience shorter attacks lasting as little as 2 hours (8,9). In contrast to the unilateral location of migraine in adults, more than 80% of children and adolescents with migraine experience bilateral symptoms (9). With the availability of more migraine-specific therapeutic interventions for children, recognizing and diagnosing migraine is becoming increasingly important. For most children, acute migraine treatments, along with behavioral and lifestyle modifications, are effective for preventing headaches and do not necessitate further pharmacologic or biobehavioral preventive treatment (10). However, when headaches occur frequently and with significant severity, resulting in disability related to migraine, additional prevention strategies may be considered.

In the United States, the only Food and Drug Administration (FDA) approved medications for the preventive treatment of migraine are valproate semisodium, topiramate, propranolol, and timolol (11). Sodium valproate is an FDA-approved antiseizure drug used for the prevention of migraine (12). The antimigraine action of sodium valproate in patients has been attributed to various functions. Still, its exact mechanism is not yet fully understood due to the complex nature of migraine pathophysiology and the multiple biochemical effects of the drug migraines (13-15). However, the FDA has not yet approved sodium valproate for pediatric migraines. Therefore, this systematic review aims to assess the efficacy of sodium valproate as a prophylaxis treatment for pediatric migraines. We present this article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-279/rc) (16).

Highlight box

Key findings

- Sodium valproate may be an effective prophylactic measure in managing pediatric migraine.

What is known and what is new?

- The Food and Drug Administration has approved sodium valproate and topiramate for preventing migraines in adults. More recently, topiramate gained approval for pediatric migraines, whereas sodium valproate did not. Nevertheless, the off-label utilization of these drugs for pediatric migraines is widespread.
- The present review indicates sodium valproate may be an effective prophylactic alternative for managing pediatric migraines.

What is the implication, and what should change now?

- The effectiveness of sodium valproate in migraine treatment has shown encouraging outcomes, although these studies have predominantly centered on adult patients rather than pediatric or adolescent populations.
- Future studies should adhere to a consistent protocol framework and implement blinding techniques across outcome evaluation, participants, and researchers. These measures are crucial in reducing potential biases.

Methods

Protocol and registry

The protocol of this study was registered with PROSPERO (CRD42023454491). However, a meta-analysis was not performed due to high heterogeneity in the included studies. An electronic search was conducted of indexed databases PubMed, Embase, Scopus, Web of Science, and Cochrane without time restriction up to May 2024. Two authors screened the titles and abstracts of studies identified

with the abovementioned protocol, and the full texts of relevant studies were read independently. The reference lists of pertinent original studies and review articles were also hand-searched to identify studies that might have been missed in the previous step. Disagreements were resolved through discussion and consultation with a third researcher.

Eligibility criteria

The current systematic review incorporated randomized controlled clinical trials that compared the effectiveness of sodium valproate as a prophylactic treatment for pediatric migraine with other commonly used migraine prophylactic medications. The primary research question aimed to determine the efficacy of sodium valproate as a preventive treatment for pediatric migraine compared to other frequently used drugs for pediatric migraine prevention. This comparison was based on the following Participants-Interventions-Comparisons-Outcome-Study design (PICOS) approach. (P): pediatric and adolescent patients with migraine; (I): sodium valproate; (C): other migraine prophylactic medications; (O): migraine prophylaxis parameters: migraine frequency, intensity, duration, complete cessation of attacks, Pediatric Migraine Disability Assessment (PedMIDAS); (S): randomized controlled clinical trials. The current study excluded case reports, case series, letters to the editor, commentaries, reviews, retrospective, experimental, non-randomized, and cross-sectional studies.

Study selection, data collection, and risk of bias (RoB)

The articles underwent independent review by two investigators (G.A. and O.A.), who screened the titles and abstracts of the identified studies. Any irrelevant articles, duplicates, or studies not addressing the focused question were excluded. In cases of disagreement, the reviewers resolved the issues through mutual discussion. If a consensus could not be reached through discussion, a third reviewer (M.A.) and a fourth reviewer (J.K.) were engaged to provide input. All the information from the included studies was synthesized by tabulating the data according to (I) study design; (II) migraine classification, frequency, intensity, duration, and PedMIDAS score; (III) sodium valproate and control medication dosages, frequency, and route of administration; (IV) duration and interval of the follow-up treatment; and (V) study outcomes of the efficacy of sodium valproate versus other medications on pediatric patients with migraine. Furthermore, a quality assessment was carried out. Two authors (G.A. and O.A.) assessed the RoB in the included studies using the Cochrane Collaboration's RoB tool for randomized controlled trials (RCTs) (17). Any disagreements in the RoB assessment were addressed as stated previously.

Results

Search strategy

An electronic search was performed without time restrictions up to and including May 2024. Search database engines, including PubMed, Embase, Web of Science, and Cochrane, revealed 984 articles. After removing duplicates, 478 studies were left. Additionally, three articles were identified through manual searching of the references in relevant articles and were added for further screening. Following the review of titles and abstracts, 43 articles underwent a comprehensive full-text assessment for eligibility, excluding 38 articles. The current systematic review included five RCTs (*Figure 1*).

General characteristics of included studies

Four RCTs followed a parallel group design (18-21). They consisted of an intervention group receiving sodium valproate and a control group receiving other medications commonly used for pediatric migraine prevention. Among the four RCTs with a parallel group design, three had their control group using propranolol (18-20), while one RCT had its control group utilizing topiramate (21). The fifth RCT (22) included in this systematic review adopted a parallel group design with three groups in a 1:1:1 ratio (22). The intervention group received sodium valproate, and the two control groups received cinnarizine and placebo, respectively.

The included RCTs had a participant range of 63 to 158, and the mean ages of the participants ranged from 5 to 16 years. Both male and female patients were included in all the RCTs. Variability was observed among the included RCTs concerning the allowance of rescue medications during the study period. In this systematic review, two randomized controlled RCTs provided information on the rescue medications permitted for patients (21,22). In contrast, three RCTs did not specify whether patients could use rescue medications during the study (18-20). The studies' duration ranged from 6 weeks to 4 months, as

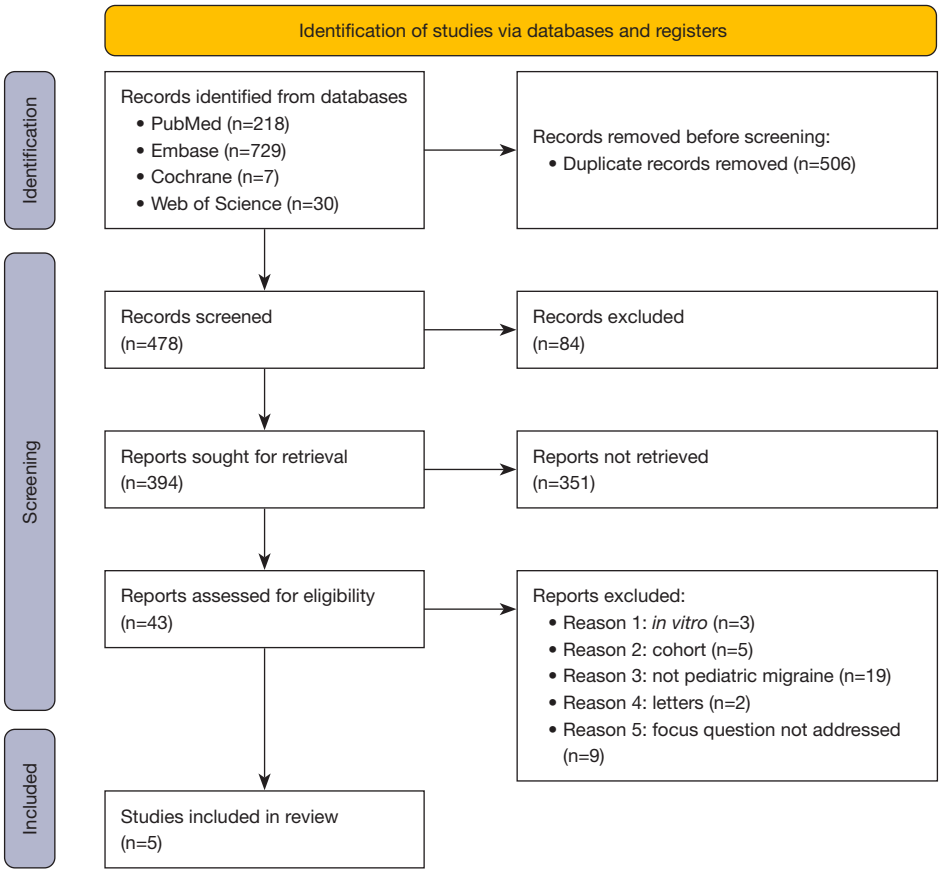

Figure 1 PRISMA flow chart.

reported in all RCTs (18-22) (*Table 1*).

General characteristics of sodium valproate

Among the five RCTs, four specifically enrolled patients diagnosed with pediatric migraine without aura (18-21). However, in one of the randomized RCTs, the patient cohort consisted of individuals diagnosed with pediatric migraine, encompassing both those with and without aura (22). Four of the five RCTs in the review provided data on migraine frequency and standard deviation before treatment (18,20-22). At the same time, one RCT did not report this information (19). Regarding migraine intensity, two RCTs reported it (21,22), while the remaining three RCTs did not include this data. Additionally, only one RCT presented the duration of migraine attacks along with the standard deviation and the PedMIDAS score (21). The medications were administered orally in this systematic review's RCTs (18-22). Moreover, all RCTs provided information on the dosage of the drugs; however, there were variations in the dosages among the studies. Amanat *et al.* administered sodium valproate at 15 mg/kg/day, divided equally into two daily doses (22). For patients aged between 6 and 12 years, cinnarizine was given at a daily dose of 37.5 mg divided into two equal doses per day. For patients between 12 and 17 years, the daily dose of cinnarizine was 50 mg, similarly administered in two equally divided daily doses. Gajbhiye *et al.* (20) and Ashrafi *et al.* (18) employed comparable dosages in their studies for sodium valproate, starting at 10 mg/kg/day and gradually escalating to 40 mg/kg/day (18,20). The administration was divided into two equally divided doses per day. Moreover, both studies employed propranolol in the control group, with a dosage range of 1–3 mg/kg/day, also given in two equally divided daily doses. On the other hand, Yadav *et al.* employed a dosage range of 10–20 mg/kg/day for sodium valproate and 1–2 mg/kg/day for topiramate (21). However, the frequency of medication administration was not specified in their study. Bidabadi *et al.* administered sodium valproate at a dosage of 15 mg/kg/day and propranolol at a dosage of

Table 1 Characteristics of included studies

Author, year	Study design	Country	No. of participants†	No. of parallel groups	Age (years), mean/range ± SD	Male/female, n	Rescue medication, n	Study duration
Amanat *et al.*, 2020 (22)	Double blind RCT	Iran	Total: n=158 [149]	Three parallel groups in a 1:1:1 ratio (SV, CN, P)				12 weeks
			SV: n=53 [51]		SV: 11.2±2.9	SV: 33/20	SV: none, 1; analgesics, 31; triptan, 16; ergotamine, 1; combination, 4	
			P: n=52 [49]		P: 11.2±3.1	P: 27/25	P: none, 5; analgesics, 26; triptan, 17; ergotamine, 1; combination: 3	
			CN: n=53 [49]		CN: 10.4±2.8	CN: 30/23	CN: none, 3; analgesics, 22; triptan, 18; ergotamine, 4; combination, 6	
Yadav *et al.*, 2017 (21)	Prospective, double-blind RCT	India	Total: n=88 [82]	Two parallel groups in a 1:1 ratio (SV, T)			NR (analgesics were allowed as abortive treatment)	12 weeks
			SV: n=40		SV: 10.9±3.02	SV: 18/22		
			T: n=42		T: 11±2.87	T: 20/22		
Gajbhiye *et al.*, 2021 (20)	RCT	India	Total: n=100	Two parallel groups in a 1:1 ratio (SV, PL)			NR	6 weeks
			SV: n=50		SV: 5–16±NR	SV: 28/22		
			PL: n=50		PL: 5–16±NR	PL: 28/22		
Bidabadi *et al.*, 2010 (19)	Double blind RCT	Iran	Total: n=63 [60]	Two parallel groups in a 1:1 ratio (SV, PL)			NR	4 months
			SV: n=31 [30]		SV: 9.93±2.57	SV: 21/9		
			PL: n=32 [30]		PL: 9.79±2.80	PL: 19/11		
Ashrafi *et al.*, 2005 (18)	RCT	Iran	Total: n=120 [115]	Two parallel groups in a 1:1 ratio (SV, PL)			NR	3 months
			SV: n=60 [57]		SV: 10±2.3	SV: 36/21		
			PL: n=60 [58]		PL: 9.7±2.7	PL: 40/18		

†, data are presented as No. of participants at recruitment [No. of participants that completed the study]. RCT, randomized controlled trial; SD, standard deviation; SV, sodium valproate; P, placebo; CN, cinnarizine; T, topiramate; NR, not reported; PL, propranolol.

2 mg/kg/day in children weighing less than 35 kg, with both medications given in two equally divided doses per day (19) (*Table 2*).

General characteristics of outcome variables

All RCTs in this study used assessments by patients' parents to evaluate the outcomes. The RCTs had variations in the specific aspects they measured. In all the included RCTs, migraine frequency was evaluated as one of the parameters (18-22). Among these RCTs, four also measured migraine duration (18-21). Three RCTs (18-20) assessed migraine severity (18-20). Amanat *et al.* (22) and Yadav *et al.* (21) examined migraine intensity and the rate of patients who experienced a 50% reduction in symptoms using the PedMIDAS score. Additionally, Bidabadi *et al.* evaluated complete cessation of migraine attacks (19), while Ashrafi *et al.* reported the response to rescue medication (18).

The included RCTs displayed variation in the timing of their follow-up intervals. In Amanat *et al.*'s study, patients were monitored 1, 4, 8, and 12 weeks after receiving the medication (22). Yadav *et al.* conducted follow-ups at 4-, 8-, and 12-week marks after medication administration (21). Bidabadi *et al.* conducted monthly follow-ups for 4 months post-medication (19). Ashrafi *et al.* performed two follow-ups, one at 4 weeks and another at 3 months post-medication (18). However, Gajbhiye *et al.* did not specify the intervals they used for following up with patients to evaluate outcome measures (20). Only three of the RCTs included provided information about the rate

at which patients discontinued their participation in the studies, specifically Amanat *et al.* (22) recorded a dropout rate of 5% (22), Bidabadi *et al.* noted a dropout rate of 4.7% (19), and Ashrafi *et al.* observed a dropout rate of 4.1% (18). However, Yadav *et al.* and Gajbhiye *et al.* did not present data on patient dropout rates in their respective studies (20,21).

All the RCTs consistently reported that there were no statistically significant differences in the effectiveness of sodium valproate as a prophylactic treatment for pediatric migraine compared to other medications. Amanat *et al.* reported no notable statistical distinction between sodium valproate and cinnarizine when employed as prophylaxis for pediatric migraine (22). They concluded sodium valproate might be an effective preventive measure for migraine in children and adolescents. Similarly, Yadav *et al.* found no significant difference in efficacy between sodium valproate and topiramate as prophylactic treatments for pediatric migraine (21). They concluded that sodium valproate effectively prevents migraine headaches in this age group. Gajbhiye *et al.*, did not provide specific p-values or detailed statistical analyses for migraine severity and duration (20). Still, they did report no statistically significant difference in migraine frequency between sodium valproate and propranolol for pediatric migraine prevention. They concluded sodium valproate exhibited greater efficacy and safety in migraine prevention than propranolol. Bidabadi *et al.* reported no statistically significant difference between sodium valproate and propranolol in terms of their effectiveness for pediatric migraine prevention according to IHS criteria (19). Lastly, Ashrafi *et al.* reported sodium valproate and propranolol significantly improved headache frequency, severity, duration, and response to rescue medication (18). They concluded that there were no statistically significant differences between the two treatments. All these RCTs collectively suggest that sodium valproate holds promise as an effective prophylactic treatment for pediatric migraine, with no significant differences observed compared to other commonly used medications (18-22) (*Table 3*).

RoB within studies

Among the five RCTs incorporated into this study, two of them exhibited a generally low RoB (19,22). In contrast, the remaining RCTs (18,20,21) demonstrated a high risk for bias (18,20,21) (*Table 4*, *Figures 2,3*).

Discussion

On a global scale, migraine is the second leading contributor to the loss of disability-adjusted life-years (DALYs) due to neurological conditions, accounting for 16.3% of the DALYs attributed to such disorders (23). The prevalence of migraine, standardized for age on a global level, saw an increase of 1.7% (ranging from 0.7% to 2.8%) between 1990 and 2019. In 2019, there were an estimated 1.1 billion prevalent cases of migraine (with a range of 0.98 to 1.3 billion) and a calculated 525.5 years lived with disability (YLDs) per 100,000 population (24). In the United States, individuals afflicted by migraine bore a significantly more significant economic burden compared to those without the condition (25). Among both males and females, the age bracket of 10 to 14 years witnessed the highest occurrence rate and the most significant count of newly occurring cases of migraine (24). In the year 2019, although the count of YLDs began to rise from birth, it reached its highest point within the 30 to 34 years age categories, subsequently showing a gradual decrease for both genders (24). In the context of pharmacotherapy, the available treatment choices for children and adolescents have primarily relied on findings from studies conducted on adults. Out of the antiseizure medications, only sodium valproate and topiramate have received approval from the FDA for preventing adult migraine. More recently, topiramate gained approval for pediatric migraine, whereas sodium valproate did not. Nevertheless, the off-label utilization of these drugs for pediatric migraine is widespread (26).

Earlier research assessing the effectiveness of sodium valproate in migraine treatment has shown encouraging outcomes, although these studies have predominantly centered on adult patients rather than pediatric or adolescent populations. Hering and Kuritzky reported sodium valproate effectively prevented migraine or reduced their frequency, severity, and duration in 86.2% of patients during 8 weeks (27). Mathew *et al.* reported that 48% of individuals treated with divalproex experienced a 50% or more reduction in migraine frequency compared to their baseline over a 12-week duration (28). Furthermore, Shaygannejad *et al.* indicated treatment with sodium valproate significantly reduced migraine duration, monthly frequency, and intensity after 8 weeks (29). Takeshima *et al.* reported that the efficacy of sodium valproate was measured at 59.7% 2 months after the commencement of treatment (30).

All RCTs in this review have concluded that sodium

Table 2 Characteristics of sodium valproate

Author, year	Migraine classification	Migraine type, n	Migraine frequency, mean ± SD	Migraine intensity, mean ± SD	Duration of episode (hours), mean ± SD	PedMIDAS, mean ± SD	Intervention	Control	Phases			Route	Dosage	Medication frequency
									1	2	3			
Amanat *et al.*, 2020 (22)	Pediatric migraine IHS	W/o aura: SV: 8; CN: 12; P: 14	SV: 12.1±5.0	SV: 6.2±2.2	NR	NR	SV	CN	2 weeks of physical and neurological screening	4 weeks migraine baseline recording	Medication	Oral	SV: 15 mg/kg/day	SV: 2 doses/day
		W/o aura: SV: 45; CN: 41; P: 38	CN: 11.1±5.4	CN: 7.0±1.8				P					CN: 37.5 mg/day (ages 6–12 years); 50 mg/day (12–17 years)	CN: 2 doses/day
			P: 10.7±4.7	P: 6.3±1.9									P: N/A	P: N/A
Yadav *et al.*, 2017 (21)	Pediatric migraine w/o aura IHS	W/o aura: SV: 40; T: 42	SV: 6.87±1.45	SV: 2.15±0.76	SV: 6.95±1.85	SV: 45.62±12.48	SV	T	4 weeks baseline phase	12 weeks of treatment	N/A	Oral	SV: 10–20 mg/kg/day	NR
			T: 7.04±1.49	T: 2.3±0.81	T: 6.6±2.5	T: 45.59±12.99							T: 1–2 m g/kg/day	
Gajbhiye *et al.*, 2021 (20)	Pediatric migraine w/o aura IHS	W/o aura: SV: 50; PL: 50	SV: 8±NR	NR	NR	NR	SV	PL	N/A	N/A	N/A	Oral	SV: 10 mg/kg/day increased up to 40 mg/kg/day	SV: 2 doses/day
			PL: 8.2±NR										PL: 1–3 mg/kg/day	PL: 2 doses/day
Bidabadi *et al.*, 2010 (19)	Pediatric migraine w/o aura	W/o aura: SV: 30; PL: 30	NR	NR	NR	NR	SV	PL	N/A	N/A	N/A	Oral	SV: 15 mg/kg/day	SV: 2 doses/day
													PL: 2 mg/kg/day (in children who weighed <35 kg)	PL: 2 doses/day
Ashrafi *et al.*, 2005 (18)	Pediatric migraine w/o aura	W/o aura: SV: 60; PL: 60	SV: 7.8±NR	NR	NR	NR	SV	PL	4 weeks baseline recording	Medication Administration for 4 weeks of titration and adjustment	fixed-dose reached (2 months)	Oral	SV: 10 mg/kg/day slowly titrated up to 40 mg/kg/day	SV: 2 doses/day
			PL: 7.9±NR										PL: 1–3 mg/kg/day	PL: 2 doses/day

PedMIDAS, Pediatric Migraine Disability Assessment; SD, standard deviation; IHS, International Headache Society; w/o, without; SV, sodium valproate; CN, cinnarizine; P, placebo; NR, not reported; N/A, not available; T, topiramate; PL, propranolol.

Table 3 Study outcomes

Author, year	Who assessed study outcomes	Interval of follow-ups	Adverse events [n]	Dropout rate	Parameters assessed	Statistical group comparisons		Outcome
						Comparison	P value	
Amanat *et al.*, 2020 (22)	The patient's parents	1, 4, 8, and 12 weeks after phase 3	SV: sedation [2]; nausea/vomiting [1]; anorexia [1]; dizziness [1]	6% (9/158)	Migraine frequency	SV *vs.* CN	>0.05	Sodium valproate may be effective as a preventive treatment for migraine in children and adolescents
						SV *vs.* P	<0.05	
						CN *vs.* P	<0.05	
			CN: sedation [2]; tremor [1]		Migraine intensity	SV *vs.* CN	>0.05	
						SV *vs.* P	<0.05	
						CN *vs.* P	<0.05	
			P: nausea/vomiting [1]		>50% responder rate	SV *vs.* CN	>0.05	
Yadav *et al.*, 2017 (21)	The patient's parents	At 4, 8, and 12 weeks	SV: mild somnolence [2]; weight gain [3]; abdominal pain [1]	NR	Migraine frequency	SV *vs.* baseline	<0.05	Sodium valproate demonstrated efficacy in the prevention of migraine headaches in children and adolescents
						T *vs.* baseline	<0.05	
						SV *vs.* T	>0.05	
			T: mild appetite loss [2]; weight loss [2]; fatigue [1]		Migraine intensity	SV *vs.* baseline	<0.05	
						T *vs.* baseline	<0.05	
						SV *vs.* T	>0.05	
					Migraine duration	SV *vs.* baseline	<0.05	
						T *vs.* baseline	<0.05	
						SV *vs.* T	>0.05	
					>50% responder rate	SV *vs.* baseline	<0.05	
						T *vs.* baseline	<0.05	
					PedMIDAS score	SV *vs.* baseline	<0.05	
						T *vs.* baseline	<0.05	
Gajbhiye *et al.*, 2021 (20)	The patient's parents	NR	NR	NR	Migraine frequency	SV *vs.* baseline	<0.05	Sodium valproate is statistically more productive and safer in migraine prophylaxis as compared with propranolol
						PL *vs.* baseline	<0.05	
						SV *vs.* PL	>0.05	
					Migraine severity	NR	NR	
					Migraine duration	NR	NR	
Bidabadi *et al.*, 2010 (19)	The patient's parents	Monthly	SV: abdominal pain [7]; mild drowsiness [3]; mild weight gain [1]	4.8% (3/63)	Migraine frequency	SV *vs.* PL	<0.05	Both sodium valproate and propranolol are adequate for the prophylaxis of pediatric migraine defined by IHS
			PL: transient vertigo [1]; mild insomnia [2]		Migraine duration	SV *vs.* PL	>0.05	
					Migraine severity	SV *vs.* PL	>0.05	
					Complete cessation of migraine attacks	SV *vs.* PL	>0.05	

Table 3 (*continued*)

Table 3 (*continued*)

Author, year	Who assessed study outcomes	Interval of follow-ups	Adverse events [n]	Dropout rate	Parameters assessed	Statistical group comparisons		Outcome
						Comparison	P value	
Ashrafi *et al.*, 2005 (18)	The patient's parents	4 weeks and 3 months	NR	4.2% (5/120)	Migraine frequency	SV *vs.* baseline	<0.05	Both sodium valproate and propranolol have shown significant improvement in the frequency, severity, and duration of headaches, as well as better response to rescue medications
						PL *vs.* baseline	<0.05	
					Migraine severity	SV *vs.* baseline	<0.05	
						PL *vs.* baseline	<0.05	
						SV *vs.* PL	>0.05	
					Migraine duration	SV *vs.* baseline	<0.05	
						PL *vs.* baseline	<0.05	
						SV *vs.* PL	>0.05	
					Response to rescue medication	SV *vs.* baseline	<0.05	
						PL *vs.* baseline	<0.05	
						SV *vs.* PL	>0.05	

SD, standard deviation; SV, sodium valproate; CN, cinnarizine; P, placebo; T, topiramate; NR, not reported; PL, propranolol; IHS, International Headache Society; PedMIDAS, Pediatric Migraine Disability Assessment.

Table 4 Cochrane Collaboration's tool for assessing RoB

Domain	Amanat *et al.*, 2020	Yadav *et al.*, 2017	Gajbhiye *et al.*, 2021	Bidabadi *et al.*, 2010	Ashrafi *et al.*, 2005
Random sequence generation	Low	Unclear	Unclear	Unclear	Unclear
Allocation concealment	Low	Unclear	Unclear	Low	Unclear
Blinding of participants and researchers	Low	Low	High	Low	High
Blinding of outcome assessment	Low	Unclear	Low	Low	High
Incomplete outcome data	Low	Low	Unclear	Low	High
Selective outcome reporting	Low	Unclear	Unclear	Low	High
Other bias	Low	Unclear	Unclear	Low	Unclear
Overall	Low	High	High	Low	High

RoB, risk of bias.

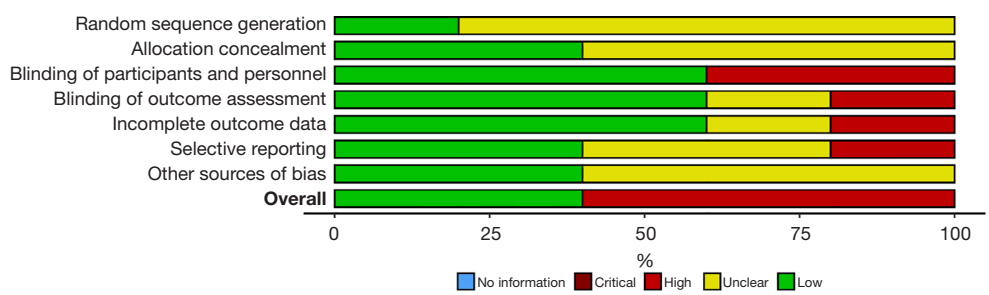

Figure 2 RoB of included studies. RoB, risk of bias.

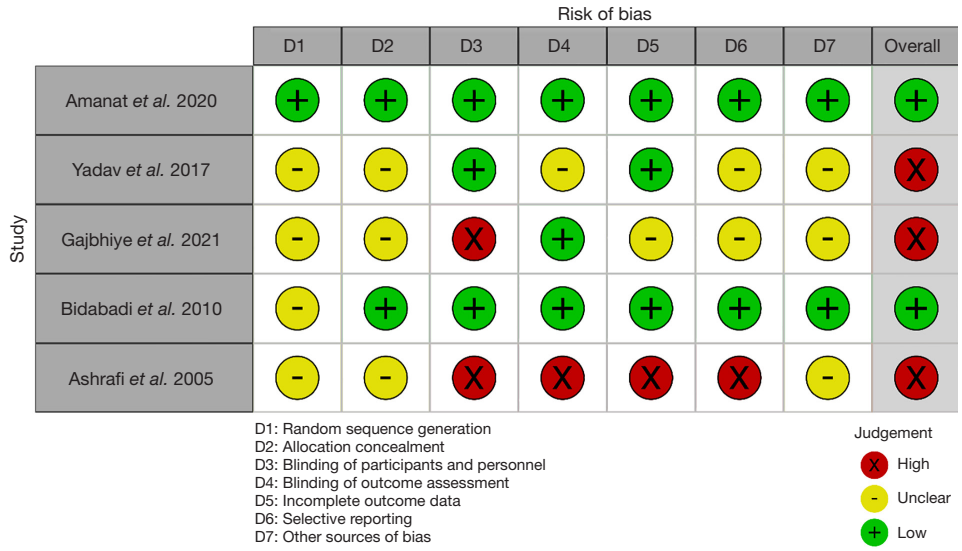

Figure 3 Traffic plot (RoB). RoB, risk of bias.

valproate is an effective preventive treatment for pediatric migraine (18-22). Nevertheless, there exists a disparity in the criteria employed to evaluate sodium valproate's effectiveness. Due to the participants' age range, spanning from 5 to 16 years, the parents reported a subjective assessment of study outcome parameters. Furthermore, variability was observed in the dosage and frequency of sodium valproate administration. This is due to the absence of a definitive consensus on the most effective dosage. Gajbhiye *et al.* (20) and Ashrafi *et al.* (18) initiated sodium valproate at 10 mg/kg/day and gradually increased it to 40 mg/kg/day (18,20). Conversely, Amanat *et al.* (22) and Bidabadi *et al.* (19) reported utilizing a 15 mg/kg/day dosage, while Yadav *et al.* (21) adopted a dosage of 10 mg/kg/day. Amanat *et al.* included patients diagnosed with pediatric migraine, with and without aura (22), whereas the remaining RCTs enrolled patients diagnosed with pediatric migraine without aura (18-21). There were slight variations in the study duration, which was relatively short for an adequate evaluation of migraine prophylactic treatments, ranging from 6 weeks to 4 months—notably, only Amanat *et al.* provided details about the types of rescue medications allowed during the study and reported the number of patients who utilized such rescue medications (22). The remaining RCTs did not disclose whether rescue medications were permitted during their studies or specify the type and frequency of such medications (18-21). This absence of information could potentially introduce bias when assessing the efficacy of sodium valproate as a prophylactic treatment for pediatric migraine.

Yurekli *et al.* investigated the effectiveness of sodium valproate in managing daily headaches; they identified common adverse effects such as drowsiness, tremors, impotence, and hair loss (31). Amanat *et al.* reported that sodium valproate was linked to adverse events like sedation, nausea/vomiting, anorexia, and dizziness (22). In the study by Yadav *et al.* mild tiredness, weight gain, and abdominal pain were reported as side effects associated with sodium valproate (21). Bidabadi *et al.* reported abdominal pain, slight drowsiness, and minor weight gain as possible side effects (19). However, Gajbhiye *et al.* and Ashrafi *et al.* did not provide information about the associated side effects of sodium valproate (18,20).

In children and adolescents, primary headache disorders, mainly migraine, have been reported to be associated with several comorbid conditions that include psychiatric and neurological comorbidities (32). Literature reports have revealed the association of an emotional component with headache, a bidirectional relationship between psychological comorbidities and migraine, and these psychological factors have a contributory role in headache persistence or reactivity (33). Studies have found an increased risk of anxiety disorder in children and adolescents with migraine, and anxiety could predict the persistence of migraine and headache-related disability (32,33). Pastorino *et al.*, in a cross-sectional observational study, reported the bidirectional link between migraine and epilepsy in

children, as both these conditions share common substrates, such as alterations in neuronal transmission or genetic basis, and have similar triggers comprising sleep deprivation, stress, and bright flashing lights. The prevalence of depressive symptoms was observed to be higher in pediatric patients with comorbid headache and epilepsy compared to epilepsy alone (33). Furthermore, there is evidence that sleep deprivation in children could result in the onset of headache and nocturnal migraine attacks (32). Therefore, it is essential to recognize the presence of comorbid conditions in children with of migraines to develop more effective treatment strategies. In addition, it could contribute to better treatment outcomes and improve the patient's overall well-being and quality of life. However, the relationship between migraine, depression, epilepsy, and other comorbid conditions, such as sleep disorders in the pediatric population, needs to be further investigated.

This study has certain limitations. The findings are derived from a limited number of clinical trials (five RCTs), each with a relatively small sample size ranging from 63 to 158 patients. This limited scope reduces the applicability of the study's outcomes to a broader population. Furthermore, only two RCTs within this study were assessed as having a low RoB (19,22), while the other three RCTs were identified as having a high RoB (18,20,21). The primary sources of bias stemmed from inadequate reporting related to participant randomization across different study groups, the concealment of allocation to various study groups, lack of blinding in outcome assessment, and selective reporting of outcome results. The heightened RoB across the included RCTs makes it challenging to place complete confidence in the conclusions drawn from this systematic review. Lastly, all the RCTs incorporated participants diagnosed with pediatric migraine without an aura, except for the study conducted by Amanat *et al.*, which included patients with pediatric migraine both with and without an aura, introducing heterogeneity in this systematic review.

Conclusions

Based on the findings derived from the RCTs included in this study, it can be concluded that sodium valproate may serve as an effective prophylactic measure for treating pediatric migraine. Notably, no significant differences were identified compared to other frequently employed medications. Sodium valproate was shown to significantly enhance various migraine-related aspects, including frequency, intensity, severity, duration, and response to rescue medication. It is essential for future research to incorporate improved methodological standards and ensure uniform treatments in RCTs. This will enable a comprehensive assessment of the effectiveness of sodium valproate in comparison to other commonly prescribed medications for migraine prophylaxis in pediatric patients. Furthermore, future studies should adhere to a consistent protocol framework and implement blinding techniques across outcome evaluation, participants, and researchers. These measures are crucial in reducing potential biases.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-279/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-279/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-279/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and

first among young women: findings from GBD2019. J Headache Pain 2020;21:137.
2. Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev 2017;97:553-622.
3. Dodick DW. Migraine. Lancet 2018;391:1315-30.
4. Abu-Arafeh I, Razak S, Sivaraman B, et al. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 2010;52:1088-97.
5. Victor TW, Hu X, Campbell JC, et al. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia 2010;30:1065-72.
6. Lipton RB, Manack A, Ricci JA, et al. Prevalence and burden of chronic migraine in adolescents: results of the chronic daily headache in adolescents study (C-dAS). Headache 2011;51:693-706.
7. Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: association with school performance. Neurology 2012;79:1881-8.
8. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
9. Hershey AD, Winner P, Kabbouche MA, et al. Use of the ICHD-II criteria in the diagnosis of pediatric migraine. Headache 2005;45:1288-97.
10. Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2019;93:500-9.
11. Lovell BV, Marmura MJ. Valproate semisodium ER for migraine and cluster headache prophylaxis. Expert Opin Drug Metab Toxicol 2010;6:495-504.
12. Khani S, Hejazi SA, Yaghoubi M, et al. Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium valproate therapy in the prevention of migraine headaches: a randomized controlled double-blind trial. J Headache Pain 2021;22:21.
13. Spasić M, Živković M, Lukić S. Prophylactic treatment of migraine by valproate. Med Biol 2003;10:106-10.
14. Sprenger T, Viana M, Tassorelli C. Current Prophylactic Medications for Migraine and Their Potential Mechanisms of Action. Neurotherapeutics 2018;15:313-23.
15. Cutrer FM, Limmroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. Cephalalgia 1997;17:93-100.
16. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2016;354:i4086.
17. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
18. Ashrafi MR, Shabanian R, Zamani GR, et al. Sodium Valproate versus Propranolol in paediatric migraine prophylaxis. Eur J Paediatr Neurol 2005;9:333-8.
19. Bidabadi E, Mashouf M. A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatr Drugs 2010;12:269-75.
20. Gajbhiye V, Yashwant RL, Quazi S. Comparing efficacy and safety of sodium valproate with propranolol in paediatric migraine prophylaxis. International Journal of Research in Pharmaceutical Sciences 2021;12:926-30.
21. Yadav R, Singh TP, Shukla SK. Sodium valproate versus topiramate for prophylaxis of migraine among children and adolescents: A randomised trial. Journal, Indian Academy of Clinical Medicine 2017;18:180-3.
22. Amanat M, Togha M, Agah E, et al. Cinnarizine and sodium valproate as the preventive agents of pediatric migraine: A randomized double-blind placebo-controlled trial. Cephalalgia 2020;40:665-74.
23. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459-80.
24. Safiri S, Pourfathi H, Eagan A, et al. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. Pain 2022;163:e293-309.
25. Bonafede M, Sapra S, Shah N, et al. Direct and Indirect Healthcare Resource Utilization and Costs Among Migraine Patients in the United States. Headache 2018;58:700-14.
26. Huang P, Kuo PH, Lee MT, et al. Age-Dependent Anti-migraine Effects of Valproic Acid and Topiramate in Rats. Front Pharmacol 2018;9:1095.
27. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 1992;12:81-4.
28. Mathew NT, Saper JR, Silberstein SD, et al. Migraine prophylaxis with divalproex. Arch Neurol 1995;52:281-6.
29. Shaygannejad V, Janghorbani M, Ghorbani A, et al. Comparison of the effect of topiramate and sodium valporate in migraine prevention: a randomized blinded

crossover study. Headache 2006;46:642-8.
30. Takeshima T, Nishikawa W, Yoneda H, et al. Efficacy and safety of valproate in a series of Japanese migraine sufferers. Japanese J Headache 2013;39:306-11.
31. Yurekli VA, Akhan G, Kutluhan S, et al. The effect of sodium valproate on chronic daily headache and its subgroups. J Headache Pain 2008;9:37-41.
32. Bellini B, Arruda M, Cescut A, et al. Headache and comorbidity in children and adolescents. J Headache Pain 2013;14:79.
33. Pastorino GMG, Olivieri M, Viggiano A, et al. Depressive symptoms in children and adolescents with epilepsy and primary headache: a cross-sectional observational study. Front Neurol 2024;15:1395003.

Cite this article as: Askar G, Askar O, Altuhafy M, Nagi R, Khan J. Efficacy of prophylactic sodium valproate in pediatric migraines: a systematic review of randomized clinical studies. Transl Pediatr 2024;13(12):2254-2266. doi: 10.21037/tp-24-279