

# A Comparison of Acute Treatment Regimens for Migraine in the Emergency Department

Richard G. Bachur, MD, Michael C. Monuteaux, ScD, Mark I. Neuman, MD, MPH

## abstract

**BACKGROUND AND OBJECTIVES:** Migraine headache is a common pediatric complaint among emergency department (ED) patients. There are limited trials on abortive therapies in the ED. The objective of this study was to apply a comparative effectiveness approach to investigate acute medication regimens for the prevention of ED revisits.

**METHODS:** Retrospective study using administrative data (Pediatric Health Information System) from 35 pediatric EDs (2009–2012). Children aged 7 to 18 years with a principal diagnosis of migraine headache were studied. The primary outcome was a revisit to the ED within 3 days for discharged patients. The primary analysis compared the treatment regimens and individual medications on the risk for revisit.

**RESULTS:** The study identified 32 124 children with migraine; 27 317 (85%) were discharged, and 5.5% had a return ED visit within 3 days. At the index visit, the most common medications included nonopioid analgesics (66%), dopamine antagonists (50%), diphenhydramine (33%), and ondansetron (21%). Triptans and opiate medications were administered infrequently (3% each). Children receiving metoclopramide had a 31% increased odds for an ED revisit within 3 days compared with prochlorperazine. Diphenhydramine with dopamine antagonists was associated with 27% increased odds of an ED revisit compared with dopamine antagonists alone. Children receiving ondansetron had similar revisit rates to those receiving dopamine antagonists.

**CONCLUSIONS:** The majority of children with migraines are successfully discharged from the ED and only 1 in 18 required a revisit within 3 days. Prochlorperazine appears to be superior to metoclopramide in preventing a revisit, and diphenhydramine use is associated with increased rates of return.

**WHAT'S KNOWN ON THE SUBJECT:** Migraine headaches are a common presenting complaint in emergency departments. Abortive treatment in this setting is not well studied, leading to considerable variation in treatment. The relationship between acute medications and emergency department revisits has not been studied.

**WHAT THIS STUDY ADDS:** Eighty-five percent of children with migraine are successfully discharged from the emergency department; only 1 in 18 children require a return visit. Prochlorperazine is associated with less revisits than metoclopramide, and diphenhydramine use is associated with increased risk of return visits.

*Division of Emergency Medicine, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts*

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Address correspondence to Richard Bachur, MD, Division of Emergency Medicine, Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: [richard.bachur@childrens.harvard.edu](mailto:richard.bachur@childrens.harvard.edu)

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Migraine headache is common in children with a prevalence of 8% to 23% by 15 years of age<sup>1</sup> and has significant morbidity associated with missed school, reduced participation in sports, and depression.<sup>2,3</sup> Although previous publications have discussed the management of pediatric migraine in the emergency department (ED),<sup>4-6</sup> there is only a single pediatric controlled trial conducted in the ED setting<sup>7</sup>; therefore, most of the recommendations are based on treatment trials in adults or other non-ED settings with off-label use of medications.

By the time children present to an ED for migraine care, the headache has typically been present for 2 to 3 days,<sup>6,8</sup> and most patients have already tried some abortive therapy.<sup>5,6</sup> Treatment in a pediatric ED rather than a general ED has been associated with increased use of dopamine antagonists, less use of opioids, and increased rates of headache resolution.<sup>9</sup> ED studies in adults have investigated the efficacy of dopamine receptor antagonists, analgesics including nonsteroidal medications and opiates, and triptans.

In the absence of controlled ED studies in the treatment of pediatric migraine, a large health care database may provide evidence for best treatment practices. We aimed to compare the effectiveness of the most common acute treatment regimens for pediatric migraine in preventing revisit after ED discharge.

## METHODS

### Data Source and Design

This retrospective study used administrative data obtained from the Pediatric Health Information System (PHIS), which is managed by the Children's Hospital Association (Overland Park, KS), a business alliance of freestanding pediatric hospitals. Data quality and reliability were ensured through a joint effort

between the Children's Hospital Association and participating hospitals. The data warehouse function for the PHIS database is managed by Thomson Reuters (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Forty of these hospitals also submit resource utilization data (eg, pharmaceuticals, imaging, and laboratory) into PHIS; 35 of the hospitals have gone through a more detailed data validation of ED data and will be used for this investigation. Data are deidentified at the time of data submission and are subject to a number of reliability and validity checks before being included in the database. No patient-level clinical data exists in the database, but this administrative database has been used previously for comparative effectiveness research.<sup>10,11</sup>

### Study Patients

We included children aged 7 to 18 years who were evaluated in the ED from 2009 through 2012, inclusive, and had a principal diagnosis of migraine (*International Classification of Disease, Ninth Revision*, code 346.XX). We excluded children with a complex comorbid condition<sup>12</sup> (examples include congenital heart disease, myopathies, cystic fibrosis, sickle cell anemia) as well as children transferred to the study institution. For this study, we also assumed any diagnostic testing or therapeutic interventions were performed for the purpose of evaluating and treating the migraine headache.

### Analytic Plan

The primary outcome was defined as revisits to the ED within 3 days for patients who were discharged from the index encounter. All revisits within the 3-day window were included, regardless of principal diagnosis or disposition associated with the revisit. If a patient

experienced >1 repeat visit, only the first revisit was included in the analysis. For the purposes of describing the patient population and ED evaluation, all interventions performed on the encounter day were considered to have occurred in the ED; for patients who are discharged from the hospital, this assumption is always correct; however, this may not hold true for admitted patients who are described but were not the focus of this investigation. Accordingly, the effectiveness of treatment regimens to prevent admission at the index visit was not studied.

A severity measure was applied to every ED encounter to account for patient acuity. This was done using the Severity Classification System (SCS), an *International Classification of Disease, Ninth Revision* diagnosis-based classification approach specifically designed and validated for use in pediatric emergency medicine.<sup>13</sup> For each encounter, a severity score was calculated based on the most severe diagnosis assigned.

The primary analysis compared the most common treatment regimens on the risk for ED revisits; both classes of medications as well as individual medications were compared. We estimated a logistic regression model with revisit status as the dependent variable and treatment regimen as the primary predictor. This variable was coded categorically, with observations classified according to the most commonly occurring treatment regimens and the "nonopioid analgesics" category set as the referent. Although patients who only received nonopioid analgesics are more likely to have milder headaches than those receiving more intensive migraine therapy, we felt this group would serve as a logical reference to compare rates of return visits. We also included the following covariates: gender, age, race, insurance status, intravenous fluid treatment, lumbar puncture,

cranial computed tomography, cranial magnetic resonance imaging, and SCS score as the independent variables. All treatment and procedure covariates refer to those that occurred at the index ED visit only. Given that our data were taken from several hospitals, the assumption of independent observations may not hold. To accommodate these data, our regression model used clustered sandwich SE estimates, which allow for intrahospital correlation, relaxing the assumption that observations from the same hospital are independent.

### General Considerations

All statistical tests were performed by using the software package Stata 12.0 (College Station, TX). All statistical tests were 2-tailed, and  $\alpha$  was set at 0.05.

The institutional review board and the administrators of the PHIS database approved the study. In accordance with Children's Hospital Association policies, the identity of the institutions will not be reported.

## RESULTS

### Study Subjects

There were 32 124 patients aged 7 to 18 years with a principal diagnosis of migraine identified in the database. Basic demographic information, treatment, and principal diagnoses are displayed in Table 1. The median age was 14 years (interquartile range 12–16 years), and 67% were female. Of note, 85% of the children were discharged from the ED and were eligible for our primary outcome analysis.

### Main Results

The most common medications and medication regimens are shown in Table 2. Common medications included nonopioid analgesics (66%), dopamine receptor antagonists (50%), and diphenhydramine (33%). Of those discharged at the initial encounter, 5.5% of children had

**TABLE 1** Demographic and Clinical Characteristics of Children Treated in the ED for Migraine Across 35 Academic Children's Hospitals, 2009–2012

Demographic/Clinical Characteristic	Patients With Migraine (n = 32 124) n (%)
Gender (female)	21 498 (66.9)
Age, y (median, IQR)	14 (12–16)
Race	
White	20 295 (63.2)
Black	6905 (21.5)
Asian	223 (0.7)
Other	2757 (8.6)
Source of payment	
Private	15 062 (47.6)
Public	12 757 (40.3)
Other	3833 (12.1)
Time of visit	
12 AM–8 AM	3020 (14.9)
8 AM–4 PM	8517 (41.9)
4 PM–12 AM	8802 (43.3)
Disposition	
Discharged from the ED	27 317 (85.0)
Admitted (inpatient or observation)	4807 (15.0)
Length of stay (admitted patients only), d	
1	2090 (43.5)
2	1231 (25.6)
3	664 (13.8)
≥4	822 (17.1)
Treatments and tests in the ED	
Intravenous fluids	17 892 (55.7)
Lumbar puncture	504 (1.6)
Cranial computed tomography	4414 (13.7)
Cranial MRI	1098 (3.4)
Moderate SCS <sup>13</sup> score (% with score of ≥3)	28 854 (93.2)
Principal diagnosis	
346.9× (Migraine, unspecified)	28 061 (87.4)
346.8× (Other forms of migraine)	1200 (3.7)
346.7× (Chronic migraine without aura)	216 (0.7)
346.5× (Persistent migraine aura without cerebral infarction)	45 (0.1)
346.4× (Menstrual migraine)	37 (0.1)
346.2× (Variants of migraine, not elsewhere classified)	632 (2.0)
346.1× (Migraine without aura)	751 (2.3)
346.0× (Migraine with aura)	1182 (3.7)

Values in table represent frequency (%), unless otherwise noted. IQR, interquartile range; MRI, magnetic resonance imaging.

a return visit within 3 days. The median time to return was 2 days [interquartile range 1–2]. The return visit rates by drug regimen are shown in Table 3 with and without adjustment for age, gender, race, insurance status, intravenous fluids, lumbar puncture, cranial computed tomography, cranial MRI, and SCS score. Children who received atypical abortive migraine medications such as antiepileptic medications were more likely to experience a revisit to the ED within 3 days of their index visit.

Comparisons of the common treatment regimens are displayed in Table 4. Children receiving metoclopramide had a 31% increased odds of an ED revisit within 3 days compared with children receiving prochlorperazine. Use of diphenhydramine with dopamine antagonists was associated with 27% increased odds of an ED revisit compared with the use of dopamine antagonists alone. Children receiving ondansetron and dopamine antagonists had similar revisit rates.

**TABLE 2** Pharmaceutical Treatments Administered in the ED for Migraine to 32 124 Children Aged 7 to 18 Years Across 35 Academic Children's Hospitals, 2009–2012

	All Patients, <i>n</i> = 32 124, <i>n</i> (%)	Discharged Patients, <i>n</i> = 27 317, <i>n</i> (%)	Admitted Patients, <i>n</i> = 4807, <i>n</i> (%)
Medication classes (not mutually exclusive)			
Nonopioid analgesics	21 077 (65.6)	17 530 (64.2)	3547 (73.8)
Dopamine receptor antagonists	16 019 (49.9)	13 258 (48.5)	2761 (57.4)
Diphenhydramine	10 659 (33.2)	8605 (31.5)	2054 (42.7)
Ondansetron	6774 (21.1)	5128 (18.8)	1646 (34.2)
Antiepileptic agents	2931 (9.1)	1238 (4.5)	1693 (35.2)
Corticosteroids	2020 (6.3)	1291 (4.7)	729 (15.2)
Opioids	1800 (5.6)	1080 (4.0)	720 (15.0)
Triptans	1032 (3.2)	876 (3.2)	156 (3.3)
Dihydroergotamine mesylate	997 (3.1)	159 (0.6)	838 (17.4)
Most common treatment regimens			
No treatment	6284 (19.6)	5820 (21.3)	464 (9.7)
Dopamine antagonists and nonopioid analgesics	4495 (14.0)	4263 (15.6)	232 (4.8)
Dopamine antagonists, nonopioid analgesics, and diphenhydramine	4061 (12.6)	3771 (13.8)	290 (6.0)
Nonopioid analgesics	3240 (10.1)	2929 (10.7)	311 (6.4)
Analgesics and ondansetron	1921 (6.0)	1774 (6.5)	147 (3.1)
Dopamine antagonists and diphenhydramine	1160 (3.6)	1108 (4.1)	52 (1.1)
Dopamine antagonists	877 (2.7)	837 (3.1)	40 (0.8)
Analgesics, ondansetron and diphenhydramine	823 (2.6)	764 (2.8)	59 (1.2)
Dopamine antagonists, analgesics, antiepileptics, and diphenhydramine	715 (2.2)	394 (1.4)	321 (6.7)

## DISCUSSION

Using a large database of academic pediatric institutions, we were able to characterize the treatment of children with migraines in the nation's largest pediatric EDs. Similar to previous investigations, we observed that the vast majority of children with migraines treated in the ED setting

are discharged. Additionally, consistent with the American Academy of Neurology recommendations, opiate medications are rarely used for the treatment of migraines in children.<sup>14</sup> The analysis allowed calculation of revisit rates for children and comparison of the common treatment regimens. Not

surprisingly, children who received combinations of medications were more likely to require a return visit than those who only required simple nonopiate analgesics. Related to effectiveness, prochlorperazine appears to have an advantage over metoclopramide for preventing revisits. The addition of diphenhydramine with dopamine antagonists increases the risk of revisit, although the absolute increase in risk is small (1.5%), and it cannot be determined whether the diphenhydramine was given as part of the initial treatment plan or administered in response to extrapyramidal side effects. Finally, we were unable to show any additional effectiveness of dopamine antagonists over ondansetron, yet dopamine antagonists were administered more than twice as often.

Despite migraine headaches being a common ED complaint, there are a limited number of studies investigating optimal migraine treatment of children presenting for emergency care. Previous studies have focused on variation in care,<sup>9,15</sup> comparing treatments in pediatric

**TABLE 3** Multivariate Model Predicting 3-Day Revisits Among 27 317 Children Aged 7 to 18 Years Receiving Pharmacological Treatment in the ED for Migraine and Discharged From the ED Across 35 Academic Children's Hospitals, 2009–2012

Most Common Treatment Regimens	<i>n</i>	Unadjusted 3-d ED Revisit Rate %	Adjusted 3-d ED Revisit Rate, <sup>a</sup> %	Adjusted Odds of 3-d ED Revisit (95% CI) <sup>a</sup>
Nonopioid analgesics	2746	3.8	4.4	1.0 (referent)
Nonopioid analgesics, dopamine antagonists, and diphenhydramine	3322	6.8	6.4	1.47 (1.21–1.80)
Nonopioid analgesics and dopamine antagonists	3866	5.4	5.1	1.17 (0.93–1.47)
Nonopioid analgesics and ondansetron	1663	5.0	5.3	1.20 (0.95–1.52)
Dopamine antagonists and diphenhydramine	969	5.5	5.3	1.22 (0.81–1.84)
Dopamine antagonists	775	5.9	5.8	1.34 (0.97–1.86)
Nonopioid analgesics, ondansetron, and diphenhydramine	709	4.9	5.0	1.14 (0.79–1.63)
Dopamine antagonists, nonopioid analgesics, antiepileptics, and diphenhydramine	299	11.4	10.1	2.44 (1.80–3.31)
All other permutations	4870	7.2	7.2	1.70 (1.39–2.08)

<sup>a</sup> Adjusted for age, gender, race, insurance status, intravenous fluids, lumbar puncture, cranial computed tomography, cranial magnetic resonance imaging, and SCS score. CI, confidence interval.

**TABLE 4** Comparisons Between Select Medication Regimens and 3-Day Revisits Among Pediatric Patients Aged 7 to 18 Years Seen in the ED for Migraine and Discharged From the ED Across 35 Academic Children's Hospitals, 2009–2012

Comparison	<i>n</i>	Unadjusted ED Revisit Rate (%)	Adjusted ED Revisit Rate (%) <sup>a</sup>	Adjusted Odds of ED Revisit <sup>a</sup>
Prochlorperazine vs metoclopramide				
Prochlorperazine	6265	5.9	5.8	Referent
Metoclopramide	6360	7.4	7.5	1.31 (1.11–1.55)
Prochlorperazine vs promethazine				
Prochlorperazine	6265	5.9	5.8	Referent
Promethazine	733	6.2	6.4	1.11 (0.77–1.60)
Dopamine antagonist (any) and diphenhydramine vs dopamine antagonists without diphenhydramine				
Dopamine antagonists without diphenhydramine	6357	5.8	5.8	Referent
Dopamine antagonists and diphenhydramine	6901	7.3	7.3	1.27 (1.07–1.51)
Prochlorperazine without diphenhydramine	2816	5.4	5.5	Referent
Prochlorperazine with diphenhydramine	3031	6.3	6.3	1.15 (0.91–1.46)
Metoclopramide without diphenhydramine	2701	6.2	6.3	Referent
Metoclopramide with diphenhydramine	3065	8.5	8.6	1.40 (1.15–1.70)
Dopamine antagonists vs ondansetron				
Dopamine antagonists without ondansetron	11972	6.5	6.4	Referent
Ondansetron without dopamine antagonists	3842	5.6	5.8	0.90 (0.77–1.07)

The specified regimens are not necessarily exclusive of other medications.

<sup>a</sup> Adjusted for age, gender, race, insurance status, intravenous fluids, lumbar puncture, cranial computed tomography, cranial magnetic resonance imaging, and SCS score.

EDs to general EDs,<sup>9</sup> safety of specific medications,<sup>6,16,17</sup> and the value of treatment protocols using available evidence.<sup>5,18</sup>

The current study population is similar to previous reports in which up to one-third of patients do not require specific migraine treatment but are presenting to the ED for a diagnostic evaluation of the headache.<sup>9</sup> In agreement with previous publications of pediatric migraine in ED's,<sup>5</sup> one-half of the children receive intravenous fluids as part of the treatment or to prevent some of the mild hypotension associated with administration of dopamine receptor antagonists.

Dopamine receptor antagonists can alleviate the symptoms of a migraine headache, as well as the associated nausea and vomiting. The most common agents are prochlorperazine, chlorpromazine, promethazine, and metoclopramide. Although metoclopramide was the most common agent in previous reports of pediatric<sup>5,8</sup> and adult<sup>19</sup> migraine treatment in the ED setting, we observed that prochlorperazine and metoclopramide are used with equal frequency. Previous reports from adults have suggested that

prochlorperazine might be more efficacious than metoclopramide,<sup>20</sup> and prochlorperazine's safety and effectiveness has been previously reported.<sup>6,7,16</sup> Before our study, there has not been a direct comparison of metoclopramide and prochlorperazine for the treatment of migraine in children. In the absence of rich clinical trial data, this study provides observational evidence of the comparative effectiveness of these medications; however, the safety profile of medications, which cannot be addressed in the current study, must also be considered along with a medication's effectiveness when making any therapeutic decision.

Side effects of the dopamine antagonists include extrapyramidal effects such as akathisia and dystonia; 1 previous study in adults showed the benefit of diphenhydramine in preventing these side effects, although it also increases sedation.<sup>21</sup> In the current study, diphenhydramine was used in nearly one-third of children and was found to increase the risk of revisit. We cannot determine whether the diphenhydramine was administered as part of the treatment regimen or in response to adverse effects of other

medications; the reported rates of definite akathisia with dopamine antagonists is only 5%,<sup>22</sup> suggesting that the diphenhydramine was more likely administered prophylactically. For those that experienced extrapyramidal symptoms, these symptoms can be prolonged beyond the ED visit and therefore may account for some revisits being attributed to diphenhydramine use. This small increased risk of revisit associated with diphenhydramine administration must be balanced against the risk of preventing side effects; fortunately, most extrapyramidal side effects are mild and occur during the visit thereby allowing clinicians to recognize and treat when necessary.

Nonopioid analgesics were frequently administered in the current study and have been shown to be efficacious for migraine<sup>23</sup>; the use in the ED setting is difficult to study retrospectively because many patients are given acetaminophen or ibuprofen before arrival in the ED.<sup>5,8</sup> Triptans, a serotonin receptor agonist, have been increasingly used for treatment of acute migraine. Although they have the greatest value early in the course of illness,<sup>24</sup> most children with



migraine present to the ED after experiencing prolonged symptoms at home.<sup>5,8</sup> Despite this, studies in adults have shown triptans to be effective as abortive therapy in the ED setting,<sup>25</sup> but there have not been any ED-based pediatric studies. The evidence for pediatric use of triptans in the outpatient setting is strong,<sup>26–29</sup> yet only 3% of children received a triptan in the current study.

Revisits related to migraines have not been well studied. A limited number of studies have addressed acute recurrence of a migraine. In 1 study by Legault et al, 184 children with migraine headache were studied, and 11% returned to the ED within 1 month; of those that returned, 71% returned within 4 days of the initial visit.<sup>8</sup> No specific treatment at the initial encounter was associated with the return visit, although small sample size limited the ability to detect differences between treatments. In another study on the use of prochlorperazine, 100% had improvement in their migraine during the ED visit, but 68% had a partial relapse of their headache within 1 week of discharge<sup>6</sup>; the authors did not report the rate of revisit to an ED. We showed that revisit rates occurred in 5.5% of children and are influenced by choice of dopamine

antagonist and use of an antihistamine. Revisits were more common among children who received combination therapy, especially with atypical migraine medications (including antiepileptic medications); this likely represents children with more severe or refractory migraines.

This study has limitations. The most significant is related to the use of administrative data without patient-level clinical information. Thus, we cannot account for migraine severity nor discriminate acute versus chronic migraines, and the study design prevents any determination of the reason for revisits. We are also unable to evaluate medication use before the ED visit or treatments prescribed or administered after discharge from the ED. Although the PHIS database contains a unique identifier that allows for tracking of patients over time, ED revisits were limited to returns to the same institution; visits to other hospitals or primary care providers cannot be determined. Finally, the ideal outcome would be a combination of successful discharge and not requiring a return visit; we were unable to study the relationship between medications and initial disposition from the ED because we could not ascertain the time of medication delivery for those patients

who were admitted (ie, whether administered in the ED or inpatient area on day of visit).

## CONCLUSIONS

We applied a comparative effectiveness approach to study treatment strategies for migraine management in children using a large administrative database. The majority of children with migraines are successfully discharged from the ED, which infers the effectiveness of abortive therapy in the ED. In accordance with available evidence for migraine treatment, the most common medication regimen includes dopamine antagonists with nonopioid analgesics. Prochlorperazine appears to be superior to metoclopramide in preventing a repeat ED visit, and diphenhydramine use is associated with a small increase rate of return. Although ondansetron is not endorsed for the emergency treatment of migraine, it was administered in nearly one-fifth of children. In contrast, triptans are well studied for the treatment of acute migraine, but they are infrequently administered to children in the ED setting. These findings should inform further research into the optimal treatment regimens of acute migraine in children.

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