

Topiramate as Migraine Prophylaxis in Pediatric Patients: An Integrated Summary of Randomized Controlled Trials

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Abstract

Background: An integrated analysis of five randomized, placebo-controlled studies in migraine prophylaxis was conducted to assess topiramate's efficacy and safety in pediatric patients.

Methods: Study 1, a pivotal study (50-, 100 mg/day; aged 12-17 years), Study 2 (flexibly-dosed 2-3 mg/kg/day; aged 6-15 years), and Studies 3, 4 and 5 [50-, 100-, 200 mg/day; aged \geq 12 years].

Results: Percent reduction in the average monthly migraine attack rate: Study 1: the 100 mg/day group improved versus placebo (72% versus 44%, $p=0.0164$); Study 2: topiramate was not significantly different from placebo (58% versus 48%); Studies 3, 4 and 5: positive trend in the 100 mg/day group versus placebo (75% versus 37%). \geq 50% reduction responder rate: Study 1 - the 100 mg/day group improved versus placebo (83% versus 45%, [$p=0.0048$]); no significant effect for topiramate versus placebo was seen in either Study 2 (56% versus 49%), or Studies 3, 4 and 5 (69% versus 33%). Most common treatment-emergent adverse events in topiramate group were influenza-like symptoms, language problems and paresthesia.

Conclusion: Overall, topiramate was efficacious for migraine prophylaxis in adolescent patients (12-17 years). The most consistent results were observed with topiramate 100 mg/day dose, which was generally well-tolerated.

Keywords: Children; Efficacy; Migraine; Safety; Topiramate

Abbreviations

AE: Adverse Event; AMPA: α -Amino-3-Hydroxy-5-Methyl-4-Isioxazolepropionic Acid; ANCOVA: Analysis of Covariance; BL: Baseline; BQL: Below the Limit of Quantification; CV: Coefficient of Variance; DB: Double Blind; FDA: Food and Drug Administration; GABA: Gamma-Aminobutyric acid; IHS: International Headache Society; ITT: Intent-to-Treat; SD: Standard Deviation; TPM: Topiramate

Introduction

Migraine is a disabling neurological disorder and may affect school activities and overall functioning in children. Migraine headaches are also associated with the anxiety, sadness and emotional distress in children [1-4]. The main treatment goal for migraine is to reduce frequency, severity and disability. Therefore, development of an effective and safe agent for the prophylaxis of migraine headaches in children is essential for improving the short-term condition and long-term educational and social outlook [5-7].

Several medications are available for the treatment of migraine [8]. Triptans, ergots and analgesics are commonly used acute medications for migraine [9], however, these are associated with medication overdose headaches [10,11]. Also, for triptans, additional issues are patient dissatisfaction with safety, and suboptimal efficacy [12]. Preventive therapy is a crucial component of the management strategy to reduce migraine disability, and is indicated in about a third of patients with migraine. The choice of migraine preventive agent is based on effectiveness, side effect profile, and the comorbidities of the individual patient. Preventive migraine treatments include antiepileptic drugs (valproic acid, gabapentin, topiramate), serotonin antagonists (pizotifen, methysergide), calcium channel blockers (flunarizine, verapamil), tricyclics (amitriptyline) and β -blockers (propranolol, metoprolol, timolol) [8]. US evidence-based guidelines recommend the beta-blockers propranolol, metoprolol and timolol and the AEDs

sodium valproate/divalproex sodium and topiramate as medications with established efficacy in prevention of migraine [13].

Topiramate is approved by the United States Food and Drug Administration (FDA), for use as both monotherapy and adjunctive treatment for partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome (the latter only for adjunctive treatment), in both adults and in children, 2 years of age and older. In the US, topiramate is also approved for migraine prophylaxis in adults and adolescents 12 years of age and older. Topiramate is the first and only FDA-approved medication for use in migraine prophylaxis in patients 12 years and over. Precise mechanisms responsible for its anticonvulsant and migraine prophylaxis effects are unknown. However, preclinical studies have revealed four possible mechanisms, including blockage of sodium channels, enhancing gamma-aminobutyric acid (GABA) induced influx of chloride, and inhibition of kainite/ α -amino-3-hydroxy-5-methyl-4-isioxazolepropionic acid (AMPA) glutamate receptors and carbonic anhydrase enzyme, all of which may contribute to topiramate's efficacy. Topiramate's action on excitatory neurotransmitter receptors and voltage-gated ion channels suggest that topiramate may be an effective compound to reduce the frequency of migraine attacks [14,15].

Until the US FDA approval of topiramate for migraine prophylaxis in adolescents in 2014, there were no drugs approved for the

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prophylaxis of migraine in children and adolescents. The approval was based on five randomized placebo-controlled clinical studies with similar study designs, conducted by Janssen Pharmaceutical, (sponsor), to evaluate the efficacy and safety of topiramate in migraine prophylaxis [1,6,16,17]. However, topiramate dosages and treatment periods differed across studies. Thus, in order to more comprehensively assess the efficacy and safety of topiramate in migraine prophylaxis for children and adolescents, an integrated analysis was conducted that included pooling of efficacy and safety data from pediatric patients (aged 6–17 years) enrolled in these five controlled studies.

Methods

Studies contributing efficacy and safety data

The clinical studies designed to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine in pediatric patients included five phase-3 studies (Study 1: NCT00210535; Study 2: NCT00237302; Study 3: NCT00236561; Study 4: NCT00231595; Study 5: NCT00236509) performed in pediatric patients (6-15 years). Study 1 was a pivotal placebo- controlled fixed-dose study involving pediatric patients aged 12-17 years. The other four studies provided key supportive evidence for the efficacy and safety of topiramate for the prophylaxis of migraine in pediatric patients. Study 2 was a placebo-controlled, flexible dose study that included patients 6-15 years old. Studies 3, 4 and 5 were placebo-controlled, fixed-dose studies that included mostly adults with a small number of pediatric patients aged ≥ 12 years. These three studies had the same design with minor differences in the treatment arms [18] (Table 1).

All five sponsor-conducted double-blind (DB) phase-3 studies of topiramate in migraine prophylaxis are presented in this analysis, including the individual data, from Studies 1 and 2. As studies 3, 4 and 5 were similarly designed and both adult and pediatric populations were enrolled, the pooled pediatric data were included in this review to strengthen the statistical analyses. For all studies, patients were required to meet the International Headache Society (IHS) criteria for migraine headaches for study entry [19] (Table 1).

Efficacy and safety endpoints

Percent reduction and $\geq 50\%$ reduction in the average monthly migraine attack rate from baseline (BL) to the last 12 weeks of the DB phase (based on 48 h rule, which considers a single migraine attack to include all recurrences of migraine symptoms within 48 h of onset) were the primary and key secondary efficacy endpoints (respectively) from the study. Treatment-emergent adverse events (TEAEs) were summarized in this review.

Subgroup analysis

Efficacy endpoints were analyzed by age groups 6 to 11 and 12 to 17 years of age for those studies that also included the younger population.

Pharmacokinetics

Topiramate plasma concentration data obtained from four studies (Studies 1, 3, 4 and 5) were pooled and presented as mean (% coefficient of variation [CV]) concentrations based on age ranges of 12-14 years, 15-17 years, and 18 years and older, at dosages of 50 mg/day, 100 mg/day, and 200 mg/day.

Statistical methods

Intent-to-treat (ITT) analysis set included all randomized patients with baseline and post-baseline migraine data and it was used for efficacy and safety analyses of all studies included in the review. The percent reduction from baseline was analyzed using an analysis of covariance (ANCOVA) model on ranks that include age group (Study 1 only; stratified into 2 groups, aged 12 to 14 and 15 to 17 years), treatment group, and analysis center as factors, and monthly migraine attack rate during the baseline phase as a covariate. Descriptive statistics (n, median, and range), and p-values are presented. The $\geq 50\%$ responder rate was analyzed using the Cochran-Mantel-Haenszel test for pairwise comparisons between topiramate and placebo groups, controlling for analysis center and age group (Study 1 only; stratified into 2 groups, aged 12 to 14 and 15 to 17 years). The difference in percentage of responders between topiramate and placebo groups was estimated and 95% confidence intervals were provided. The p-values were adjusted for multiplicity using Hochberg's procedure to keep the overall α level at 0.05.

Results

Demographics at baseline

Data from 309 patients from Study 1 (N=103; topiramate, n=70), Study 2 (N=157; topiramate, n=108), and Studies 3, 4 and 5 (N=49; topiramate, n=37) were analyzed in this review. Approximately 80% or more of patients across all the treatment groups completed Studies 1 and 2. However, completion rates were higher for topiramate-treated patients (64% to 85% in the 50, 100 and 200 mg/day groups) as compared with placebo-treated patients (42%) in Studies 3, 4, and 5. The majority of patients included in Study 1 and Studies 3, 4 and 5 were girls (Study 1: [61%]; Studies 3/4/5: [71%]) with an approximate mean age of 14 years, while in Study 2 majority of patients were boys (52%) with an approximate mean age of 11 years. No notable baseline

	Study 1	Study 2	Study 3	Study 4	Study 5
NCT No.	NCT00210535	NCT00237302	NCT00231595	NCT00236509	NCT00236561
Participants	103 total, 70 TPM	157 total, 108 TPM	469 total, 354 TPM	468 total, 354 TPM	568 total, 282 TPM
Study Design	Randomized, DB, parallel assignment, placebo-controlled				
Age Range	12-17 years	6-15 years	12-65 years	12-65 years	12-65 years
Enrolment Criteria	IHS Criteria				
Study Duration	DB: 16 weeks	DB: 20 weeks	DB: 26 weeks	DB: 26 weeks	DB: 26 weeks
Study Drug Dose	50 and 100 mg/day or placebo (Fixed dose)	2-3 mg/kg/day, or placebo (Flexible dose)	50, 100, 200 mg/day or placebo (Fixed dose)	50, 100, 200 mg/day or placebo (Fixed dose)	100 and 200 mg/day, or placebo, or propranolol 160 mg/day (Fixed dose)

DB: Double Blind Phase; IHS: International Headache Society; NCT: National Clinical Trials; TPM: Topiramate Note: Study 1 was a pivotal, fixed dose, RCT that evaluated pediatric patients only; Studies 2, and 3/4/5 were supportive because of flexible dose design (Study 2), or inclusion of adults primarily in Studies 3/4/5

Table 1: Study design.

migraine characteristics differences between treatment groups of Study 1 and Study 2 were observed (Table 2). In these 2 studies, the mean (SD) monthly migraine attack rate (48 h rule) ranged from 4.1 (1.3) to 4.2 (1.7) across topiramate groups and 4.1(1.5) to 4.3 (1.4) in the placebo groups. However, in the Studies 3, 4 and 5, the migraine attack rate for the topiramate-treated group was higher than for the placebo group (Table 2).

Extent of exposure

The majority of patients were exposed for at least 106 days in Study 1 and for at least 140 days in Study 2. Overall (“Any TPM” group), the majority of patients received the study drug for ≤ 180 days, although 54% of patients in the 200 mg/day group (Studies 3, 4 and 5) received the study drug for >180 days. Mean concentrations were similar across age groups at the same dosage level (100 mg/day or 200 mg/day). No data available for the 50 mg/day dose level.

Pharmacokinetics

The pooled data from studies 1, 3, 4 and 5 (Table 3) showed

that topiramate plasma concentrations were below the limit of quantification (BQL) at the 50 mg/day dosage in patients aged 12-14 years and 15-17 years. In general, mean concentrations were similar across age groups (12-14 years, 15-17 years, and 18 years and older) at the same dose level (100 mg/day or 200 mg/day). Additionally, mean plasma concentrations tended to increase with increasing topiramate doses. Mean concentrations increased with increasing doses (Table 3).

Efficacy

The median percent reduction in the 100 mg/day dosage group in pivotal Study 1 was significantly different from placebo (p=0.0164). However, 50 mg dosage group of this study did not show significant change as compared with placebo (p=0.798). In supportive studies 3, 4 and 5 that included patients randomized to the 100 mg/day dosage group, the median percent reduction from baseline was generally consistent with the pivotal study 1(72% vs. 75%). Overall, for each supportive study group (Study 2, 3, 4 and 5) median percent reduction in the average monthly migraine attack rate from BL to the last 12

	Study 1		Study 2		Study 3/4/5	
	Placebo (N=33)	TPM (N=70)	Placebo (N=49)	TPM (N=108)	Placebo (N=12)	TPM (N=37)
Sex, n (%)						
Boys	12 (36)	28 (40)	26 (53)	55 (51)	3 (25)	11 (30)
Race, n (%)						
White	29 (88)	59 (84)	43 (88)	78 (72)	9 (75)	34 (92)
Black	4 (12)	7 (10)	5 (10)	28 (26)	2 (17)	2 (5)
Asian	0	0	1 (2)	0	0	0
Other	0	4 (6)	0	2 (2)	1 (8)	1 (3)
Age Category, n (%)						
6-11 years	0	0	31 (63)	59 (55)	0	0
12-17 Years	33 (100)	70 (100)	18 (37)	49 (45)	12 (100)	37 (100)
Mean (SD)	14.4 (1.71)	14.2 (1.6)	10.7 (2.6)	11.3 (2.5)	14.8 (1.9)	14.2 (1.6)
DB baseline weight (kg)						
Mean (SD)	57.5 (11.8)	56.7 (13.4)	46.0 (15.1)	50.6 (24.9)	59.4 (14)	66.1 (16.8)
Monthly migraine attack rate (using 48 h rule)						
Mean (SD)	4.1 (1.5)	4.2 (1.7)	4.3 (1.4)	4.1 (1.3)	3.3 (1.4)	4.2 (1.6)
Monthly migraine day rate						
Mean (SD)	6.1 (3.0)	6.6 (2.9)	5.4 (1.9)	5.3 (1.7)	5.5 (2.5)	7.0 (3.2)
Monthly headache day rate						
Mean (SD)	6.8 (3.1)	7.4 (3.1)	6.1 (2.2)	5.7 (1.9)	6.4 (2.5)	7.8 (3.1)
Monthly migraine attack rate (using 24 h rule)						
Mean (SD)	4.9 (2.0)	4.7 (2.0)	4.9 (1.6)	4.7 (1.6)	3.8 (1.6)	4.7 (2.0)
Monthly migraine day with rescue medication rate						
Mean (SD)	3.5 (2.8)	4.0 (3.0)	4.6 (2.2)	4.1 (2.1)	3.7 (2.2)	4.3 (2.5)
Monthly rate - Migraine with aura						
Mean (SD)	1.4 (2.2)	0.8 (1.6)	0.6 (1.5)	0.6 (1.4)	0.2 (0.4)	0.6 (1.2)
Monthly rate - Migraine without aura						
Mean (SD)	3.9 (3.4)	4.3 (2.6)	4.7 (1.8)	4.7 (2.0)	4.2 (2.5)	4.4 (2.3)
Monthly rate - Migraine Aura only						
Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.2)	0.0 (0.1)	0.0 (0.0)	0.1 (0.2)
Monthly rate - Non-migraine headache						
Mean (SD)	0.7 (2.0)	0.7 (1.2)	0.7 (1.3)	0.4 (0.9)	1.0 (1.0)	0.9 (1.6)
Monthly rate - Aura only						
Mean (SD)	0.0 (0.2)	0.1 (0.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

TPM: Topiramate; DB: Double-Blind

Table 2: Demographics and baseline characteristics.

Age Group (Years)	50 mg/day (25 mg/12 h)	100 mg/day (50 mg/12 h)	200 mg/day (100 mg/12 h)
12 to 14	n=21 BQL	n=28 2.78 (69.4)	n=14 5.17 (40.4)
15 to 17	n=12 BQL	n=19 2.29 (103.9)	n=9 5.80 (28.8)
≥ 18 years	n=133 2.46 (18.0)	n=529 3.68 (28.4)	n=488 5.00 (42.2)

BQL: Below Quantitation Limits; * Study 2 did not obtain this information

Table 3: Mean (% coefficient of variation) plasma topiramate concentrations (µg/mL), pooled across studies (Studies 3, 4, 5 and Study 1)*, by treatment and age groups.

weeks of the DB phase was greater in each topiramate dosage group as compared with placebo-treated patients. Also, in all topiramate dosage groups (“Any TPM” group), the median percent reduction from baseline in Studies 3, 4 and 5 was significantly different from placebo ($p=0.0289$) (Figure 1).

The responder rate in the 100 mg/day dosage group in pivotal Study 1 was significantly different from placebo after multiple comparison adjustment ($p=0.0048$). However, 50 mg group of Study 1 did not show a significant difference ($p=1.0$) in the responder rate. Across supportive Studies 2, 3, 4 and 5, all topiramate dosage groups showed a >50% responder rate that was higher than the corresponding placebo group. For all topiramate dosage groups combined (“Any TPM” group), the responder rate was fairly consistent across studies, ranging from 56% to 68% (Table 4).

Efficacy by age

The median percent reduction in the 12 to 17 year old age group in Study 2 (66.67%) was significant as compared with placebo, and was comparable to the 100 mg/day group of Study 1 (72.22%) and with all the dosage groups in Studies 3, 4 and 5 (50 mg/day: 75.00%; 100 mg/day: 75.40%; 200 mg/day: 66.67%). In Study 2, a greater median percent reduction from baseline was observed in the 12- to 17-year-old age group (66.67%) as compared with the 6 to 11 year old age group (52.38%).

In Study 2, the percentage of topiramate-treated patients meeting the criteria for ≥ 50% responder rate was slightly higher in the 12 to 17 year old age group (59%) than in the 6 to 11 year old age group (53%).

Safety

Overall, AEs were reported for 68 out of 94 (72%) placebo-treated patients and 176 out of 215 (82%) topiramate-treated patients. Most of the treatment-emergent adverse events (TEAEs) reported in topiramate (TPM group) patients were mild or moderate in severity. Most commonly reported TEAEs in patients in any topiramate group were: influenza-like symptoms, language problems, paresthesia, gastroenteritis, weight decrease, anorexia, difficulty with concentration/attention, somnolence, viral infection, rhinitis, sinusitis, and urinary tract infections (Table 5).

Paresthesia (Topiramate: 15% versus Placebo: 3%), anorexia (Topiramate: 12% versus Placebo: 6%), and decreased weight (Topiramate: 10% versus Placebo: 5%) occurred in at least 10% of patients in the topiramate group. Paresthesia was more frequently reported among patients 12 years and older (15%) than younger patients (7%), while anorexia and weight decrease were reported at comparable frequencies in the two age groups. All these three TEAEs showed some evidence of dose dependence in patients aged 12-17 years (data in lower age group patients were insufficient to evaluate dose dependence).

Serious TEAEs occurred in 2/94 (2%) placebo-treated patients and 6/215 (3%) topiramate-treated patients. Serious TEAEs were less frequent in topiramate-treated patients of 12 to 17 years age group (2%) as compared with the 6 to 11 years age group (5%). All SAEs were assessed as having no relationship or doubtful relationship to topiramate, except for the case of suicide attempt, which occurred in a male patient (Study 2).

Treatment-limiting TEAEs that occurred in the 12 to 17 years age group were higher in incidence in placebo groups as compared to topiramate groups (5/63 [8%] vs. 10/156 [6%]). Among treatment-limiting TEAEs, fever, abdominal pain, constipation, hypokalemia and ketosis were observed only in placebo groups. Treatment-limiting AEs that occurred in >1 patient were observed in the 12 to 17 years age group and included fatigue, headache, and somnolence (1% each in topiramate group). The overall frequency of treatment-limiting AEs did not show any dose dependency. One renal AE (renal calculus) occurred in a topiramate-treated patient in the 12 to 17 years age group. For the 6 to 11 years age group, treatment-limiting TEAEs occurred in 0/94 placebo-treated patients, which was lower than the 4/59 (7%) occurrence in topiramate-treated patients. For the 6 to 11 years age group, cognition related AEs were slightly more frequent (placebo: 0/31; topiramate: [12%] 7/59) as compared to the 12 to 17 years age group (placebo: [5%] 3/63; topiramate: [7%] 11/156).

Changes from baseline values for all vital sign parameters were small and comparable between the placebo and topiramate treatment groups, across all age groups and treatment groups.

Discussion

The efficacy of various migraine treatments has been studied in adults, and data from these studies are often extrapolated to pediatric patients. There is a lack of controlled studies on the pharmacological treatment of migraine in children and adolescents. Currently, topiramate is the only FDA-approved migraine medication for use in patients 12 years and over, based on 5 controlled clinical studies that evaluated the efficacy and safety of topiramate in migraine prophylaxis [1,6,16,17]. However, topiramate dosages and treatment periods differed across these studies. In order to assess the efficacy and safety of topiramate more comprehensively in migraine prophylaxis for children and adolescents, an integrated analysis on the data from children and adolescents was conducted.

In pivotal Study 1, topiramate 100 mg/day was consistently superior to placebo for the key efficacy endpoints. In supportive Study 2, which was a flexible dose study, the actual average daily dosages (mean and median) were similar to those in the 100 mg/day; topiramate-treated patients demonstrated a clear numerical trend in the key efficacy endpoints but with no statistically significant effect compared with placebo. Consistent with Study 1, the pooled adolescent data from supportive Studies 3, 4, and 5 showed that the topiramate 100 mg/day

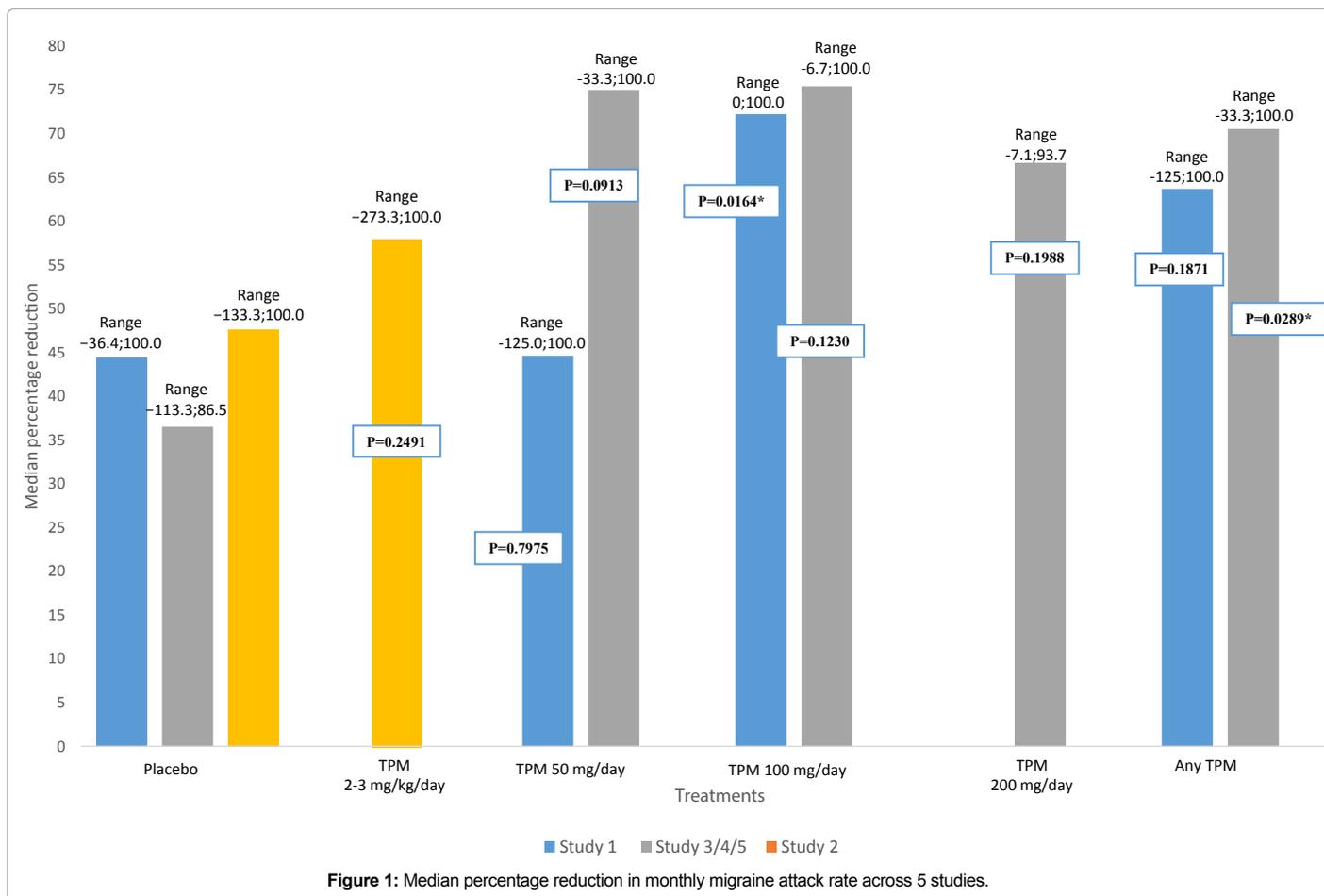


Figure 1: Median percentage reduction in monthly migraine attack rate across 5 studies.

group had greater reductions in all efficacy outcomes in topiramate patients but these endpoints did not show a significant effect compared with placebo. This may be related to the small number of adolescent patients in these pooled studies.

Across the study groups, the results (magnitude of changes) for the key endpoints were generally comparable for patients in the adolescent age range (12 to 17 years), when considering the topiramate 100 mg/day group (Study 1, 3, 4 and 5) and the 2-3 mg/kg/day group of Study 2.

To assess the effectiveness of migraine medications, a decrease in migraine or headache days per month from baseline and the proportion of responders (patients with $\geq 50\%$ decrease in migraine days per month after treatment) are the most commonly used measures [20]. Most of the medications used in the treatment of migraine have demonstrated an improvement of not more than 50% in 50% of patients in a clinical trial [20]. This summary includes pooled efficacy data from pediatric patients who were enrolled in 5 randomized placebo-controlled clinical studies. In the pivotal Study 1, topiramate 100 mg/day was consistently superior to placebo for percent reduction in the average monthly migraine attack rate and $\geq 50\%$ responder rate in adolescents 12-17 years old. However, topiramate 50 mg/day did not show any significant differences from placebo for any of the two endpoints. In the supportive Study 2, a flexible dose study in patients 6-15 years old, the actual average daily dosages were similar to those in the 100 mg/day groups of other studies, and pooled adolescent data from Studies 3,4 and 5, topiramate-treated patients (50 mg/day, 100 mg/day, 200 mg/day) demonstrated a greater percent reduction in the average monthly

migraine attack rate and a higher percentage of patients meeting the criteria for $\geq 50\%$ responder rate as compared with placebo. However, the results for the topiramate-treated patients did not differ significantly from placebo-treated patients. In study 2, this may be related to flexible dosing and the younger patient population (6 to 11 years old), who have generally slightly different migraine characteristics and a greater tendency to respond to placebo [21].

A larger proportion of males and younger population in Study 2 compared to other studies and small number of adolescent patients in pooled data from Studies 3, 4 and 5 may be the reason for the non-significant results. The larger proportion of males in Study 2 may be related to the younger age group in this study, because pre-pubertal boys have a higher incidence of migraine than girls in this age group [22]. Also, demographic differences like migraine attack rate in patients enrolled in Studies 3, 4, 5 and 1 may account for the different efficacy outcomes observed in these studies.

Overall, the efficacy of topiramate (100 mg/day) for prophylaxis of migraine headache in adolescents (≥ 12 years) is similar to that already established in studies that included an adult population [1,16,17].

Pharmacokinetic results showed BQL concentrations at 50 mg/day dosage in patients aged 12-14 years and 15-17 years which may be partly due to the fact that the analytical method used for sample analysis had a higher limit of quantification (2.00-2.01 $\mu\text{g/mL}$). No differences in mean topiramate plasma concentrations among age groups ranging from 12 years to adults (18 years and older) supports

Study 1	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)		Any TPM (N=70)
Number of Responders	15	16	29		64
Responder Rate (%)	45	46	83		19
Difference (%)		0	37		(-2, 39)
95% CI		(-23, 24)	(16, 58)		0.0874
P-Value vs. Placebo		1.0000	0.0048*		
Study 2	Placebo (N=49)	TPM 2-3 mg/kg/day (N=108)			
Number of Responders	24	60			
Responder Rate (%)	49	56			
Difference (%)		7			
95% CI		(-10, 23)			
P-Value vs. Placebo		0.5650			
Study 3/4/5	Placebo (N=12)	TPM 50 mg/day (N=11)	TPM 100 mg/day (N=13)	TPM 200 mg/day (N=13)	Any TPM (N=37)
Number of Responders	4	7	9	9	25
Responder Rate (%)	33	64	69	69	68
Difference (%)		30	36	36	34
95% CI		(-9, 69)	(-1, 73)	(-1, 73)	(4, 65)
P-Value vs. Placebo		0.3009	0.3009	0.3009	0.0799

CI: Confidence Interval; DB: Double-Blind; TPM: Topiramate

*: Difference from placebo, using p-value adjusted by Hochberg's procedure

Table 4: ≥ 50% reduction in the average monthly migraine attack rate from baseline to the last 12 weeks of the DB phase.

Age Group	Placebo	Topiramate					Any TPM
		2-3 mg/kg/d	50 mg/d	100 mg/d	200 mg/d	n (%)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age 6-11 Years, N	31	59	0	0	0	59	
Total patients with adverse events	27 (87)	50 (85)	0	0	0	50 (85)	
Fatigue	4 (13)	2 (3)	0	0	0	2 (3)	
Influenza-like symptoms	1 (3)	3 (5)	0	0	0	3 (5)	
Injury	4 (13)	5 (8)	0	0	0	5 (8)	
Language problems	0	1 (2)	0	0	0	1 (2)	
Paraesthesia	0	4 (7)	0	0	0	4 (7)	
Abdominal pain	4 (13)	5 (8)	0	0	0	5 (8)	
Gastroenteritis	2 (6)	7 (12)	0	0	0	7 (12)	
Weight decrease	1 (3)	5 (8)	0	0	0	5 (8)	
Anorexia	4 (13)	7 (12)	0	0	0	7 (12)	
Difficulty with concentration/attention	0	3 (5)	0	0	0	3 (5)	
Somnolence	3 (10)	5 (8)	0	0	0	5 (8)	
Infection viral	0	2 (3)	0	0	0	2 (3)	
Otitis media	3 (10)	3 (5)	0	0	0	3 (5)	
Pharyngitis	7 (23)	4 (7)	0	0	0	4 (7)	
Rhinitis	3 (10)	2 (3)	0	0	0	2 (3)	
Sinusitis	1 (3)	6 (10)	0	0	0	6 (10)	
Upper respiratory tract infection	5 (16)	10 (17)	0	0	0	10 (17)	
Age 12-17 Years, N	63	49	46	48	13	156	
Total patients with adverse events	41 (65)	43 (88)	34 (74)	37 (77)	12 (92)	126 (81)	
Fatigue	6 (10)	5 (10)	3 (7)	4 (8)	2 (15)	14 (9)	
Influenza-like symptoms	1 (2)	5 (10)	0	1 (2)	0	6 (4)	
Injury	7 (11)	3 (6)	4 (9)	5 (10)	1 (8)	13 (8)	
Language problems	1 (2)	1 (2)	0	0	2 (15)	3 (2)	
Paraesthesia	3 (5)	5 (10)	9 (20)	9 (19)	5 (38)	28 (18)	
Abdominal pain	6 (10)	6 (12)	3 (7)	7 (15)	2 (15)	18 (12)	
Gastroenteritis	2 (3)	3 (6)	1 (2)	1 (2)	0	5 (3)	
Weight decrease	4 (6)	8 (16)	3 (7)	2 (4)	4 (31)	17 (11)	
Anorexia	2 (3)	7 (14)	4 (9)	5 (10)	2 (15)	18 (12)	
Difficulty with concentration/attention	1 (2)	2 (4)	0	1 (2)	2 (15)	5 (3)	
Somnolence	1 (2)	4 (8)	1 (2)	3 (6)	2 (15)	10 (6)	
Infection viral	2 (3)	1 (2)	2 (4)	4 (8)	2 (15)	9 (6)	
Otitis media	0	1 (2)	0	0	1 (8)	2 (1)	
Pharyngitis	8 (13)	8 (16)	2 (4)	3 (6)	0	13 (8)	
Rhinitis	1 (2)	2 (4)	3 (7)	3 (6)	1 (8)	9 (6)	
Sinusitis	6 (10)	5 (10)	4 (9)	2 (4)	2 (15)	13 (8)	
Upper respiratory tract infection	8 (13)	11 (22)	12(26)	11 (23)	3 (23)	37 (24)	

Table 5: Treatment-emergent adverse events in at least 10% patients in any treatment group for the pooled double-blind migraine prophylaxis studies.

similar dose regimen in adolescent patients as recommended for adults.

Safety data, evaluating topiramate treatment for migraine prophylaxis demonstrated that the safety profile of topiramate in adolescents was generally consistent with the known safety profile of topiramate in adults. In this integrated summary, the incidences of TEAEs in topiramate-treated pediatric patients were generally consistent to that already established in adults, and to those observed in pediatric patients receiving topiramate monotherapy for epilepsy [1,13,16,17]. The incidences of paresthesia, anorexia and decreased weight in all dosage groups of topiramate were less than those in the previously conducted pivotal studies with adult population [1,16,17]. Overall, incidences of SAEs in “Any TPM” group were limited and comparable with the placebo group (Any TPM: 3%; Placebo: 2%).

Overall, this integrated analysis confirms the therapeutic efficacy and safety of topiramate 100 mg/day total dose for migraine prophylaxis in adolescent patients (12-17 years). Safety and tolerability were favorable without any new safety concerns in these patients.

Conflict of Interest Statement and Disclosures

This study was funded by Janssen Research & Development, LLC, New Jersey, USA. All authors are employed by Janssen Research and Development.

Authors' Contributions

Drs. Ford and Shi were involved in all aspects of study design, study conduct and data interpretation of the studies included in this review; Dr. Manitpitikul and Mr. Shalayda were involved in data analysis, interpretation and manuscript composition. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to present these data.

Registration

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