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Review Article

Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic Review

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Objective.—We sought to conduct a qualitative systematic review to evaluate the safety and efficacy of available treatments for pediatric patients with migraine or benign primary headache in the emergency department, in an effort to inform future practice.

Methods.—Scopus, Medline, and PubMed databases were searched for randomized controlled trials retrospective reviews, review articles, and case studies discussing migraine or benign primary headache management that were conducted in the emergency room or outpatient acute care setting in pediatric patients (less than 18-years old). Meeting abstracts and cited references within articles were also evaluated. Multiple variables were recorded, including type of treatment, study design, dosing, primary outcome, and side effects. Therapeutic gain was calculated in studies with a placebo arm. Treatments were subjectively assessed based on methodology and number of trials for a particular therapy.

Results.—Thirty-one studies were included in the final analysis. Of these, 17 were randomized controlled trials, 9 were retrospective reviews, and 5 were prospective chart review studies. One pertained to IV fluids, 2 to nonspecific analgesic use, 5 to dopamine receptor antagonists, 2 to valproic acid, 1 to propofol, 1 to magnesium, 1 to bupivicaine, 13 to triptan medications, and 3 to dihydroergotamine (DHE). Treatments considered effective for acute migraine or benign primary headache in the analgesic category include ibuprofen, and to a lesser degree acetaminophen. Ketorolac was not compared to other NSAIDs, but was found to be less effective than prochlorperazine. Of the phenothiazines, prochlorperazine was considered most effective. Of the triptan medications, almotriptan, rizatriptan, zolmitriptan nasal spray, sumatriptan nasal spray, and combination sumatriptan/naproxen are effective agents for acute treatment. Treatments considered probably effective included IV fluids, chlorpromazine, valproate sodium, injectable sumatriptan, and IV DHE. Treatments with oral zolmitriptan showed inconsistent results, while treatments considered ineffective included isolated oral sumatriptan and oral DHE. There is insufficient evidence to comment on propofol, magnesium, and bupivicaine efficacy.

Conclusions.—Of the available evidence, ibuprofen, prochlorperazine, and certain triptan medications are the most effective and safe agents for acute management of migraine and other benign headache disorders in the pediatric population. Additional studies in this population are needed, and should take into consideration variables such as dosing, co-administered medications, treatment duration, and length of treatment effect.

Key words: pediatric headache, emergency room headache treatment, acute pediatric migraine

Abbreviations: DHE dihydroergotamine, ED emergency department, NSAIDs non-steroidal anti-inflammatory drugs, RCT randomized controlled trial, VPA valproic acid

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INTRODUCTION

Headache is a common reason for pediatric patients to present to the emergency department (ED), with national estimates of 250,000 visits occurring annually.[1] At the time of ED presentation, most pediatric headaches have been ongoing for 2-3 days,[2–4] and most patients have already used more than one abortive therapy.[2,5] Headaches are also costly, with an average total cost of adult patient ED visits estimated at $900 (U.S.).[6]

There is a paucity of pediatric randomized controlled trials (RCTs) for treatment of primary headache performed in an ED setting. Pediatric studies are often complicated by polypharmacy, as multiple medications are often administered at home prior to ED visits, in addition to a high placebo responder rate. Historical studies have also often been limited to retrospective reviews, which are methodologically less rigorous than controlled trials. Much of the current practice for emergency room treatment of pediatric headache is, therefore, based on adult trials or trials performed in non-ED settings. There is also variation in pediatric acute migraine management across institutions,[2,4,7] and evidence-based treatment is not always administered. A retrospective, observational study across four states found that close to half (46%) of pediatric patients presenting with migraine are not prescribed or recommended medication, while a much larger percentage (84%) are not prescribed or recommended evidence-based medication.[8]

We sought to conduct a qualitative systematic review to evaluate the safety and efficacy of available treatments for pediatric patients with migraine or benign primary headache in the ED, in an effort to inform future practice and research. In the course of our search, we also identified and included important acute therapies administered in outpatient and home settings.

METHODS

Search Strategy.—Scopus, Medline, and PubMed databases were searched independently between December 8, 2014 and May 23, 2015. Refer to Figure 1 for a study selection flowchart.

1. A Scopus search was performed using the terms "(headache OR migraine) AND (emergency room OR emergency department) AND (child OR pediatric OR teen OR adolescent)."
2. A PubMed search was performed using the terms "pediatric and emergency room and headache treatment."
3. A Medline search was incorporated in an effort to capture more potential articles not listed in the PubMed search. The following terms were used: "((((((‘Headache Disorders, Primary’[Mesh]) OR (‘Headache Disorders’[Mesh] OR ‘Headache’[Mesh])) AND ‘Pediatrics’[Mesh]) OR ‘Hospitals, Pediatric’[Mesh]) OR ‘Adolescent’[Mesh]) AND ‘Emergency Medicine’[Mesh]) AND ‘Emergency Service, Hospital’[Mesh]."
4. A search was performed in PubMed to capture the minority of articles that are part of PubMed, but not in Medline, using the terms "((pediatric* OR child* OR teen* OR adolescent*) AND (headache* OR migraine*) AND (emergency department OR emergency room)) NOT medline[sb]."

Cited references within selected articles were also evaluated, and American Headache Society scientific abstracts from 2014 to 2015 were searched separately using the terms "pediatric," "child," and "adolescent" for relevance to the topic.

Study Selection and Data Collection Process.—In this qualitative systematic review, studies were included for review if they (1) discussed migraine or benign primary headache management, (2) if they were conducted in the emergency room or outpatient setting, and (3) if they enrolled pediatric patients (age less than 18 years). Due to the narrow scope of this topic and the paucity of RCTs in the pediatric population, we chose to include RCTs, retrospective reviews, review articles, and case studies. Reviewed therapies included those pertaining to antiemetic use, fluids, opioids, and headache targeted therapy (NSAIDs, acetaminophen, 5HT receptor agonists, dopamine receptor antagonists, anesthetics). Studies were excluded if they were in

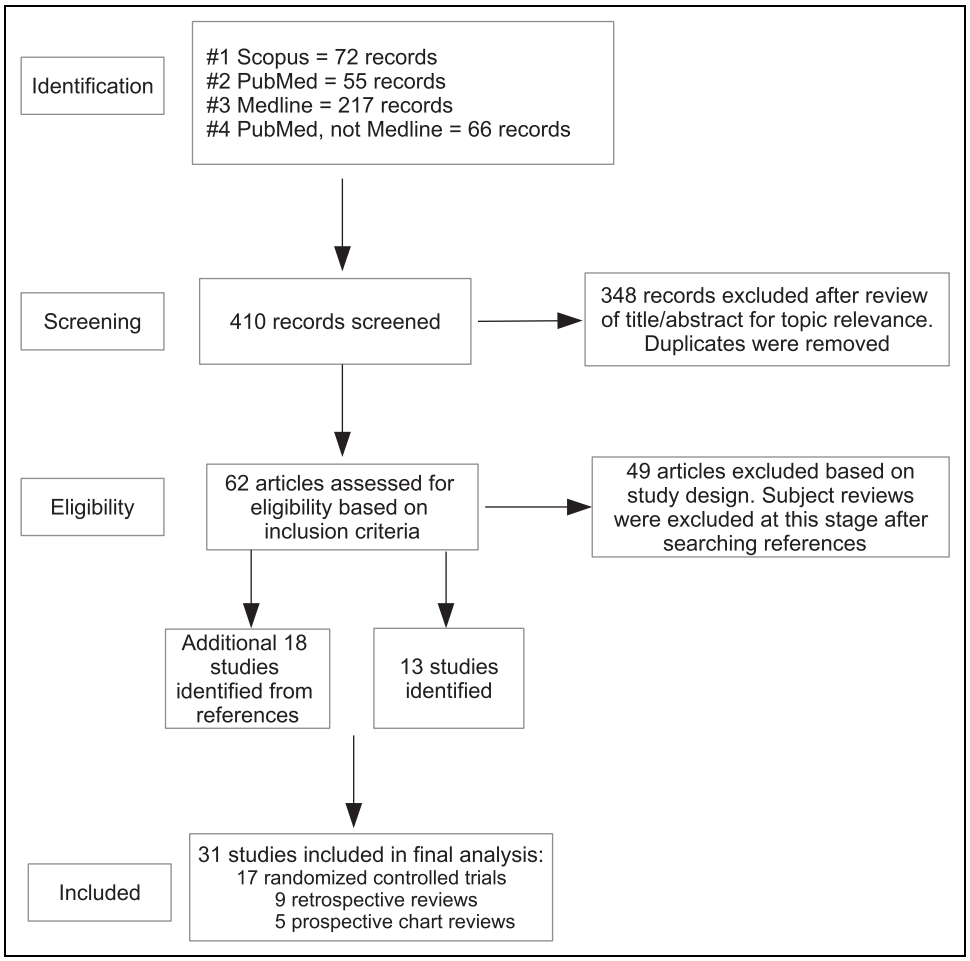

Fig. 1.—Flow diagram for systematic review.

a language other than English, dealt with secondary headache disorders (concussion, TBI, mild head injury, stroke), and if they pertained to headache diagnosis rather than treatment, such as imaging studies.

After the electronic database searches were conducted, the resulting titles and abstracts were reviewed to assess whether they met the inclusion criteria above. Review articles on pediatric headache management were also reviewed and references sections hand-searched to identify additional references.

For those therapeutic categories for which there was more than one study, data were abstracted into a table format. Abstracted variables included: author and year of publication, study design and location, ages enrolled, treatment type, dosing, primary outcome, side effects, and authors' conclusions. The comments section was reserved for points deemed important by the review authors, including potential biases.

The International Headache Society (IHS) Clinical Trials Subcommittee recommendations for controlled drug trials in acute migraine recommend that percentage of patients pain-free at 2 hours, prior to use of any rescue medication, should be the primary measure of efficacy.[9] While a few studies measured this as the primary outcome, analysis of the evidence was limited due to disparate trial designs and differing primary outcomes. As migraine attacks can be shorter in pediatric patients,[10] it is also possible that the most appropriate primary outcome measure for efficacy in pediatric migraine trials might be different.

Due to the high placebo response rate seen in some pediatric migraine studies, therapeutic gain

was computed, defined as the difference in the response rate between the treatment group and the placebo group. This variable was included as a primary summary measure in the summary tables, and was factored into interpretation of the studies. However, comparison of therapeutic gain between studies must be interpreted with caution given the inherent differences in study design and study population. Medications considered effective were ones with a positive response in one or more RCTs. Medications were termed probably effective if there were positive results in more than one retrospective and/or prospective study. Medications with both positive and negative results were considered inconsistent, while medications with negative results were considered ineffective. This systematic review was not registered.

RESULTS

A total of 410 studies were screened for analysis and 62 were assessed for eligibility. Review of those studies identified an additional 18 studies from references sections. A total of 31 studies were included in the final analysis. Of these, 17 were RCTs, 9 were retrospective reviews, and 5 were prospective chart review studies (Figure 1). One study pertained to IV fluids, 2 to analgesic use, 5 to dopamine receptor antagonists, 2 to valproic acid, 1 to propofol, 1 to magnesium, 1 to bupivicaine, 14 to triptan medications, and 3 to dihydroergotamine (DHE).

What follows is a narrative review of the trials, with table summaries when a treatment had more than one associated study. A summary table of the studies is also provided (Table 8). All table summaries are at the end.

Fluids.—There is one single-blind, randomized parallel-group trial assessing efficacy of a 10 mL/kg IV normal saline bolus in patients between the ages of 5 and 17 years presenting to the ED with migraine.[11] Both groups received a fluid bolus, with group A not having the expectation of concurrent medication and group B given the expectation that they may receive simultaneous medication. The primary outcome assessed was mean change from baseline on the visual analog scale (VAS) at 30 minutes, and no statistical difference between the two groups was found. Of the participants, 17.8% (95% CI 6.1–29.4%) did, however, experience a minimum clinically significant improvement on the VAS. These findings suggest that fluids do have a beneficial effect for some, perhaps in those with associated symptoms of nausea and emesis who may be more susceptible to the effects of dehydration. Future studies could address analysis of a fluid plus medication group compared to a medication only treatment group, as giving hydration may lead to increased likelihood of a medication yielding a useful treatment effect. Increasing bolus volume may also be more beneficial.

Analgesics.—Acetaminophen and ibuprofen have been studied for the treatment of acute migraine in children in a home setting. A randomized, double-blinded, placebo-controlled crossover study of 4 to 16-year olds evaluated acetaminophen 15 mg/kg, ibuprofen 10 mg/kg, and placebo.[12] The primary endpoint was 2-hour reduction in severe or moderate headache by at least 2 grades on a 5-point scale. Investigators found that at 2 hours, ibuprofen had nearly three times the odds of efficacy as placebo (OR 2.9, 95% CI 1.0-8.1), and twice the odds as acetaminophen (OR 2.2, 05% CI 1.1-4.0). Acetaminophen was, however, superior to placebo. Another randomized, double-blind, placebo-controlled, parallel group study evaluated the efficacy of treating one migraine attack with a single dose of ibuprofen 7.5 mg/kg vs placebo.[13] The primary endpoint of 2-hour reduction in headache from severe or moderate to mild or none on a 4-point scale was reached in 76% of responders vs 53% of placebo ($p = .006$). They found an interaction with sex, with 84% of boys treated with ibuprofen experiencing relief vs 65% of girls; the latter being closer to the placebo response rate which was 53% ($p = .8$).

These studies demonstrate the effectiveness of ibuprofen and, to a lesser degree, acetaminophen in the treatment of acute migraine in children (Table 1) prior to ED arrival. When given early, they may prevent headache escalation and avoid the need for more aggressive intravenous therapies. Maximizing the ibuprofen dose to 10 mg/kg may be the most beneficial for headache relief and resolution.

Table 1.—Evidence Evaluating Acetaminophen and Ibuprofen for the Treatment of Acute Migraine in the Pediatric Population

Authors	Hamalainen et al.[12]	Lewis et al.[13]
Study type and location	Randomized, double-blind, placebo-controlled crossover; multicenter, home treatment	Randomized, double-blind, placebo-controlled, parallel group; single-center, home treatment
Ages (years) and study size	4-16, n = 88	6-12, n = 84
Treatment arms	Acetaminophen, ibuprofen, or placebo	Single attack with ibuprofen vs placebo
Dosing	Acetaminophen 15 mg/kg; ibuprofen 10 mg/kg	Ibuprofen 7.5 mg/kg
Primary outcome	2 hour pain reduction ≥2 grades on a 5-point scale	2 hour pain reduction ≥2 grades on a 4-point scale
Results	Ibuprofen superior to placebo: OR 2.9, (95% CI 1.0-8.1); ibuprofen superior to acetaminophen (OR 2.2, 95% CI 1.1-4.0); and acetaminophen superior to placebo (OR 2.0, 95% CI 0.9-4.3)	Ibuprofen group achieved primary outcome in 76% vs 53% of placebo ($p = .006$)
Therapeutic gain	N/A	23%
Side effects	Few; no statistically significant difference	Not reported
Author's conclusions	Acetaminophen and ibuprofen are effective for acute attacks, with ibuprofen being superior	Ibuprofen is effective for acute attacks, but interaction by sex implies boys' attacks were more likely to respond than girls'

Dopamine Receptor Antagonists.—Dopamine receptor antagonists are used frequently for acute migraine treatment in the ED setting.[14] Different categories of dopamine receptor antagonists include the phenothiazines, butyrophenones, and metoclopramide. The butyrophenones include droperidol and haloperidol, which are not widely used in children due to the risk of *torsade de pointes* observed in the adult population. Metoclopramide is used in pediatric EDs for for acute migraine management, however, is not as well studied for migraine as the phenothiazines.

The phenothiazines consist of prochlorperazine, chlorpromazine, and promethazine. Potential side effects include akathisia and dystonic reactions. Chlorpromazine can also cause orthostatic hypotension. All medications in this class have the potential to prolong the QTc, hence electrocardiogram (ECG) evaluation prior to administration may be prudent in children.

Three studies looked specifically at prochlorperazine effectiveness in pediatric migraine (Table 2). The first trial was a retrospective review of 20 consecutive children seen in the ED for a severe, intractable migraine attack.[15] Subjects were patients of a Headache Center who were advised to present to the ED for IV prochlorperazine (0.15 mg/kg) and IV hydration if their home regimen was ineffective. Patients were contacted 24 hours after discharge and asked about overall responsiveness at 1 hour, 3 hours, and 24 hours after prochlorperazine administration. There were 15/20 (75%) of patients who reported a ≥50% reduction in headache severity at 1 hour, with 12/15 (80%) reporting headache resolution. There were 19/20 (95%) patients with a ≥50% reduction in their headache severity by 3 hours. By 24 hours, 18/20 (90%) were pain free. The patients' responses were also positive, with 55% rating benefit from prochlorperazine as "good," and 35% as "great," While results were encouraging, there was no placebo arm for comparison.

A more recent prochlorperazine trial prospectively studied 79 patients ages 8-18 treated with intravenous prochlorperazine (0.15 mg/kg), along with intravenous diphenhydramine (0.5 mg/kg IV; max 25 mg).[5] No IV fluids were administered concurrently. Among the patients with a migraine

Table 2.—Evidence Evaluating Phenothiazines for the Treatment of Acute Migraine in the Pediatric Population

Authors	Kabbouche et al.[15]	Trottier et al.[5]	Trottier et al.[16]	Brousseau et al.[17]	Kanis et al.[18]
Study type and location	Retrospective review; Pediatric ED	Prospective study over 25 months; tertiary Pediatric ED	Retrospective review; tertiary Pediatric ED	Prospective, randomized, double-blind, cross-over design; multicenter Pediatric ED	Retrospective cohort review; Pediatric ED
Ages and study size	8-17; n = 20	8-18; n = 79	7-17; n = 92	5-18; n = 62	12-21; n = 349
Treatment	IV prochlorperazine and fluids	IV prochlorperazine and IV Benadryl	IV prochlorperazine and IV Benadryl	IV prochlorperazine and NS bolus vs IV ketorolac and NS bolus	IV chlorpromazine, fluids, and ketorolac (if not given at home) vs IV prochlorperazine (comparison), fluids, and ketorolac (if not given at home)
Dosing	Prochlorperazine (0.15 mg/kg); fluids mean 17 cc/kg	Prochlorperazine (0.15 mg/kg), max 10 mg; diphenhydramine 0.5 mg/kg, max 25 mg	Prochlorperazine (0.15 mg/kg), max 10 mg; diphenhydramine 0.5 mg/kg, max 25 mg	Prochlorperazine (0.15 mg/kg), max 10 mg; ketorolac (0.5 mg/kg, max 30 mg); NS 10 cc/kg bolus	Chlorpromazine (0.1 mg/kg); NS 20 cc/kg up to 1 L; prochlorperazine not recorded; ketorolac 15 mg (if < 50 kg), 30 mg (if ≥50 kg)
Primary endpoint	≥50% reduction in headache at 1 hour and 3 hours	≥50% reduction in headache at 1-2 hours	Treatment failure (further rescue therapy, hospitalization, return within 48 hours)	≥50% reduction in headache at 30 or 60 minutes	Treatment failure (further rescue therapy, hospitalization, return within 48 hours)
Results	75% reached 1° endpoint at 1 hour, 90% at 3 hours. Headache resolved in 95% at 24 hours	94% reached 1° endpoint. Hundred percent pain free at discharge. Of patients with confirmed migraine, 68% with HA relapse in first week.	Treatment failure in 14%	By 60 minutes, 55.2% in ketorolac and 84.8% in prochlorperazine groups successfully treated (95% CI 8-52%).	40% (30/75) of chlorpromazine group and 15% (41/274) of the prochlorperazine group had treatment failure. Patients who received chlorpromazine had a higher rate of admission (16% vs 4.7%, $p < .0008$) and received more rescue medication (29.3% vs 9.9%, $p < .0001$)
Therapeutic gain	N/A (no placebo)	N/A (no placebo)	N/A (no placebo)	N/A (no placebo)	N/A (no placebo)

Table 2.—*Continued*

Authors	Kabbouche et al.[15]	Trottier et al.[5]	Trottier et al.[16]	Brousseau et al.[17]	Kanis et al.[18]
Side effects	None reported	5% with confirmed akathisia, 34% with suspected akathisia	1 patient (1%) with confirmed akathisia, 5% with suspected akathisia	1 patient with muscle rigidity, 1 with agitation (6% total)	Hypotension in the chlorpromazine group (12%) and sedation, and akathisia in the prochlorperazine group (12%)
Author's conclusions	Prochlorperazine is effective in aborting intractable migraine	Prochlorperazine very effective for short-term migraine relief	Prochlorperazine well tolerated, but akathisia is still possible despite diphenhydramine administration	Prochlorperazine IV is superior to ketorolac IV	Chlorpromazine IV is associated with higher rates of hypotension, greater need for rescue meds and hospitalization

diagnosis confirmed either by IHS criteria or a neurologist, 43/46 (94%) observed a $\geq$50% reduction in migraine intensity following prochlorperazine at first evaluation (1 or 2 hours post-treatment). While 50% were pain free at discharge, 68% total patients had recurrence of headache within the first week of discharge. About a third (34%) may have had akathisia, despite diphenhydramine premedication. However, only 5% of patients presented with both subjective and objective signs of akathisia, which were measured with an akathisia rating scale. Of those patients, half were successfully treated with an additional dose of diphenhydramine. The other 28% of patients reporting symptoms of akathisia had a subjective component without noted objective signs. The study authors emphasized prochlorperazine's use as a short-term agent for migraine attacks.

The same authors conducted a retrospective chart review 2 years earlier examining prochlorperazine failure rates in children ages 7–17 being treated in a tertiary pediatric ED for migraine.[16] Treatment failure, defined as a patient needing further rescue medication, becoming hospitalized, or returning to the ED for symptom recurrence or medication side effects within 48 hours, occurred in 13/92 (14%) of patients. Of these, akathisia was diagnosed in one patient, and resolved following subsequent diphenhydramine administration. Akathisia was suspected, based on descriptions of restlessness, in another 5 cases (5%).

A prospective randomized, double-blind study trial of children with migraine ages 5-17 presented to the emergency room compared the effectiveness of intravenous prochlorperazine (0.15 mg/kg; max 10 mg) to intravenous ketorolac (0.5 mg/kg; max 30 mg).[17] All patients concurrently received a 10 mL/kg normal saline bolus. The primary outcome was a reduction of $\geq$50% in pain score at 30 or 60 minutes. If this outcome was not achieved, subjects then received the alternate medication. By 60 minutes, 16/29 (55%) of subjects who received ketorolac vs 28/33 (85%) of those who received prochlorperazine were successfully treated (95% CI for difference 8-52%). Recurrent headache within 48 hours occurred in 7/26 (27%) of the prochlorperazine successes and 4/13 (31%) of the ketorolac successes. Of those patients who

received the second medication 1 hour after the initial medication, 12/16 (75%) met criteria for treatment success at 120 minutes. While this result suggests that the combination of intravenous prochlorperazine and ketorolac may be more effective than each agent alone, it should be interpreted with caution given the lingering effects of the first medication in addition to the brevity of migraine attacks in children. The medications were well tolerated, with one child who received prochlorperazine experiencing mild muscle stiffness that resolved on its own after a few hours, and another child who received prochlorperazine after ketorolac experiencing agitation that resolved after intravenous diphenhydramine. Limitations included lack of a placebo arm in addition to the use of validated Prensky and Sommer pediatric migraine criteria instead of IHS criteria for migraine.

Lastly, another retrospective cohort study of 12 to 21-year-old patients compared treatment failure and adverse effects of chlorpromazine to prochlorperazine for acute migraine treatment during a prochlorperazine shortage.[18] Forty percent (30/75) of the chlorpromazine group vs 15% (41/274, $p < .0001$) of the prochlorperazine group had treatment failure, defined as the need for additional therapy, hospitalization, or return to the ED within 48 hours. Patients who received chlorpromazine had a higher rate of admission (16% vs 4.7%, $p < .0008$) and were more likely to receive rescue medication (29.3% vs 9.9%, $p < .0001$). Adverse effects included documented but largely asymptomatic hypotension (BP < 90/50) in the chlorpromazine group (12%), and sedation and akathisia in the prochlorperazine group (12%). Both groups had similar decreases in pain scores, however, more patients were pain free after prochlorperazine (72%) vs chlorpromazine (55%, $p = .0049$).

Of the above studies, only one utilized a prospective, randomized controlled design. With this limitation in mind, it appears that for treatment of pediatric migraine in the emergency room IV prochlorperazine is more effective than IV ketorolac or IV chlorpromazine: with headache improvement seen in 75% or more of participants.[15]

More recently, a retrospective study using administrative data from 35 pediatric EDs[14] found that children receiving prochlorperazine for acute migraine treatment had a lower chance of ED revisit compared with metoclopramide. The authors also found that the addition of diphenhydramine with dopamine antagonists increased the risk of revisit, although the absolute increase in risk was small (1.5%). It was also unclear whether diphenhydramine was given as part of initial treatment plan, or in response to extrapyramidal side effects. Based on the available studies (Table 2), the potential benefits seem to outweigh the risks of using diphenhydramine with phenothiazines to prevent potential extrapyramidal side effects.

Valproate Sodium.—Valproic acid (VPA) is thought to modulate GABA receptors and affect sodium/calcium channels involved in neuronal inhibition.[19] There is one retrospective review (Table 3) of intravenous VPA treatment in 31 adolescent children with a mean age of 15 ± 2 years.[20] The study was conducted in an outpatient headache clinic, and most received 1000 mg of IV VPA, with 6 (19%) requiring an extra 500 mg bolus. Pain responses were graded on a 10-point scale, and those 25 (80%) patients who received one dose achieved a 40% reduction in pain, with a time to maximum relief of 63 ± 31 minutes. The authors found that 14 (47%) of patients had at least major relief, defined as a 51–80% reduction in pain scores. Side effects included cold sensation, dizziness, nausea, possible absence seizure, paresthesia, and tachycardia. A limitation was that patients had already received multiple medications that could have influenced pain responses, including concomitant dexamethasone and ondansetron.

One case series (Table 3) studied 12 pediatric patients (≤19 years, mean age 15) with migraine who received a single dose of either 500 mg or 1000 mg IV VPA in the ED.[21] Mean (SD) pain reduction on a 10-point pain scale from time of presentation to before VPA administration was 17% (18%). After VPA administration, an additional 36% (SD 34.2%) reduction in pain was experienced

Table 3.—Evidence Evaluating Valproic Acid for the Treatment of Acute Migraine in the Pediatric Population

Authors	Reiter et al.[20]	Sheridan et al.[21]
Study type and location	Retrospective chart review; outpatient pediatric headache clinic	Retrospective case series; multicenter pediatric ED
Ages and study size	13-17; n = 31	Less than 19; n = 12
Treatment	IV Valproic acid	IV Valproic acid
Dosing	Valproic acid 1000 mg, infused at 50 mg/min; 6 patients received an additional 500 mg	Valproic acid 1000 mg (9/12) or 500 mg (3/12)
Primary outcome	Reduction in pain on a 10-point numerical scale (0-10) pre and post infusions. Graded as no significant relief (0-50%), major relief (51-80%), and complete relief (81-100%)	Mean pain reduction on a 10-point numerical scale (0-10) pre and post infusions
Results	At least major improvement in headache pain in 14 (47%) of patients (either 1 or 2 doses); patients receiving only one dose (n = 25, 80%) experienced 40% reduction in pain	Mean pain reduction prior to VPA was 17%. VPA administration led to another 36% reduction in pain (SD 34.2%). Ten (83%) patients were discharged home after administration
Therapeutic gain	N/A	N/A
Side effects	Cold sensation, dizziness, nausea, possible absence seizure, paraesthesia, and tachycardia	Not assessed
Author's conclusions	IV VPA is well tolerated and may play a role in acute pediatric migraine management	IV VPA should be considered as migraine abortive therapy, especially prior to admission or use of narcotics
Comments	Pain score documentation not ideal; many patients received concomitant medications, including dexamethasone and ondansetron	Patients had received abortive medication prior to VPA administration

and 10 (83%) were discharged home after administration. As with the above study, one of the limitations is not being able to completely separate other medication effects from VPA. Nevertheless, the authors suggest that VPA administration can be considered before narcotics or admission.

Propofol.—Propofol is an anesthetic medication thought to act through GABA and calcium channels in the central nervous system.[22] There is one retrospective chart review comparing 7 pediatric patients who received propofol to 7 matched controls who received standard institutional acute migraine therapy with non-steroidal anti-inflammatories, prochlorperazine, and diphenydramine.[23] The average total dose of propofol given was 1.7 mg/kg, divided over an average of 3 boluses. Each bolus dose ranged from 10 to 50 mg, and was considered subanesthetic dosing. Patients who received propofol achieved significantly greater reduction in pain scores (80.1% vs 61.1%; $p < .05$) compared with matched controls. Their ED stay was shorter (122 minutes vs 203 minutes; $p = .2$) after treatment, however, this difference was not statistically significant. While no adverse events such as hypotension, respiratory depression, or hypoxia were recorded in either group, 2 patients in the propofol group were admitted for further pain monitoring. Limitations of this study include the very small sample size, and the potential for drug interactions with other central nervous system (CNS) acting medications. The controlled setting of the ED also likely contributed to propofol's low side effect profile, and more research in carefully controlled settings is needed before using this therapy broadly.

Magnesium.—Magnesium oral supplements have been studied in pediatric migraine prevention and found to lower severity.[24] There is one retrospective pediatric chart review study looking at IV

magnesium for acute treatment for headaches.[25] The authors reviewed 20 patients aged 13 to 18-years old who received IV magnesium sulfate based on their ED protocol of 30 mg/kg with a maximum dose of 2000 mg. Infusions were given over 30 minutes, and could be repeated in 2 hours if serum magnesium levels remained below an acceptable level. Pain improvement was defined as a decrease in perceived pain from severe to moderate, or a decrease of 3 points or more on a 10-point pain rating scale. Of the 7 (35%) patients who showed a favorable response, 5 of them were in status migrainosus, 1 was diagnosed with migraine, and 1 with tension type headache. Potential side effects such as flushing and burning were not specifically queried.

Bupivicaine.—Peripheral nerve blocks are common treatments used to treat difficult headache disorders in the outpatient setting, although the mechanism of action is not known and there is some controversy around their efficacy outside of cluster headache.[26] It is possible that modulation of nociceptive input at the trigeminocervical complex via injection at trigeminal nerve branches or upper cervical nerve branches (ie, greater occipital nerve) is one mechanism underlying the perceived effect.[27,28] While outcomes of greater occipital nerve injections for chronic primary headache disorders in children have been reported,[26] we did not find data on peripheral nerve blocks for acute migraine treatment in pediatrics.

However, one retrospective chart review study evaluated the therapeutic response of muscle blocks into the bilateral paraspinous musculature of the back using 0.5% bupivicaine injections at the level of the sixth or seventh cervical vertebra.[29] Patient aged 12–17 years with a diagnosis of headache or migraine were enrolled. Baseline mean headache intensity was 9.15/10, and mean headache duration prior to presentation 3.16 days. The primary outcome of headache relief, defined as reduction to $\leq$2/10 on the pain intensity scale, was achieved in six out of 13 (46%) subjects. Five out of 13 (38%) reported partial relief, defined as some reduction in headache intensity. Two out of 13 patients did not achieve any headache relief, and one of those was subsequently diagnosed with viral meningitis by lumbar puncture. There were no procedural complications reported. Limitations of this study included small sample size, lack of clear headache diagnosis, and lack of follow-up on duration of treatment effect.

Opioids.—To the authors' knowledge, there are no studies evaluating opioids for use in acute treatment of pediatric migraine. There is concern that opioids facilitate sensitization of the central nervous system to pain, and they are implicated in the progression of episodic to chronic migraine in adults.[30] Despite these concerns, opioids are increasingly prescribed in the ED for acute migraine management in adults,[31] Opioids are not part of the American Academy of Neurology (AAN) practice parameter for pediatric pharmacologic treatment of migraine headache.[32]

One study retrospectively compared management of pediatric headache in a tertiary care vs a community hospital.[4] Results showed significantly higher use of opioids in the community hospital: 12/158 (7.6%) vs 21/63 (33.3%), $p < .001$. In a Canadian national practice variation study on treatment of children with migraine in the ED, the authors found that opioids were the second most commonly prescribed medication, at an estimated frequency of 5.5% (95% CI 3.2-9.2; $p < .001$).[2] This finding is in contrast to triptan medications, which were the least frequently prescribed medication at 0.5% (95% CI 0.1-2.6; $p < .001$).

More recently, a retrospective, observational study evaluated electronic health records during first encounters for primary migraine or headache in patients aged 6-17.[33] This study included primary care, specialty, and ED locations in metropolitan and nonmetropolitan areas across four states. Patients with a diagnosis of migraine (OR = 1.63, 95% CI 1.34–1.89, $p < .001$) or headache (OR = 1.60, 95% CI 1.42-1.80, $p < .001$) were more likely to be prescribed an opioid than those without a formal diagnosis. As age increased, so did the likelihood of being prescribed an opioid (OR = 1.14, 95% CI = 1.12–1.16, $p < .001$). These findings are concerning, especially given the risks of safety-related side effects and opioid effects on migraine sensitization.

Triptans.—While triptans are the only class of medication currently marketed specifically for treatment of acute migraine, they are commonly underutilized in the pediatric emergency room setting.[2] This may be because they have already been tried at home and found ineffective prior to ED presentation, were not used in the appropriate time window prior to headache escalation, or due to provider lack of familiarity with the medications. Furthermore, there may be hesitation to administer triptans within 24 hours of DHE therapy, which may be considered in refractory cases. There is also concern for decreased triptan effectiveness once central sensitization has occurred, based on experimentation in a rat model.[34] However, it is worth noting that even once pain has become severe, in adult migraineurs nearly half will still have pain relief at 2 hours if treated with a combination of sumatriptan and naproxen.[35] Of the articles searched in this review, none pertained to triptan use in the pediatric ED. There are nevertheless numerous studies evaluating triptan effectiveness in the pediatric population in an outpatient setting, and it is worthwhile reviewing the evidence for this class of medication in the pediatric population.

The 2004 AAN Practice parameter on the pharmacologic treatment of migraine headache in children and adolescents concluded that sumatriptan nasal spray (NS) is effective and should be considered for the acute treatment of migraine in adolescents (Level A). At that time, there were no data to support or refute the use of any oral triptan preparations.[31] Since that time, three triptans and a fourth triptan/NSAID combination have been approved by the Food and Drug Administration for acute migraine therapy in the pediatric population: almotriptan in 12 to 17-year olds (6.25 or 12.5 mg oral), rizatriptan in 6 to 17-year olds (5 mg MLT for 20–39 kg, 10 mg MLT for $\geq$40 kg), zolmitriptan NS in ages 12-17 (2.5 or 5 mg), and sumatriptan 10 mg combined with naproxen 60 mg in ages 12-17 (with option to increase dosage to 85 mg sumatriptan combined with 500 mg naproxen).[36] Studied triptans in the pediatric population include almotriptan, rizatriptan, zolmitriptan oral and NS, and sumatriptan oral, nasal, and injectible formulations.

Almotriptan.—One multicenter randomized, double-blind, placebo-controlled trial has looked at almotriptan efficacy and tolerability in 12 to 17-year olds with migraine.[37] Patients were randomized to either almotriptan 6.25 mg, 12.5 mg, 25 mg, or placebo to treat one migraine attack. The primary endpoint was headache pain relief at 2 hours, defined as a decrease from moderate or severe pain intensity to mild or no pain. Co-primary endpoints included the presence or absence of nausea, photophobia, and phonophobia 2 hours after dosing. The 2-hour pain-relief rates were significantly higher with almotriptan 6.25 mg (71.8%, $p = .001$), 12.5 mg (72.9%, $p < .001$), and 25 mg (66.7%, $p = .028$) vs placebo (53%). Almotriptan was well tolerated, and the 12.5 mg dose was considered most successful at relieving headache pain and associated photophobia and phonophobia.

Rizatriptan.—A study examining the efficacy of rizatriptan (Table 4) used a double-blind, placebo-controlled three-way crossover design in patients aged 6-17.[38] The primary endpoint was headache relief measured by reduction by at least 2 grades on a 5-point validated pain scale, 2 hours after medication administration. At 2 hours, the primary endpoint was reached in 74% and 73%, respectively, of first and second treatment groups, vs 36% of placebo ($p < .001$). The two-hour pain freedom rate was 35% after the first treatment and 31% after the second treatment, vs 18% after placebo (rizatriptan first vs placebo, $p = .015$, rizatriptan second vs placebo, $p = .037$). Side effects were mild, and included tiredness, dry mouth, a burning feeling in the head, flushing of the cheeks, and pain in the ankles.

A more recent study (Table 4) using a randomized, double-blind, placebo-controlled design in 6 to 17-year olds evaluated 2 hour pain freedom following rizatriptan administration.[39] This study aimed to address the high pediatric placebo response rate by using a run-in period wherein patients who responded to placebo within 15 minutes took no further study medication. Results in the 12 to 17-year olds showed that 2-hour pain freedom in the rizatriptan group was 30.6% vs 22% in placebo. Side effects were mild and included dizziness,

Table 4.—Evidence Evaluating Rizatriptan for the Treatment of Acute Migraine in the Pediatric Population

Authors	Ahonen et al.[38]	Ho et al.[39]
Study type and location	Double-blind, randomized, placebo-controlled 3-way crossover design; multicenter pediatric outpatient clinics	Double-blind, randomized, placebo-controlled; multicenter outpatient clinics
Ages and study size	6-17; n = 96	6-17; n = 915
Treatment	3 migraine attacks: 2 doses of rizatriptan and 1 placebo dose	2 migraine attacks: 1 placebo and 1 rizatriptan dose
Dosing	Rizatriptan 5 mg for 20-39 kg; rizatriptan 10 mg for ≥40 kg	Rizatriptan 5 mg for <40 kg; rizatriptan 10 mg for ≥40 kg
Primary outcome	2 hour pain reduction by at least 2 grades on a validated 5-point pain scale	2 hour pain freedom – used a 5-point pain scale
Results	2 hour pain reduction 74% (1st tx) and 73% (2nd tx) vs 36% of placebo ($p < .001$). Two hour pain freedom rate 35% (1st tx) and 31% (2nd tx), vs 18% after placebo (rizatriptan 1st vs placebo, $p = .015$, rizatriptan 2nd vs placebo, $p = .037$)	In the 12 to 17-year olds, 2 hour pain freedom in the rizatriptan group was 30.6% vs 22% in placebo. In 6 to 11-year olds, differences between rizatriptan and placebo were not significant
Therapeutic gain	2 hour pain reduction: 38% and 37% after 1st and 2nd doses 2 hour pain freedom: 17% and 13% after 1st and 2nd doses	2 hour pain freedom: 8.6% in 12 to 17-year olds
Side effects	Mild, and occurred in more patients at higher dosing (6% vs12%); tiredness, dry mouth, burning feeling in the head, flushing of the cheeks, and ankle pain	Mild, and included dizziness, fatigue, nausea, somnolence, upper abdominal pain, and vomiting
Author's conclusions	Rizatriptan is highly effective in treatment of pediatric acute migraine	Rizatriptan showed statistically significant improvement over placebo in eliminating pain and was generally well tolerated
Comments	5-faced pain scale instead of 4 may explain higher headache relief response rate than other trials	Initial screening occurred, where patients who responded to placebo took no further study medication

fatigue, nausea, somnolence, upper abdominal pain, and vomiting. Both of the above studies (Table 4) used a dose of 5 mg if <40 kg, and 10 mg if above 40 kg and both had a two-hour pain freedom rate of about 30% in the rizatriptan arm.

Zolmitriptan.—There are two randomized, double-blind, placebo-controlled trials evaluating oral zolmitriptan vs placebo (Table 5). One was a multicentered trial of 12 to 17-year olds (n = 850), evaluating 2 hour response rates following administration of zolmitriptan 2.5, 5, or 10 mg, or placebo.[40] The primary endpoint was headache response 2 hours post-treatment, defined as an improvement in headache pain from moderate or severe to mild or none. There was a high placebo response rate in this trial of 58%, compared with response rates of 57% at 2.5 mg dose, 53% at 5 mg dose, and 54% at 10 mg dose. Zolmitriptan was well tolerated, with the most common side effects of tightness, dizziness, nausea, and parasthesia observed in 6.7% of patients.

The other trial was smaller (n = 32), and used a cross-over design where patients at a regional outpatient headache clinic aged 6-18 received placebo, zolmitriptan 2.5 mg, and weight-based ibuprofen to treat 3 consecutive migraine attacks.[41] The authors had the same primary endpoint: pain relief at 2 hours, defined as no or mild headache after moderate or severe headache. Results showed 2 hour pain relief rates of 62% for zolmitriptan ($p < .05$), 69% for ibuprofen ($p < .05$), and 28% for placebo. Side effects occurred in about one-third of patients, and included stomach upset, fatigue, and dizziness.

Table 5.—Evidence Evaluating Zolmitriptan for the Treatment of Acute Migraine in the Pediatric Population

Authors	Rothner et al.[40]	Evers et al.[41]	Lewis et al.[42]	Winner et al.[43]
Study type and location	Randomized, double-blind, placebo-controlled trial; multicenter	Randomized, double-blind, placebo-controlled, cross-over trial; outpatient headache clinic	Randomized, double-blind, placebo-controlled; multicenter	Randomized, double-blind, parallel-group, placebo-controlled; multicenter
Ages and study size	12-17; n = 850	6-18; n = 32	12-17; n = 248	12-17; n = 798
Treatment	1 migraine attack; oral zolmitriptan or placebo	3 consecutive migraine attacks; placebo, zomitriptan, and ibuprofen	2 migraine attacks; zolmitriptan nasal spray and placebo	1 migraine attack; zolmitriptan nasal spray at 3 doses or placebo
Dosing	Zolmitriptan 2.5, 5, or 10 mg PO	Zolmitriptan 2.5 mg PO; ibuprofen 200 mg <12-years old, 400 mg in adolescents	Zolmitriptan 5 mg nasal spray	Zomitriptan 0.5 mg, 2.5 mg, or 5 mg nasal spray
Primary outcome	2 point reduction in intensity on a 4-point pain scale	2 point reduction in intensity on a 4-point pain scale	2 point reduction in intensity on a 4-point pain scale	Pain free status at 2 hours post-treament
Results	Headache response: 57% at 2.5 mg dose, 53% at 5 mg dose, 54% at 10 mg dose, and 58% placebo response	2 hour pain relief rates: 62% for zolmitriptan ($p < .05$), 69% for ibuprofen ($p < .05$), and 28% for placebo	Nasal spray demonstrated a higher headache response rate at 1 hour (58.1%) than the placebo group (43.3%; OR: 1.8; 95% CI: 1.1-2.9; $p < .05$).	Headache freedom was higher in zolmitriptan 5 mg nasal spray group (29.7%) vs placebo (16.6%, $p < .001$)
Therapeutic gain	None	34% for zolmitriptan; 41% for ibuprofen	15%	13.1%
Side effects	Well tolerated; most common side effects of tightness, dizziness, nausea, and parasthesia in 6.7% of patients	Occurred in one-third of patients: included stomach upset, fatigue, and dizziness	Most common side effect of taste disturbance in 6.5% of patients	Taste disturbance was most commonly reported AE: 0.5 mg (6.5%), 2.5 mg (6.2%), 5 mg (12.6%)
Author's conclusions	Oral zolmitriptan did not differentiate from placebo	Oral zolmitriptan 2.5 mg showed similar efficacy as ibuprofen	Zolmitriptan 5 mg NS was well tolerated and produced fast and significantly effective relief of migraine symptoms	Zolmitriptan 5 mg NS significantly improves pain-free status compared to placebo
Comments	High placebo response rate		"placebo challenge" resulted in treatment delay of up to 45 minutes	Completed a placebo challenge, if negative then were randomized. The 0.5 mg and 2.5 mg doses were discontinued in the interim analysis because they met pre-set futility criteria

Zolmitriptan (5 mg) NS has been studied in two multicenter double-blind, randomized placebo-controlled studies (Table 5) of 12 to 17-year olds.[42,43] In the first, the primary endpoint was headache response at 1 hour post-treatment, defined as a 2-point reduction in headache intensity on a 4-point scale.[42] In the 12-week treatment period, zolmitriptan NS demonstrated a higher headache response rate at 1 hour (58.1%) than the placebo group (43.3%; $p < .05$). It was well tolerated, with the most frequently reported adverse event of taste disturbance experienced by 6.5% of participants. This study attempted to limit placebo response rate by initially treating all participants with placebo NS. If no effect was noted after 15 minutes, then zolmitriptan NS or matching placebo NS was administered.

In the second study, the primary outcome was pain freedom at 2 hours post-treatment.[43] To limit placebo response rate, patients had a 30-day placebo challenge run-in period. While patients were randomized to 5 mg, 2.5 mg, 0.5 mg, or placebo, the 0.5 mg and 2.5 mg doses were discontinued at the interim analysis as they met preset futility criteria. Results showed that 29.7% of patients in the 5 mg treatment group achieved the primary outcome, compared to 16.6% of placebo ($p < .001$). Dysgeusia was the most commonly reported adverse effect, reported in 12.6% of patients in the 5 mg groups and 1.2% for placebo.

In summary, pediatric migraine studies suggest zolmitriptan NS is more effective in the pediatric population than the oral formulation.

Sumatriptan.—Intranasal sumatriptan has had 3 positive, randomized, placebo controlled trials (Table 6), and is recommended for the acute treatment of headaches in adolescents according to the 2004 AAN parameter for pharmacologic treatment of migraine in children and adolescents.[31] In the first study, 14 children ages 6–9 were administered sumatriptan 20 mg NS or placebo.[44] The primary endpoint of reduction in headache intensity by at least 2 grades after 2 hours was achieved in 86% of the treatment group, compared with 43% after placebo ($p < .031$). A subsequent multicenter trial of 510 adolescents aged 12-17 evaluated the effect of single doses of sumatriptan NS (5 mg, 10 mg, and 20 mg) or identically appearing placebo NS.[45] The primary outcome of reduction in headache from severe or moderate to mild or no headache was achieved in 66% of patients receiving 5 mg NS ($p < .05$), 63% of those receiving the 20 mg dose ($p = .059$), and 53% of placebo. This study also noted significant relief ($p < .05$) at the 5 mg, 10 mg, and 20 mg doses and a significant reduction in photophobia and phonophobia at the 20 mg dose ($p < .05$). The last study involved a cross-over design of 8 to 17-year olds ($n = 83$), and used a sumatriptan NS dose of 10 mg if <40 mg, and 20 mg if ≥40mg.[46] The primary outcome of 2 hour headache relief from severe/moderate to at least 2 grades lower on a 5 face pain scale was achieved in 64% of the treatment and 39% of placebo group ($p = .003$). In these studies, bad taste was the most common adverse effect. It appears that lower doses had similar efficacy to higher doses for pain relief, but a higher intranasal dose may be more effective at reducing associated sensitivity symptoms.

Two studies performed in the 1990's (Table 6) have evaluated the effectiveness of injectible sumatriptan in the pediatric population.[47,48] Both evaluated sumatriptan in an open-label fashion. The first evaluated 17 patients between the ages of 6 to 16-years old.[47] Patients received 3 mg if <30 kg or 6 mg if >30 mg). Headache resolved or decreased in intensity in 65% of participants. The second evaluated 50 children ages 6-18 at an outpatient child neurology clinic, using a dose of 0.06 mg/kg.[48] The primary outcome of headache reduction from severe/moderate to mild/none within 2 hours was achieved in 78%. Side effects included chest and neck discomfort.

There is one double-blind, randomized, placebo-controlled crossover trial (Table 6) evaluating oral sumatriptan effectiveness at 50 mg and 100 mg doses.[49] Children ages 8-16 were evaluated, with a primary endpoint of ≥50% decrease in pain intensity at 2 hours. Sumatriptan was not more effective than placebo.

Sumatriptan-naproxen combinations used in the adult population have shown superior efficacy to both sumatriptan and naproxen individually in the

Table 6.—Evidence Evaluating Sumatriptan for the Treatment of Acute Migraine in the Pediatric Population

Authors	Ueberall and Wenzel[44]	Winner et al.[45]	Ahonen et al.[46]	Macdonald[47]	Linder[48]	**McDonald et al.[50]**	**Derosier et al.[51]**
Study type and location	Randomized, double-blind, placebo-controlled cross-over design; outpatient	Randomized, double-blind, placebo-controlled, single-attack; outpatient multicenter	Randomized, double-blind, placebo-controlled, 2-way cross over design; outpatient multicenter	Prospective, open-label; outpatient	Prospective, open-label; outpatient	Open-label, uncontrolled, long-term (≤12 months); outpatient multicenter	Randomized, double-blind, placebo-controlled, parallel group 12 week trial; outpatient multicenter
Ages and study size	6-9; n = 14	12-17; n = 510	8-17; n = 83	6-16; n = 17	6-18; n = 50	12-17; n = 622	12-17; n = 589
Treatment	2 migraine attacks; sumatriptan nasal spray and placebo	1 migraine attack; sumatriptan nasal spray vs placebo	2 migraine attacks; sumatriptan nasal spray and placebo	sumatriptan SC	sumatriptan SC	Multiple migraine attacks; sumatriptan/naproxen sodium combination	2 migraine attacks, 1 during run-in phase; sumatriptan/naproxen combination vs placebo
Dosing	Sumatriptan 20 mg NS	Sumatriptan 5, 10, or 20 mg NS	Sumatriptan 10 mg NS if 20-39 kg, 20 mg NS if ≥40 kg	Sumatriptan SC 3 mg (<30 mg) or 6 mg (≥30 mg)	Sumatriptan SC 0.06 mg/kg	Sumatriptan PO 85 mg; naproxen sodium 500 mg	Sumatriptan/naproxen PO combinations: 10/60 mg, 30/180 mg, or 85/500 mg
Primary outcome	2 hour reduction in intensity by ≥2 grades (4-point scale)	2 hour reduction in intensity by ≥2 grades (4-point scale)	2 hour reduction in intensity by ≥2 grades (5-point scale)	2 hour headache resolution (absence of headache)	2 hour reduction in intensity by ≥2 grades (4-point scale)	Pain-freedom within 2 hours of treatment	Pain-freedom 2 hours post-treatment for moderate to severe migraine
Results	86% of sumatriptan group showed improvement vs 43% of placebo ($p < .031$)	66% of patients receiving 5 mg NS ($p < .05$), 63% of those receiving the 20 mg dose ($p = .059$), and 53% of placebo showed improvement at 2 hours	64% of tx group showed improvement vs 39% of placebo ($p = .0003$)	11/17 (65%) headache free at 2 hours vs 6/17 (35%) with resolution at 1 hour	78% of participants experienced intensity reduction	42% of migraine attacks were pain-free within 2 hours of treatment	Two hour pain free rates adjusted for age and pain severity were higher than placebo (10%) for all doses, with sumatriptan/naproxen 10/60 mg (29%; $p = .003$), 30/180 mg (27%;

Table 6.—*Continued*

Authors	Ueberall and Wenzel[44]	Winner et al.[45]	Ahonen et al.[46]	Macdonald[47]	Linder[48]	**McDonald et al.**[50]	**Derosier et al.**[51]
							adjusted $p = .003$), and 85/500 mg (24%; adjusted $p = .003$)
Therapeutic gain	43%	13% at 5mg; 10% at 20mg	25%	N/A	N/A	N/A	10/60mg: 19%30/180mg: 17%85/500: 14%
Side effects	Taste disturbance	Taste disturbance	Taste disturbance, sometimes followed by nausea or vomiting	Brief and mild; neck pressure	Present in 80%; mild and transient; chest and neck discomfort	Nausea (7%), dizziness (3%), muscle tightness (3%), and chest discomfort (3%)	Present in 11%, and included nasopharyngitis, hot flush, and muscle tightness
Author's conclusions	Sumatriptan NS is significantly better than placebo for relieving migraine headache	Sumatriptan NS is effective and well-tolerated, with 20-mg dose providing best overall efficacy and tolerability	Sumatriptan NS is effective and well-tolerated for migraine attacks in children over 8 years of age	Subcutaneous sumatriptan can be safe and effective as abortive agent in juvenile migraine	Subcutaneous sumatriptan can be safe and effective in childhood migraine	Sumatriptan/naproxen sodium provided freedom from migraine pan over time and improved medication satisfaction and quality of life	All doses of sumatriptan/naproxen were well tolerated, providing similarly effective acute treatment of adolescent migraine pain and associated symptoms
Comments		Also noted a significant reduction in photophobia and phonophobia at 20 mg dose ($p < .05$).		Most also reported marked improvement in associated symptoms (nausea and photophobia)	46% of participants responded within 60 minutes; gender disparity – 91% of males and 68% of females responded		Had a single-blind 12-week run in phase during which treated 1 migraine with placebo. Placebo nonresponders were randomly assigned in the double-blind phase

Table 7.—Evidence Evaluating DHE for the Treatment of Acute Migraine in the Pediatric Population

Authors	Linder[56]	Kabbouche et al.[57]	Hamalainen et al.[58]
Study type and location	Retrospective chart review; inpatient pediatric hospital	Retrospective chart review; inpatient pediatric hospital	Double-blind, placebo controlled, cross-over study; multicenter inpatient pediatric hospitals
Ages and study size	8-22; n = 30	12-16; n = 32	6-15; n = 12
Treatment	Low dose IV DHE; metoclopramide premedication	IV DHE; metoclopramide or prochlorperazine premedication for first 3 doses, then ondansetron for rest	Oral DHE
Dosing	IV DHE – age 6-9, 0.1 mg/dose; age 9-12, 0.15 mg/dose; age 12-16, 0.2 mg, increasing by 0.05 mg as tolerated (q6 hours for 5-8 doses); premedication with oral metoclopramide 0.2 mg/kg, 30 minutes prior to DHE doses	IV DHE 1 mg if >25 kg or >9 y.o.; 0.5 mg if <25 kg or <9 y.o., every 8 hours for 5-20 doses. All patients received D5NS 20 mg/kg NS bolus; metoclopramide, prochlorperazine, ondansetron doses not specified	Oral DHE 20 μg/kg, or DHE 40 μg/kg
Primary outcome	Response to DHE: (1) excellent: >90% reduction in either headache intensity or frequency or a >75% reduction in both, (2) good: >75% reduction in either headache intensity or frequency or a >50% reduction in both, (3) fair: >50% reduction in either headache intensity or frequency, (4) poor: <50% reduction in both headache intensity or frequency	Headache freedom	2 hour headache reduction by $\geq$2 grades on a 5-point scale
Results	Excellent response 24/30 (80%); Fair response 3/30 (10%); poor response 3/30 (10%)	On discharge, 74% of patients were headache free. Mean pain severity on d/c was 1.02 ± 2.22 (on a 0 to 10-point scale)	7/12 (58%) in treatment group, 2/12 (17%) after placebo – 95% CI 14-70%. Not statistically significant
Therapeutic gain	N/A	N/A	41.00%
Side effects	DHE: flushing, extremity tingling, leg cramping, transient increase in headache	DHE: nausea/vomiting (91.5%), chest tightness (6%), hives (2.8%), face flushing (2.8%) increased blood pressure (2.8%)	Nausea and vomiting with DHE and placebo
Author's conclusions	Patients with prolonged migraine without aura can be safely treated with short-term DHE hospitalization	DHE is a very effective therapy for migraine headache in children and adolescents	DHE efficacy appears superior to placebo, although statistical significance was not reached
Comments	Headache duration ranged between 5 days and 3 months	40% headache free by 5th dose, 67% headache free by dose 12-13	Dose could be repeated after 1 hour

resolution of acute migraine attacks.[35] In the pediatric literature, there has been a multicenter, open-label study of sumatriptan 85 mg/naproxen sodium 500 mg in adolescents (Table 6) aged 12–17.[50] The authors found that in over 12,000 exposures to sumatriptan/naproxen, 42% of the attacks culminated in pain freedom within 2 hours. In another randomized, double-blind, placebo-controlled, parallel group 12-week trial in 12 to 17-year olds with episodic migraine, patients were randomized to

Table 8.—Summary Impression of Medication Efficacy for Acute Migraine Based on Available Trials

Medications	Number of trials	Outcome Pain reduction	Outcome Pain freedom	Outcome Treatment failure rate	Therapeutic gain (%)
Fluids	1	+			
Analgesics					
Acetaminophen vs ibuprofen	1*	+			
Ibuprofen alone	1	+			23
Dopamine receptor antagonists					
Prochlorperazine	3	+ +	+ +	+	
Prochlorperazine vs ketorolac	1* (no placebo)	+			
Chlorpromazine vs prochlorperazine	1			+	
Valproate sodium	2	+ +			
Propofol	1	+			
magnesium	1	+			
Bupivicaine	1	+			
Triptans					
Almotriptan	1*	+	+ (12.5 mg dose)		14.7-20
Rizatriptan	2*	+	−		8.6-38
Zolmitriptan oral	2*	−/+			None to 34
Zolmitriptan nasal	1*	+			15
Sumatriptan oral	1*	−			
Sumatriptan nasal	3*	+ + +			10-43
Sumatriptan injectible	2	+	+		
Sumatriptan/naproxen combination	2* (1 study)		+ +		14-19
DHE IV	2	+	+		
DHE oral	1*	−			41 (large CI)

+ = positive results (within limits of study design).− = negative result (if compared with placebo).* = randomized placebo-controlled trial, except if indicated.

either placebo or a sumatriptan/naproxen combination dose: 10/60 mg, 30/180 mg, or 85/500 mg.[51] The primary end point was pain freedom at 2 hours for those headaches that were moderate/severe prior to treatment. Two hour pain free rates adjusted for age and pain severity were higher than placebo (10%) for all doses, with sumatriptan/naproxen 10/60 mg (29%; $p = .003$), 30/180 mg (27%; adjusted $p = .003$), and 85/500 mg (24%; adjusted $p = .003$). The medication was well-tolerated, with 11% of subjects reporting side effects, the most common of which were nasopharyngitis, flushing, and muscle tightness. This study led to the combination of oral sumatriptan/naproxen becoming FDA labeled for acute migraine in adolescents.

Dihydroergotamine.—Dihydroergotamine mesylate (DHE) is an ergot alkaloid that has been extensively used in acute and chronic migraine.[52] While it is available in intramuscular, intravenous, and oral forms, the oral form has very poor bioavailability and the intravenous formulation has a lower T_{max} compared with the intramuscular, intranasal, and oral formulations.[53] DHE for migraine has been well studied in the adult population,[54,55] however, there are fewer studies in the pediatric population (Table 7). One retrospective review of 30 hospitalized patients aged 8-22 used low dose intravenous DHE ranging from 0.1 mg to 0.5 mg per dose for a range of 3–8 doses.[56] They received anti-nausea premedication with metoclopramide 30 minutes before each infusion. Eighty

percent of patients reported an excellent response, defined as >90% reduction in either headache intensity or frequency, or a >75% reduction in both. The study did not follow the patients long-term to know how long the positive response was sustained.

Another retrospective study has looked at the use of IV DHE in 32 children and adolescents in status migraine.[57] The patients were administered IV DHE every 8 hours at a dose of 1 mg if >25 kg or older than 9 years, and 0.5 mg if younger and lighter. They were also premedicated with antiemetics half an hour prior to each DHE dose. The doses were repeated for a minimum of 5 doses, and continued for one dose after patients achieved headache freedom (maximum of 20 doses). At discharge, 74.4% of patients reported headache freedom, and the mean headache severity was 1.02 ± 2.22 on a 0 to 10-point scale. Side effects of nausea and/or vomiting were present in a vast majority of the patients, and other side effects included chest tightness (6%), hives (2.8%), face flushing (2.8%), and increased blood pressure (2.8%). The patients were not followed after discharge to assess for headache recurrence.

Oral DHE, which has <1% bioavailability,[53] has been studied in children in one double-blind, placebo-controlled cross-over study of 2 doses.[58] While 7/12 (58%) children reached the primary endpoint of reduction of headache by at least 2 grades on a 5 grade pain scale at 2 hours, the results did not reach statistical significance.

DISCUSSION

When looking at the studies as a whole, treatments considered effective for acute migraine or benign primary headache (Table 8) in the analgesic category include ibuprofen, and to a lesser degree acetaminophen. Ketorolac was not compared to other NSAIDs, but was found to be less effective than prochlorperazine. Of the phenothiazines, prochlorperazine seems most effective but formal comparative efficacy studies are needed. Of the triptan medications, almotriptan, rizatriptan, zolmitriptan nasal spray, sumatriptan nasal spray, and combination sumatriptan/naproxen are effective agents for acute treatment of migraine in adolescents. Treatments considered probably effective include IV fluids, chlorpromazine, valproate sodium, injectable sumatriptan, and IV DHE. Treatments with inconsistent results included oral zolmitriptan; oral DHE was ineffective. While oral sumatriptan on its own was not different from placebo, oral sumatriptan in combination with naproxen is effective for migraine treatment in adolescents and is now FDA labeled for this indication. There is insufficient evidence to comment on propofol, magnesium, and bupivicaine efficacy. The treatments were overall well tolerated, with the most side effects occurring with prochlorperazine.

There are several limitations to this review. There have been few RCTs for pediatric migraine in the emergency room setting, therefore, we included uncontrolled studies which are methodologically less rigorous. The search could also have been expanded to include abstracts from other journals in addition to *Headache*. Another limitation was the variability in outcome measures between studies, which limits comparison between studies. Other factors that could affect interpretation include the cumulative effect of other medications administered prior to presentation in trials performed in the ED, although this is more of an issue in uncontrolled studies.

Migraine can be an incapacitating primary headache disorder, with a 1-year prevalence in the adolescent population of 6.3% (5.0% in boys and 7.7% in girls).[59] This article has reviewed the available studies on acute therapeutic options in children and adolescents with migraine, with the hope that future studies will expound on the most safe and effective therapeutic treatments to use in the pediatric ED setting.

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