ARTICLE

COMPARATIVE EFFECTIVENESS RESEARCH

Migraine Therapeutics in Adolescents

A Systematic Analysis and Historic Perspectives of Triptan Trials in Adolescents

Haihao Sun, MD, PhD; Eric Bastings, MD; Jean Temeck, MD; P. Brian Smith, MD, MPH, MHS; Angela Men, MD; Veneeta Tandon, PhD; Dianne Murphy, MD; William Rodriguez, MD, PhD

Objectives: To conduct a systematic review and analysis of trial data submitted to the US Food and Drug Administration (FDA) to identify possible causes for the failure of pediatric trials of triptans for treatment of migraines.

Data Source: The FDA website for drug information and published literature.

Study Selection: All pediatric efficacy and pharmacokinetics trial data of drugs used for abortive treatment of migraine submitted to the FDA from January 1, 1999, through December 31, 2011.

Main Outcome Measures: Patient demographic baseline characteristics, inclusion and exclusion criteria, trial designs, efficacy end points, and pharmacokinetic profiles were analyzed and compared across drug products.

Results: We analyzed data for sumatriptan succinate nasal spray and zolmitriptan, eletriptan hydrobromide, almotriptan malate, and rizatriptan benzoate tablets. Seven efficacy trials had a randomized, double-blinded, placebo-controlled, parallel-group trial design. In 4 trials, patients were required to have a history of migraine attacks lasting at least 4 hours. High response rates for placebo were observed in all trials, with pain relief at 2 hours ranging from 53% to 57.5%. Nonrandomization of patients with an early placebo response design was used in the rizatriptan trial in 2011. Compared with the rizatriptan trial conducted in 1999, the 2011 rizatriptan trial reduced the placebo response rate by 6% for headache freedom at the 2-hour posttreatment end point owing to study design. The pharmacokinetic profiles between adolescents and adults were statistically similar.

Conclusions: High placebo response rates are consistent across all trials and may represent the principal challenge in pediatric trials of drugs for abortive treatment of migraine. Enrichment with selection of subjects with long-lasting migraine attacks is not sufficient to overcome high placebo response rates. Another enrichment strategy, the nonrandomization of patients with an early placebo response, successfully reduces the high placebo response rate for rizatriptan and is a trial design that should be considered for future pediatric trials of abortive migraine therapeutics.

JAMA Pediatr. 2013;167(3):243-249.
Published online January 28, 2013.
doi:10.1001/jamapediatrics.2013.872

Author Affiliations: Office of Pediatric Therapeutics and the Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Drs Sun, Bastings, Temeck, Men, Tandon, Murphy, and Rodriguez); and Department of Pediatrics, Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina (Dr Smith).

AMONG YOUNGER CHILDREN (aged 5-9 years), migraine is found predominantly among boys, whereas in adolescents, migraine is more prevalent in girls. Estimates of the prevalence of migraine in adolescents ranges from 6% to 20%.[1,2] Disability due to migraine can be significant, with many days lost from school or play.[3,4] Although published trials[3,5-12] reported the efficacy of some abortive therapeutics to treat migraine in adolescents, only almotriptan malate (2009) and rizatriptan benzoate (2011) have been found by the US Food and Drug Administration (FDA) to be safe and effective and therefore indicated for the pediatric population.

For editorial comment see page 300

This study investigated potential reasons for or factors that may contribute to the failure or the success of pediatric trials of drugs for abortive treatment of migraine submitted in response to an FDA-issued Written Request for sumatriptan succinate nasal spray and zolmitriptan, eletriptan hydrobromide, and rizatriptan tablets or submitted outside the context of a Written Request (almotriptan tablets). We also share the lessons that we have learned from the analysis of the trial data. This information may in turn be used to improve drug development for migraine treatment in the future and to help parents, caretakers, and clinicians understand the need or the lack thereof for the use of these medications in some adolescents

with migraine. Similarly, the pattern of the migraine attack may help the investigators to select the appropriate candidates for inclusion in studies of classes of antimigraine medications such as the triptans.

Since 1997, the US Congress has enacted legislation to encourage the conduct of pediatric trials and require the development of pediatric drugs.[13-17] The legislation gave the FDA the authority to require pediatric trials for certain new drugs and biological products and the authority to provide a financial incentive to drug companies to conduct pediatric trials voluntarily. The legislation also requires the FDA to make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric trials conducted in response to a Written Request issued by the FDA.[15] However, the law does not permit the FDA to discuss required study data submitted before 2007, when the trial findings were negative. The data included in this analysis are permitted by the law or permitted by the sponsors if the data came from negative trials and were submitted to the FDA before 2007.

From February 1, 1998, through January 31, 2012, these laws resulted in 439 labeling changes for pediatric uses, including new dosing recommendations, safety, and effectiveness findings. More than one-fifth of the products studied were found to have substantial differences in effectiveness, dosing, or safety in pediatric compared with adult populations.[18] In 80 of those labeling changes, safety and effectiveness were not established in pediatric patients for the indication studied as of January 31, 2011. We define a negative pediatric study as a study that failed to demonstrate effectiveness in the pediatric population. Among these negative pediatric studies, clusters were observed in drugs that are used to treat hypertension, psychiatric conditions, diabetes, migraine, and malignant disease. Results from a data analysis of several failed trials of antihypertensives in pediatric patients have been reported.[19] Although the trial data from the products used to treat psychiatric conditions, diabetes mellitus, and malignant disease are still under analysis, we would like to provide the historical perspectives that we have learned from the systematic review of trials of abortive therapeutics for pediatric migraine submitted to the FDA. This collective experience could enhance the quality of future trials.

METHODS

We conducted a systematic review and analysis of pediatric data submitted to the FDA from January 1, 1999, through December 31, 2011, for 5 drugs that the FDA approved for abortive therapy for adult migraine. At least 1 pharmacokinetic (PK) trial and 1 efficacy trial were submitted for each drug (with 2 efficacy trials submitted for sumatriptan and rizatriptan). We extracted data of interest, such as trial design, primary end points, enrollment eligibilities, and PK data, from the FDA clinical and pharmacology reviews.[20] The PK trial data from 4 of the 5 products and all efficacy trial data can be found on the FDA website for drug information (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) or in published literature.[5-9,12,21-29] We requested eletriptan PK data from the sponsors and obtained their permission to publish because the data were not available to the public at the time. For the PK trials, we examined and compared dosing and PK characteristics (absorption, bioavailability, and clearance) between pediatric and adult patients for the same drug and across drug products. We then obtained the trial data sets for the PK trials through the FDA's electronic document room repository. Source data were converted to an analysis format using a commercially available analysis software (WinNonlin Phoenix, version 6.0; Pharsight), and the PK variables were calculated sequentially using a noncompartmental model. Each PK variable was further explored using a descriptive statistical method. In addition, for pivotal efficacy trials, we examined patient demographics and baseline characteristics, enrollment eligibility, and trial design and assessed their relationship with outcome.

RESULTS

EFFICACY

Until 2008, among the 5 drugs analyzed, only 1 (almotriptan) was demonstrated to be efficacious in adolescents. The other 4 drugs (sumatriptan, eletriptan, rizatriptan, and zolmitriptan) failed to show efficacy in adolescents. In 2011, the second rizatriptan trial was submitted to the FDA and demonstrated efficacy in the pediatric population. We hereinafter refer to the first rizatriptan trial as rizatriptan 1999 and the second rizatriptan trial as rizatriptan 2011.

Trial Designs and Enrollment Eligibility

All efficacy trials used a randomized, double-blind, placebo-controlled, parallel-group trial design (**Table 1**). The rizatriptan 2011 trial also enriched the study population by using an investigative approach that included 2 stages and double randomization in the trial design, as shown in the **Figure**. Stage 1 was designed to identify the placebo responders and exclude them from the remainder of the study. After the randomization and treatment in stage 1, patients were excluded from further trial participation if they responded to the placebo treatment. Placebo nonresponders in stage 1 were eligible to proceed to stage 2 of the trial and were randomized again into placebo or rizatriptan treatment groups for the primary efficacy analysis.

The inclusion criteria varied across efficacy trials. The almotriptan, sumatriptan, zolmitriptan, and rizatriptan 2011 trials attempted to exclude patients with a history of early resolution or expected fast spontaneous headache improvement by enrolling only subjects with a history of migraine attacks lasting at least 4 hours. The eletriptan and rizatriptan 1999 trials did not define a specific requirement for the duration of migraine attacks. Subjects were required to have at least a 6-month history of migraine attacks of moderate or severe intensity in the almotriptan, sumatriptan, rizatriptan 1999, and rizatriptan 2011 trials. The length of migraine history was not specified in the eletriptan and zolmitriptan trials. The dosing regimens in all trials conducted in 2009 or earlier used a fixed dose, independent of body weight, whereas a weight-based dose was used in the rizatriptan 2011 trial. The dose ranges were the same as those used in adult trials.

Table 1. Trial Design and Enrollment Eligibility for Trials Submitted to the FDA

Drug Trial (No. of Subjects)	Year	Trial Design	Inclusion Criteria	Exclusion Criteria
Rizatriptan benzoate 2 (n = 360)	2011	Phase III, multicenter, 2-stage, randomized, DB, PC, parallel-group outpatient efficacy study with weight-based doses	1. Male or nonpregnant female aged 12-17 y and weight ≥20 kg 2. Unilateral or bilateral migraine with or without aura as defined by IHS criteria and ≥6-mo history of migraine attacks 3. 1-8 Moderate or severe migraine attacks monthly in the 2 mo before screening, with duration of untreated migraine attack (excluding sleep) ≥3 h 4. No satisfactory relief of migraine pain with NSAIDs or acetaminophen	1. No satisfactory relief of migraine pain from prior treatment with ≥2 courses of 5-HT_1 agonists 2. History of cardiovascular disease, congenital heart disease, cerebrovascular pathology, or other systemic disease
Almotriptan malate (n = 720)	2008	Phase III, multicenter, randomized, DB, PC, parallel-group, dose-ranging, outpatient efficacy study	1. Male or female aged 12-17 y 2. History of migraine with or without aura as defined by IHS criteria ≥1 y and ≥6-mo history of moderate- or severe-intensity migraine attacks 3. Attacks of moderate intensity, 1-6 monthly during the 2 mo preceding study enrollment, persisting >4 h when untreated and occurring at intervals >24 h between attacks 4. Able to verbalize the distinction of migraine from other types of headaches	Patients who did not have ≥1 migraine attack or had >6 moderate or severe migraine attacks during the run-in period
Sumatriptan succinate nasal spray 2 (n = 738)	2003	Randomized, DB, PC, parallel-group, dose-ranging outpatient efficacy study	1. Male or nonpregnant female migraine patients aged 12-17 y with a history of migraine with or without aura as defined by IHS criteria 2. History of mean 1-8 migraines monthly 3. History of migraine ≥6 mo and typical migraine duration ≥4 h 4. Otherwise healthy	Basilar or hemiplegic migraine Significant cardiovascular disorders History of >15 headaches of all types monthly
Zolmitriptan (n = 696)	2003	Multicenter, international, outpatient study Randomized, DB, PC, single-dose efficacy study	1. Aged 12-17 y and ≥2 migraines per month meeting the IHS definition for migraine with and without an aura and ≤10 headaches (migraine or nonmigraine) per month 2. History of untreated migraine duration ≥4 h	Typical exclusions for triptan products Pregnant or lactating female subjects
Eletriptan hydrobromide (n = 348)[a]	2003	Multicenter, DB, randomized, PC, parallel-group study	1. Migraine patients aged 12-17 y 2. No other specification stated in the WR review	No specifications stated in the WR review
Sumatriptan succinate nasal spray 1 (n = 510)	2000	Randomized, DB, PC, parallel-group, dose-ranging, outpatient efficacy study	1. Male or nonpregnant female migraine patients aged 12-17 y with a history of migraine with or without aura as defined by IHS criteria 2. History of mean 2-8 migraines monthly 3. History of migraine ≥6 mo and typical migraine duration ≥4 h 4. Otherwise healthy	Basilar or hemiplegic migraine Significant cardiovascular disorders History of >15 headaches of all types monthly
Rizatriptan benzoate 1 (n = 360)	1999	Multicenter, randomized, DB, PC, parallel, outpatient study	Otherwise healthy male or female patient aged 12-17 y with a history of migraine with or without aura, according to IHS criteria, for 6 mo before the start of the study	Patients with predominantly mild attack and those with hemiplegic or basilar migraine Pregnant or nursing female subjects

Abbreviations: DB, double-blinded; FDA, US Food and Drug Administration; 5-HT_1, serotonin; IHS, International Headache Society; NSAIDs, nonsteroidal anti-inflammatory drugs; PC, placebo-controlled; WR, Written Request.

[a] Indicates subjects who completed the efficacy study.

Demographics

Subject demographics were similar across all 6 pivotal efficacy trials for abortive migraine treatment in adolescents (eTable; http://www.jamapeds.com). The mean age was 14 (range, 12 -17) years. More girls (range, 51.4%-61.0%) than boys were included, and most of the subjects were white (range, 64.5%-92.2%). The demographic baselines for the PK trials were also similar.

Primary End Points and Efficacy Trial Results

Headache response, headache/pain relief, and headache/pain freedom were used as study end points in different trials. Headache response or headache/pain relief was defined as an improvement from moderate or severe headache at baseline to mild or no headache after treatment; headache/pain freedom was defined as a reduction of headache severity from moderate or severe at baseline to no

headache after treatment. As shown in **Table 2**, 4 trials (almotriptan, sumatriptan nasal spray trial 1, zolmitriptan, and eletriptan) used a headache response rate at 2 hours after treatment as the primary or a coprimary end point, whereas 1 trial (sumatriptan nasal spray trial 2) used the coprimary end points of headache relief at 1 hour and sustained relief 1 to 24 hours after treatment. Both rizatriptan trials used a pain-free rate at 2 hours after treatment as the primary end point. Only almotriptan was significantly more effective than placebo among the trials conducted before 2008 (Table 2). Rizatriptan was not shown to be effective in the 1999 trial but demonstrated therapeutic effectiveness in the 2011 trial. Compared with the rizatriptan 1999 trial, the rizatriptan 2011 trial reported a 6% lower rate of placebo response. Placebo response rates for all trials were much higher than the corresponding rates in adult clinical trials. For example, the placebo response rate for pain relief at 2 hours after treatment in pediatric trials ranged from 53% to 57.5%, in contrast to the placebo response rates ranging from 15% to 42.4% in adults (Table 2). For almotriptan, the response rates for pain relief at 2 hours after treatment were higher in adolescents than in adults (71.8% vs 56.0% for the 6.25-mg dose; 72.9% vs 64.2% for the 12.5-mg dose); the response rates for the other drugs were comparable between adolescents and adults (Table 2).

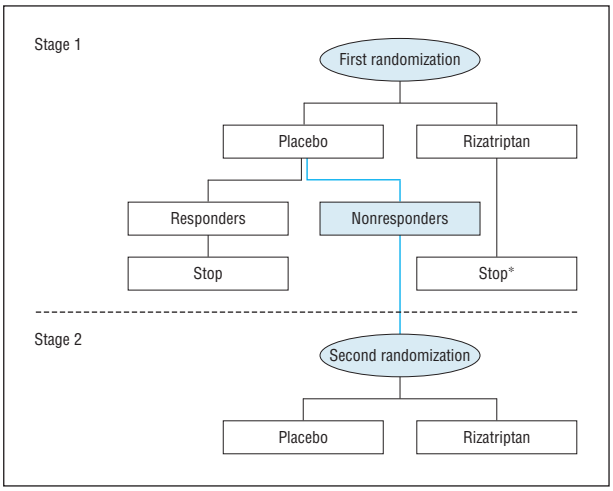

Figure. Stages in the double-randomization trial design for rizatriptan benzoate. *Nonresponders who received rizatriptan in stage 1 were allocated to receive placebo in stage 2, but were not part of the primary analysis.

PHARMACOKINETICS

Pharmacokinetic data were extracted from the corresponding New Drug Application clinical pharmacology reviews (**Table 3**). For almotriptan and zolmitriptan, the PK data were obtained in concurrent parallel control trials in which adolescents were compared directly with adults, whereas the other drugs (sumatriptan and rizatriptan) relied on historical control trials (Table 3) in which adolescent data were compared with adult data obtained in separate trials. In concurrent parallel control trials, the adolescent and the adult control groups used the same sample collection scheme and methods, with overnight fasting before dosing to improve the comparability between the age groups. In historical control trials, the scheme and methods of sample collection were comparable between the adolescent and adult control

Table 2. Primary End Points and Efficacy Trial Results for the Abortive Drugs

Drug Trial (No. of Subjects)	Primary End Point	Dose, mg	Primary Treatment End Point Outcome in ITT, %				
			Drug			Placebo	
			Adolescent	*P* Value[a]	Adult Reference Range	Adolescent	Adult Reference Range
Almotriptan malate (n = 714)	Coprimary headache pain relief, nausea, photophobia, and phonophobia at 2 h after treatment	6.25 12.50 25.00	71.8 72.9 66.7	.001 .001 .02	55-56 56.8-64.2 NA	55.3	33-42.4
Sumatriptan succinate nasal spray 1 (n = 510)	2-h Headache response rate, 20-mg vs placebo groups	20	63	.06	60-63	53	29-35
Sumatriptan succinate nasal spray 2 (n = 731)[b]	Coprimary headache relief at 1 h and sustained relief 1-24 h	5 20	53 61	.72 .09	44-60	52	32
Zolmitriptan (n = 696)	Comparison of the proportion of patients reporting headache relief at 2 h after treatment	2.5 5.0 10.0	56.6 52.8 54.3	.94 .34 .43	60-63 61-65 65-67	57.5	15-35
Eletriptan hydrobromide (n = 348)	Headache response at 2 h after treatment	40	57.0	NA	53.9-65.0	57.0	20.6-23.8
Rizatriptan benzoate 1999 (n = 296)[c]	Percentage of patients pain free at 2 h	5	32.2	.47	25.0-34.0	28.2	3.0-10.0
Rizatriptan benzoate 2011 (n = 702)	Pain free at 2 h after stage 2 dose	Weight-based, 5 or 10	30.6	.03	25.0-34.0	22.0	3.0-10.0

Abbreviations: ITT, intent-to-treat patients; NA, not available.
[a] Calculated as the drug vs placebo comparison in adolescent patients.
[b] The placebo response rate for headache relief at 2 hours was 58%, whereas the drug response rates for headache relief at 2 hours were 63% (5 mg) and 68% (20 mg).
[c] The placebo response rate for pain relief at 2 hours was 55.6%, whereas the drug response rate for pain relief at 2 hours was 65.8%.

Table 3. Summary of the PK Variables[a]

Drug (Dose, mg)	T_{max}, h		$T_{1/2}$, h		$AUC_{0\text{-inf}}$, ng/h/mL		C_{max}, ng/L		Trial Size, No. of Subjects
	Adult	Adolescent	Adult	Adolescent	Adult	Adolescent	Adult	Adolescent	
Almotriptan malate (12.5)	1.9 (0.7)	1.9 (0.7)	5.1 (0.9)	5.1 (1.5)	350.8 (56.3)	320.4 (76.8)	52.4 (8.4)	55.3 (19.0)	18 Adolescents 18 Adults (CC)
Sumatriptan succinate nasal spray (20)	1.15 (0.72)	1.61 (0.71)	1.9 (0.4)	2.1 (0.5)	50.30 (16.30)	60.14 (17.80)	14.30 (6.16)	15.19 (6.47)	15 Adolescents 24 Adults (HC)
Zolmitriptan (5)	1.6 (0.8)	1.7 (0.9)	3.75 (0.93)	3.01 (0.70)	43.7 (17.4)	51.4 (18.3)	8.58 (2.54)	9.66 (3.98)	21 Adolescents 18 Adults (CC)
Eletriptan hydrobromide (40)	1.83 (0.95)	2.70 (1.12)	3.92 (0.67)	4.11 (0.8)	608.71 (227.9)	734.00 (250.6)	88.27 (36.6)	103.70 (41.1)	7 Adolescents 18 Adult (HC)
Rizatriptan benzoate (10)	0.9 (0.4)	1.1 (0.8)	2.1 (0.3)	1.7 (0.1)	63.6 (12.6)	85.0 (24.5)	19.6 (4.9)	27.6 (11.2)	12 Adolescents 18 Adults (HC)

Abbreviations; $AUC_{0\text{-inf}}$, area under the curve from 0 to infinity; CC, concurrent control; C_{max}, maximum plasma concentration; HC, historical control; PK, pharmacokinetic; $T_{1/2}$, half time; T_{max}, time to achieve maximum plasma concentration.

[a] Unless otherwise indicated, data are expressed as mean (SD).

groups, but data were collected at separate times, and both historical control groups underwent overnight fasting before drug administration.

Overall, the PK variables were statistically comparable between adolescents and adults. However, some numerical PK differences between adolescents and adults were noted in 4 drugs that are listed in Table 3. For example, the mean time needed to achieve the maximum plasma concentration was numerically longer in adolescents than in adults for 4 drugs, but the differences were not statistically significant. In contrast, the time needed to achieve the maximum plasma concentration was the same in adolescents and adults for almotriptan. The area under the curve for almotriptan was lower in adolescents than in adults, whereas the areas under the curve for the other 4 drugs were numerically higher in adolescents than in adults; however, the differences were not statistically significant. The maximum plasma concentration was numerically higher in adolescents than in adults for all 5 drugs in Table 3, but the differences were not statistically significant.

COMMENT

The high placebo response rate has been recognized as a significant obstacle in triptan trials for treatment of adolescent migraine.[25,29-31] Consistent with previous reports, a high placebo response rate was observed in our analysis of pediatric trials of abortive therapeutics for migraine (Table 2). Although the reasons for the high placebo response rate in adolescents remain speculative, a few possible explanations and relevant solutions have been proposed. One of these possible explanations is that the shorter duration of migraine attacks in adolescents contributes to this observation, because many patients may experience spontaneous relief by the time the typical primary end point is assessed (ie, 2 hours after treatment).[30] In this context, 2 approaches to reduce the placebo response rate were proposed and reflected in the trials conducted; one uses pain relief at 1 hour after treatment as the primary end point, and the other enrolls patients with a history of migraine attack lasting at least 4 hours in trials with a typical 2-hour posttreatment primary end point. One of the trials reviewed in our analysis (sumatriptan trial 2 in Table 2) used pain relief at 1 hour after treatment as the primary end point, in an effort to reduce the rate of placebo response as reported in the study by Winner et al.[3] However, this trial failed to demonstrate a statistically significant difference between the drug and placebo or any meaningful reduction in the placebo response rate (Table 2). In addition, 4 trials in our analysis shown in Table 1 (almotriptan, sumatriptan, zolmitriptan, and rizatriptan 2011) enrolled only subjects with a history of migraine lasting at least 4 hours as a possible tool to reduce the placebo response rate. However, this method also appeared ineffective because the placebo response rates (53-57.5%) for the primary end point of 2-hour pain relief in these trials were similar to those seen in trials that did not use that enrichment strategy (ie, 56-57%). Furthermore, the use of pain freedom at 2 hours after treatment as a primary end point was also suggested as a way to reduce the placebo response rate.[30,31] The rizatriptan 1999 and rizatriptan 2011 trials used pain freedom at 2 hours as the primary end point. The rizatriptan 1999 trial failed to demonstrate a significant difference between placebo and drug for the primary outcome measure (28.2% vs 32.2%). Results of the second rizatriptan efficacy trial (rizatriptan 2011) were positive, with a 22.0% response rate for placebo vs 30.6% for the drug ($P = .02$). Compared with the rizatriptan 1999 trial, the rizatriptan 2011 trial reduced the placebo response rate by 6% owing to the study design, although the drug response rates were comparable (32.2% vs 30.6%). The rizatriptan 2011 trial also used weight-based dosing, which might have contributed to the success of the trial.

As shown in **Table 4**, the other trial with positive results, the almotriptan trial, excluded patients who did not experience any headache attack during a run-in period. The trial also ensured enrollment of patients with at least a 1-year history of migraine (Table 1). However, these measures did not appear to lower the placebo response rate impressively (Table 2). In addition, the almotriptan drug response rate in adolescents was the highest among the 5 drugs reviewed and was higher than that in adults. The reason almotriptan showed a high rate of drug response needs to be further explored.

Table 4. Summary of Trial Design, Primary End Points, and Enrollment Eligibility

Drug Trial (No. of Subjects)	RDPC Parallel Group Trial	Non-RD Placebo Responders	Headache Relief at 2 h	Headache Free at 2 h	Headache Relief at 1 h	Inc Headache Duration 3-4 h	Inc 6-mo History of Headache	Exc No Headache Run-in Period	Weight-Based Dosing
Almotriptan malate (n = 720)	x		x			x	x	x	
Sumatriptan succinate nasal spray 1 (n = 510)	x		x			x	x		
Sumatriptan succinate nasal spray 2 (n = 738)	x				x	x	x		
Zolmitriptan (n = 696)	x		x			x			
Eletriptan hydrobromide (n = 348)	x		x						
Rizatriptan benzoate 1999 (n = 360)	x			x			x		
Rizatriptan benzoate 2011 (n = 360)	x	x		x		x	x		x

Abbreviations: Exc, exclusion criterion; Inc, inclusion criterion; Non-RD, nonrandomized; RDPC, randomized placebo-controlled.

Although the placebo response rate in pediatric migraine trials has been reduced in a trial that used an enrichment trial design, the underlying reason for the high rate of placebo response remains to be investigated. Although many pathophysiological studies of migraines in adults have been conducted, no such study has been conducted in adolescents. One cannot exclude the possibility of the heterogeneity of underlying mechanisms, which may be different in adults and adolescents. Therefore, migraine in adolescents may or may not be the same as that observed in adults. Some migraines could be caused by psychological stress or anxiety. Patients with school phobia disorder often manifest symptoms of migraine, but no criteria excluded this type of migraine in the trials we examined. In general, greater precision of phenotypic characteristics defining entry criteria and response would similarly increase the probability of enriching the trial with participants most likely to respond to a drug. Pathophysiological studies of migraines in adolescents may assist in better understanding similarities and differences between adult and pediatric migraine. Another potential area for research is determining whether the differences in time needed to achieve the maximum plasma concentration between adults and adolescents, seen in some studies, are important in the lack of effectiveness seen in many of the adolescent studies.

Our analysis confirmed the high rate of placebo response as the likely main factor contributing to the failure of pediatric trials of abortive therapeutics for migraine. Our analysis also suggests that using pain relief at 1 hour after treatment as a primary end point is not effective in reducing the high placebo response rate. In addition, this review suggests that the inclusion of patients with a history of long migraine attacks (eg, ≥4 hours) is not by itself sufficient to overcome the high placebo response rate.

We believe that several options may be considered to maximize the chance of success of trials for abortive therapeutics for pediatric migraine. First, innovative trial designs intended to reduce the placebo response rate may be necessary to demonstrate a drug effect. Specifically, we have found that using a trial design in which patients with an early placebo response are excluded before randomization into the trial has been successful in reducing the placebo response rate. This approach can be used during a single treated attack, in which all patients first receive a single-blind placebo and those who respond at 30 minutes are excluded. The remaining patients are randomized to drug or placebo in a typical double-blind fashion. As an example, rizatriptan, which had failed to demonstrate efficacy in the trial submitted in 1999, was shown to be effective in the trial submitted in 2011 after adopting a trial design incorporating these features. Second, the use of formulations (eg, subcutaneous) capable of reducing the time to peak plasma exposure could be evaluated. In addition, as suggested by Lewis et al,[31] we might improve patient education regarding the importance of recording whether the medicine works or not. Explaining the concept of placebo to the patients before enrollment might be helpful. The child needs reassurance that reporting that the medicine does not help the headache is acceptable.

When we examine the history of antimigraine drug development in adolescents (Table 1), we can see a journey of pediatric trial evolution. All trials submitted from 1999 to 2003 failed to show efficacy in adolescents. From these trials, lessons were learned and incorporated into the design for the later trials. The lessons learned collectively by the entire field, including academia, industry, and the regulatory agency, have contributed to the positive findings of trials submitted in 2008 and 2011. In addition, we should consider the possibility that adolescents who have a rapid resolution have different types of migraines, and until we have better mechanisms to identify the causes of the different expressions of the disease, these patients may not require pharmacologic interventions. In general, a better understanding of the underlying physiological and genotypic differences would decrease the variability now seen in the phenotypic expression of the disease. Increased diagnostic precision in clinical practice based on such studies could then enhance the likelihood of more successful management of migraine and avoid the "therapeutic futility" of using targeted medicines in patients who are unlikely to respond.

Accepted for Publication: September 24, 2012.
Published Online: January 28, 2013. doi:10.1001/jamapediatrics.2013.872

Correspondence: William Rodriguez, MD, PhD, Office of Pediatric Therapeutics, Office of Commissioner, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (william.rodriguez@fda.hhs.gov).

Author Contributions: The authors all had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. *Study concept and design:* Sun, Murphy, and Rodriguez. *Acquisition of data:* Sun, Temeck, Men, and Tandon. *Analysis and interpretation of data:* Sun, Bastings, Smith, Men, Tandon, Murphy, and Rodriguez. *Drafting of the manuscript:* Sun and Men. *Critical revision of the manuscript for important intellectual content:* Sun, Bastings, Temeck, Smith, Men, Tandon, Murphy, and Rodriguez. *Statistical analysis:* Men and Tandon. *Administrative, technical, and material support:* Temeck, Smith, Men, Tandon, and Murphy. *Study supervision:* Murphy and Rodriguez.

Conflict of Interest Disclosures: None reported.

Disclaimer: Views expressed in this manuscript are those of the authors and do not necessarily reflect official positions or policies of the FDA.

Online-Only Material: The eTable is available at http://www.jamapeds.com.

REFERENCES

1. Pakalnis A. Current therapies in childhood and adolescent migraine. *J Child Neurol*. 2007;22(11):1288-1292.
2. Bigal ME, Lipton RB, Winner P, Reed ML, Diamond S, Stewart WF; AMPP Advisory Group. Migraine in adolescents: association with socioeconomic status and family history. *Neurology*. 2007;69(1):16-25.
3. Winner P, Rothner AD, Saper J, et al. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. *Pediatrics*. 2000;106(5):989-997.
4. Winner P. Triptans for migraine management in adolescents. *Headache*. 2002;42(7):675-679.
5. Ahonen K, Hämäläinen ML, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. *Neurology*. 2004;62(6):883-887.
6. Ahonen K, Hämäläinen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. *Neurology*. 2006;67(7):1135-1140.
7. Hämäläinen ML, Hoppu K, Santavuori P. Sumatriptan for migraine attacks in children: a randomized placebo-controlled study: do children with migraine respond to oral sumatriptan differently from adults? *Neurology*. 1997;48(4):1100-1103.
8. Lewis DW, Winner P, Hershey AD, Wasiewski WW; Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics*. 2007;120(2):390-396.
9. Linder SL, Mathew NT, Cady RK, Finlayson G, Ishkanian G, Lewis DW. Efficacy and tolerability of almotriptan in adolescents: a randomized, double-blind, placebo-controlled trial. *Headache*. 2008;48(9):1326-1336.
10. Rothner AD, Winner P, Nett R, et al. One-year tolerability and efficacy of sumatriptan nasal spray in adolescents with migraine: results of a multicenter, open-label study. *Clin Ther*. 2000;22(12):1533-1546.
11. Winner P. Triptans in childhood and adolescence. *Semin Pediatr Neurol*. 2001;8(1):22-26.
12. Linder SL, Dowson AJ. Zolmitriptan provides effective migraine relief in adolescents. *Int J Clin Pract*. 2000;54(7):466-469.
13. US Food and Drug Administration. Significant amendments to the FD&C Act. Updated April 29, 2011. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/default.htm. Accessed December 6, 2011.
14. US Food and Drug Administration. Full text of FDAMA law. Updated October 22, 2009. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm#SEC.%20111. Accessed December 6, 2011.
15. US Food and Drug Administration. Best Pharmaceuticals for Children Act. Section 9, January 4, 2002. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm#sec9. Accessed December 6, 2011.
16. Pediatric Research Equity Act of 2003. December 16, 2003. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf. Accessed December 5, 2011.
17. US Food and Drug Administration. Food and Drug Administration Amendments Act (FDAAA) of 2007. Updated December 2, 2011. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. Accessed December 6, 2011.
18. Smith PB, Benjamin DK Jr, Murphy MD, et al. Safety monitoring of drugs receiving pediatric marketing exclusivity. *Pediatrics*. 2008;122(3):e628-e633. doi:10.1542/peds.2008-0585.
19. Benjamin DK Jr, Smith PB, Jadhav P, et al. Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension*. 2008;51(4):834-840. doi:10.1542/peds.2008-0585.
20. US Food and Drug Administration. Medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under section 505A and 505B of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the FDA Amendments Act of 2007 (FDAAA). http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm. Accessed December 6, 2011.
21. Christensen ML, Mottern RK, Jabbour JT, Fuseau E. Pharmacokinetics of sumatriptan nasal spray in children. *J Clin Pharmacol*. 2004;44(4):359-367.
22. Dixon R, Engleman K, Kemp J, Ruckle JL. A comparison of the pharmacokinetics and tolerability of the novel antimigraine compound zolmitriptan in adolescents and adults. *J Child Adolesc Psychopharmacol*. 1999;9(1):35-42.
23. Eiland LS, Hunt MO. The use of triptans for pediatric migraines. *Paediatr Drugs*. 2010;12(6):379-389.
24. Fuseau E, Petricoul O, Moore KH, Barrow A, Ibbotson T. Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet*. 2002;41(11):801-811.
25. Rothner AD, Wasiewski W, Winner P, Lewis D, Stankowski J. Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents. *Headache*. 2006;46(1):101-109.
26. Visser WH, Winner P, Strohmaier K, et al; Rizatriptan Protocol 059 and 061 Study Groups. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double-blind, single-attack study and two open-label, multiple-attack studies. *Headache*. 2004;44(9):891-899.
27. Winner P, Lewis D, Visser WH, Jiang K, Ahrens S, Evans JK; Rizatriptan Adolescent Study Group. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind, placebo-controlled study. *Headache*. 2002;42(1):49-55.
28. Winner P, Rothner AD, Wooten JD, Webster C, Ames M. Sumatriptan nasal spray in adolescent migraineurs: a randomized, double-blind, placebo-controlled, acute study. *Headache*. 2006;46(2):212-222.
29. Winner P, Linder SL, Lipton RB, Almas M, Parsons B, Pitman V. Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo-controlled trial. *Headache*. 2007;47(4):511-518.
30. Evers S, Marziniak M, Frese A, Gralow I. Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. *Cephalalgia*. 2009;29(4):436-444.
31. Lewis DW, Winner P, Wasiewski W. The placebo responder rate in children and adolescents. *Headache*. 2005;45(3):232-239.