

# Diphenhydramine as Adjuvant Therapy for Acute Migraine: An Emergency Department–Based Randomized Clinical Trial

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**Study objective:** More than 1 million patients present to US emergency departments (EDs) annually seeking care for acute migraine. Parenteral antihistamines have long been used in combination with antidopaminergics such as metoclopramide to treat acute migraine in the ED. High-quality data supporting this practice do not exist. We determine whether administration of diphenhydramine 50 mg intravenously+metoclopramide 10 mg intravenously results in greater rates of sustained headache relief than placebo+metoclopramide 10 mg intravenously.

**Methods:** This was a randomized, double-blind, clinical trial comparing 2 active treatments for acute migraine in an ED. Eligible patients were adults younger than 65 years presenting with an acute moderate or severe headache meeting *International Classification of Headache Disorders–2* migraine criteria. Patients were stratified according to presence or absence of allergic symptoms. The primary outcome was sustained headache relief, defined as achieving a headache level of mild or none within 2 hours of medication administration and maintaining this level of relief without use of any additional headache medication for 48 hours. Secondary efficacy outcomes included mean improvement on a 0 to 10 verbal scale between baseline and 1 hour, the frequency with which subjects indicated they would want the same medication the next time they present to the ED with migraine, and the ED throughput time. Sample size calculation using a 2-sided  $\alpha$  of .05, a  $\beta$  of .20, and a 15% difference between study arms determined the need for 374 patients. An interim analysis was conducted when data were available for 200 subjects.

**Results:** Four hundred twenty patients were approached for participation. Two hundred eight eligible patients consented to participate and were randomized. At the planned interim analysis, the data and safety monitoring board recommended that the study be halted for futility. Baseline characteristics were comparable between the groups. Fourteen percent (29/208) of the sample reported allergic symptoms. Of patients randomized to diphenhydramine, 40% (40/100) reported sustained relief at 48 hours, as did 37% (38/103) of patients randomized to placebo (95% confidence interval [CI] for difference of 3%: –10% to 16%). One hour after medication administration, patients randomized to diphenhydramine improved by a mean of 5.1 on the 0 to 10 scale versus 4.8 for those randomized to placebo (95% CI for difference of 0.3: –0.6 to 1.1). Eighty-five percent (84/99) of the patients in the diphenhydramine arm reported they would want the same medication combination during a subsequent ED visit, as did 76% (77/102) of those who received placebo (95% CI for difference of 9%: –2% to 20%). Median ED length of stay was 122 minutes (interquartile range 84 to 180 minutes) in the diphenhydramine group and 139 minutes (interquartile range 90 to 235 minutes) in the placebo arm. Rates of adverse effects, including akathisia, were comparable between the groups.

**Conclusion:** Intravenous diphenhydramine, when administered as adjuvant therapy with metoclopramide, does not improve migraine outcomes. [Ann Emerg Med. 2015;■:1-8.]

Please see page XX for the Editor's Capsule Summary of this article.

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## INTRODUCTION

Migraine, a recurrent disorder characterized by acute headaches, causes more than 1 million visits to US emergency departments (EDs) annually.<sup>1</sup> Parenteral antihistamines including diphenhydramine and promethazine are commonly administered to migraine patients in the ED,<sup>1</sup> yet high-quality data to support efficacy do not exist. Associations among migraine, histamine, and allergy exist.<sup>2</sup>

Elevated levels of serum histamine and immunoglobulin E have been reported in patients with a history of migraine compared with healthy controls.<sup>2</sup> Among patients with a history of migraine, there is greater elevation of histamine levels during an acute migraine than during the interictal period.<sup>2</sup> This tends to be more marked among migraine patients with a history of allergy or atopy than those without one.<sup>2</sup> Prevalence of migraine is higher among patients with

**Editor's Capsule Summary***What is already known on this topic*

National emergency department treatment for migraine varies widely. The effect of antihistamines on patient outcomes is uncertain.

*What question this study addressed*

Does the addition of diphenhydramine improve headache relief in patients receiving metoclopramide?

*What this study adds to our knowledge*

Sustained headache relief at 48 hours, length of stay, and restlessness were similar in the patients receiving diphenhydramine or placebo; thus, the combination was not superior to metoclopramide alone.

*How this is relevant to clinical practice*

This treatment combination is commonly used yet does not appear to change important patient-level outcomes or adverse events at the population level. The routine use of this combination is likely not warranted.

*Research we would like to see*

More patients receiving diphenhydramine than placebo wanted "the same medication" for future treatments. A comparative trial investigating outcomes with randomization to agents influenced by patient preference is warranted.

a history of allergic rhinitis than matched controls.<sup>3,4</sup> In patients with a history of migraine, an acute headache can be induced by histamine infusion, which can be blocked by coadministration of an antihistamine.<sup>5</sup> These data are consistent with the hypothesis that histamine contributes to migraine pathogenesis, particularly among patients who are prone to allergy, and that centrally acting antihistamines may be a useful treatment for acute migraine.

Despite the large number of migraine patients who present to EDs annually, there is substantial variability in treatment.<sup>1</sup> More than 20 parenteral medications or combinations of medications are commonly used to treat acute migraine in this setting, yet the goal of sustained headache relief remains elusive.<sup>1,6</sup> When antihistamines are used to treat acute migraine in the ED, they are usually administered as part of a 2-drug combination, with the goals of increasing efficacy and decreasing adverse events such as akathisia.<sup>1</sup> However, there are no high-quality data available to support or refute this practice. Therefore,

we conducted a randomized trial to determine the efficacy of coadministering a centrally acting antihistamine with standard migraine therapy. Specifically, we wished to test the following hypothesis: In a population of patients presenting to an ED with acute migraine rated as moderate or severe intensity, diphenhydramine 50 mg intravenously+metoclopramide 10 mg intravenously results in greater rates of sustained headache relief than placebo+metoclopramide 10 mg intravenously.

**MATERIALS AND METHODS****Study Design and Setting**

This was a randomized, double-blind, clinical trial comparing 2 active treatments for acute migraine. Patients were enrolled on presentation to the ED, followed for up to 2 hours in the ED, and then contacted by telephone 48 hours later to determine headache status. The Albert Einstein College of Medicine institutional review board provided ethical oversight.

This study was performed in the ED of Montefiore Medical Center, an urban ED that receives 100,000 adult visits annually. Salaried, full-time, bilingual (English and Spanish), technician-level research associates, who gather data for studies under the supervision of the principal investigators, staffed the ED 18 to 24 hours per day, 7 days per week during the study period.

**Selection of Participants**

Eligible patients were adults younger than 65 years who presented with an acute moderate or severe headache meeting migraine criteria, as defined by the *International Classification of Headache Disorders-2* (code 1.1, migraine without aura).<sup>7</sup> Patients who met criteria for probable migraine without aura (code 1.6.1) were also included, provided they had had at least 1 similar headache previously. Status migrainosus, prolonged duration of headache (>72 hours), or early presentation (<4 hours) did not preclude participation. Patients were excluded if informed consent could not be obtained; the attending emergency physician suspected a secondary cause of headache or intended to obtain diagnostic imaging or a lumbar puncture; the maximum documented temperature before enrollment was greater than or equal to 100.4°F (38.0°C); for presence of a new objective neurologic abnormality; or allergy, intolerance, or contraindication to the study medication. Because all investigational medications used in this study are classified as pregnancy category B and are commonly used for acute migraine in pregnant patients, and because there is a need for evidence-based treatment in pregnant patients, pregnancy did not

exclude patients from participation in this study. We required the attending emergency physician's permission to enroll their patient in this clinical trial.

### Interventions

Patients were randomly allocated in a 1:1 ratio to one of the following 2 interventions: (1) metoclopramide 10 mg+diphenhydramine 50 mg, infused intravenously during 15 minutes; (2) metoclopramide 10 mg+saline solution placebo, infused intravenously during 15 minutes.

To ensure a comparable number of atopic patients in each study arm, all participants were stratified by symptoms of allergic nasal congestion as "allergic" or "not allergic." Allergic symptoms were assessed with the Congestion Quantifier 5 instrument (Appendix E1, available online at <http://www.annemergmed.com>).<sup>8</sup> Patients were categorized as allergic if they scored greater than 6 on this validated instrument.

Randomization was performed by the research pharmacist, who generated 2 sequences (allergic and not allergic) in blocks of 4, using computer-generated random-number tables available at <http://www.randomization.com>. The pharmacist performed the randomization in a location removed from the ED and inaccessible to ED personnel. In an order determined by these random-number tables, the pharmacist inserted medication into identical vials and placed these vials into sequentially numbered identical research bags. These research bags, which were maintained in a locked cabinet in the ED, were then used in a prespecified order by the research team. Only the pharmacist knew an individual patient's assignment. Every research bag contained 2 vials. The metoclopramide vial was labeled by the manufacturer and contained 2 mL of a 10 mg/2 mL solution of metoclopramide. The other vial was labeled as a research medication and contained 1 mL of a clear solution, which consisted of either 50 mg of diphenhydramine or saline solution placebo. After a subject had been enrolled, the 2 vials from each research bag were placed in a 50-mL bag of normal saline solution by a blinded nurse, which was administered as a slow intravenous drip during 15 minutes.

### Methods of Measurement

As a primary measure of headache intensity, we used a standardized ordinal headache intensity scale, in which subjects described their headache as "severe," "moderate," "mild," or "none."<sup>9</sup> Other measurement tools included a functional disability scale, in which subjects described their headache-related disability as severe ("cannot get up from bed or stretcher"), moderate ("great deal of difficulty doing what I usually do and can only do very minor

activities"), mild ("little bit of difficulty doing what I usually do"), or none, and an 11-point verbal pain rating scale.<sup>10</sup> This latter scale asks subjects to assign their pain a number between 0 and 10, with 0 representing no pain and 10 representing the worst pain imaginable. All of these measures are recommended for use in migraine research by the International Headache Society.<sup>9</sup>

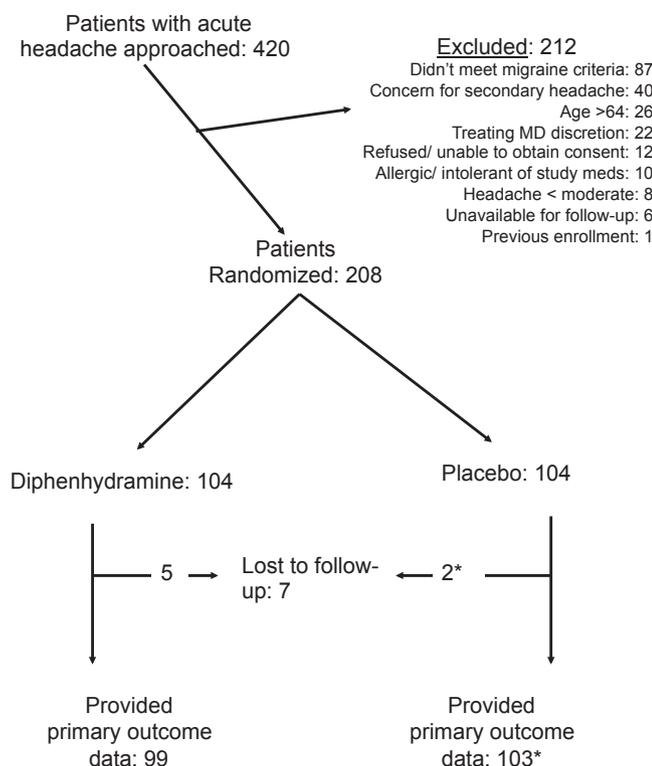
After informed consent was obtained from the patient, a pain assessment was performed. The intravenous solution was then administered as an intravenous drip between time zero and 15 minutes. Research associates ascertained the patient's headache level every 30 minutes and asked a more detailed series of questions about pain, functional limitations, and adverse events at 1 and 2 hours. If subjects requested more pain medication at or after 1 hour, they were administered additional medication at the discretion of the treating physician. A final pain assessment was performed by telephone 48 hours after randomization.

At the 48-hour telephone call, we also assessed patient satisfaction with the investigational medication they received by asking them, "Would you wish to receive the same medication the next time you visit the ED with migraine?" This question allows patients to summarize succinctly the relative efficacy and tolerability of the medication.

Adverse effects were assessed 1, 2, and 48 hours after medication administration, using open-ended questions. Two specific, expected adverse effects, drowsiness and restlessness, were assessed with 3-item Likert questions. Acute akathisia, an unpleasant but self-limited reaction characterized by restlessness and anxiety, occurs commonly after administration of intravenous antidopaminergics such as metoclopramide. Although instruments have been developed to measure this phenomenon, we have found akathisia difficult to quantify with these instruments because the time of onset of akathisia is variable and typically aborts quickly and completely in response to intravenous therapeutics such as diphenhydramine.<sup>11</sup> Therefore, we attempted to capture this phenomenon through the use of other measures: First, at the 48-hour follow-up, we asked patients whether they experienced "restlessness" at any time after receiving the medication. Those who reported that they were "very restless" were considered to have had akathisia. Second, because diphenhydramine is the rescue medication of choice for akathisia in our ED, we recorded any off-protocol use of parenteral diphenhydramine in all study patients.

### Outcome Measures

The primary outcome was sustained headache relief. In accordance with international criteria, this is defined as achieving a headache level of mild or none within 2 hours



**Figure 1.** CONSORT flow diagram. \*One patient lost to follow-up received rescue medication in the ED. Therefore, we were able to count her as having a primary outcome failure despite being unable to contact her at 48 hours.

of medication administration and maintaining that level of mild or none without the use of any additional headache medication for 48 consecutive hours posttreatment.<sup>9</sup> Patients who received rescue medication were considered to have had a primary outcome failure.

Secondary efficacy outcomes include the mean improvement in the 0 to 10 pain scale between baseline and 1 hour, the frequency of use of additional antiheadache medication during the ED visit, the frequency of poor functional scores 1 hour after investigational medication administration, the ED throughput time, defined as time elapsed between medication administration and ED discharge, and the frequency with which subjects indicated they would wish to receive the same medication the next time they presented to the ED with migraine.

The frequency of any adverse event was recorded, including the development of akathisia and the frequency of drowsiness.

### Primary Data Analysis

We collected and managed study data with REDCap electronic data capture tools hosted at Albert Einstein College of Medicine. All dichotomous outcomes were

reported as frequencies with 95% confidence interval (CI). Absolute risk reduction and number needed to treat were also reported with 95% CI. Improvement in 0 to 10 pain score is reported as mean with 95% CI.

We used the following parameters to calculate the sample size:  $\alpha$  of .05,  $\beta$  of .20, and a difference between the groups in the rate of sustained headache relief of 15% (48% in the placebo+metoclopramide arm, estimated from previous studies,<sup>12</sup> and 63% in the diphenhydramine+metoclopramide arm). This difference of 15% is equivalent to a number needed to treat of 6.67, which was chosen as a clinically relevant threshold by polling and averaging the responses of local clinical emergency physicians. Using these assumptions, we determined the need for 344 patients but intended to enroll 374 to account for those lost to follow-up.

A planned interim analysis was conducted after we collected analyzable data on 200 patients. Its purpose was to determine whether the study lacked conditional power. The following stopping rule, which was established before initiation of the trial, was implemented: If at the interim analysis, which was to take place slightly past the halfway point (200/374 patients), the absolute risk reduction was less than 7.5% (ie, <half of the between-group difference in the sample size calculation), the study was to be halted. Because we did not intend to subject the interim data to a statistical analysis, the  $\alpha$  of the final analysis was not adjusted.

## RESULTS

The study commenced in April 2013 and continued for 21 months. An interim analysis was performed in December 2014. At that time, the data and safety monitoring board recommended that the study be halted for futility. During the 21 study months, 420 patients were approached for participation and 208 were randomized (Figure 1). Some attending physicians refused to allow their patients to be enrolled in this trial, usually because they were uncomfortable administering metoclopramide without diphenhydramine (Figure 1). Baseline characteristics were comparable between the groups (Table 1). Most participants reported severe headache at baseline, although more than one third of our patients had not used any medication for headache before ED presentation (Table 1).

The primary outcome, sustained headache relief, was reported by 40 of 100 patients (40%; 95% CI 31% to 50%) randomized to diphenhydramine and 38 of 103 patients (37%; 95% CI 28% to 47%) randomized to placebo (95% CI for difference of 3%: -10% to 16%). Secondary outcomes are reported in Table 2 and Figures E1 and E2 (available online at [www.annemergmed.com](http://www.annemergmed.com)). Despite rates of sustained headache freedom of less than 20% in both

**Table 1.** Baseline characteristics.

Variable	Metoclopramide + Diphenhydramine	Metoclopramide + Placebo
Women, n/No. (%)	88/104 (85)	92/104 (89)
Age, mean (SD), y	34 (11)	36 (10)
Used medication for headache before ED visit, n/No. (%)	66/104 (64)	67/103 (65)
Visual aura, n/No. (%) <sup>*</sup>	29/104 (28)	39/104 (38)
Sensory aura, n/No. (%) <sup>†</sup>	5/104 (5)	15/104 (14)
Duration of headache, median (IQR), h	72 (24, 96)	48 (16, 72)
Baseline pain on 0–10 scale, median (IQR)	9 (8, 10)	9 (8, 10)
Number of days with functionally impairing headache during previous 90 days, median (IQR)	3 (1, 5)	3 (2, 5)
Allergic symptoms, n/No. (%) <sup>‡</sup>	15/104 (14)	14/104 (14)

<sup>\*</sup>Affirmative response to the following question: “Some people have changes in their vision with their headache. Before your headache began, did you see things such as spots, stars, lights, zigzag lines, or heat waves?”

<sup>†</sup>Affirmative response to the following question: “Some people have changes in their skin sensation with their headache. Before your headache began, did you have numbness or tingling in your face or arms?”

<sup>‡</sup>Score greater than 6 on Congestion Quantifier 5 instrument (Appendix E1, available online at <http://www.annemergmed.com>).

arms, more than three fourths of patients stated they would want to receive the same medication again (Table 2). Patients randomized to placebo had ED throughput times (median 139 minutes; IQR 90 to 235 minutes) comparable to those who received diphenhydramine (median 122 minutes; IQR 84 to 180 minutes) ( $P=.53$ , Mann-Whitney  $U$ ).

Adverse events were comparable between the study arms (Table 3). Patients randomized to placebo did not report greater rates of restlessness, nor were they more likely to require rescue doses of diphenhydramine. No patients reported unremitting muscle spasms or tremors.

At baseline, less than 15% of our patients reported symptoms of allergy, as defined by a score of 6 or greater on the Congestion Quantifier instrument (Table 4). Among this

subset, 7 of 15 patients (47%; 95% CI 25% to 70%) randomized to diphenhydramine reported sustained relief, as did 8 of 14 patients (57%; 95% CI 33% to 79%) randomized to placebo (95% CI for difference of 10%: –26% to 47%). Among the allergic participants, more patients randomized to diphenhydramine reported satisfaction with the medication received, as reflected by desire to receive the same medication for a recurrence of migraine (Table 4).

## LIMITATIONS

This study was conducted in 1 urban ED serving a predominantly socioeconomically depressed population. The effect of socioeconomic factors on our study population is apparent in some of the data, such as the high frequency with which patients presented to the ED without having received any medication for their migraine (Table 1).

When powering the study, we determined our hypothesized effect size by polling and averaging the responses of local emergency physicians because we were unable to identify an evidence-based minimum clinically significant decrease for our primary outcome (sustained headache relief). Therefore, an important assumption of our design may not reflect the widespread opinion of practicing emergency physicians. Specifically, we needed to observe an absolute 15% increase in the proportion of patients with headache relief at 48 hours. Because other emergency physicians and patients might be satisfied with less efficacious treatments, the current trial addresses only adjuvant diphenhydramine lacking a large effect. As such, our findings may have less generalizability to some patients and clinicians. As with all clinical studies, individual physicians should interpret our data in context of which outcome and number needed to treat are most relevant for them and their patients—for example, some clinicians may observe that 85% of participants who received diphenhydramine would want the same medication

**Table 2.** Outcomes among all patients.

Variable	Metoclopramide + Diphenhydramine	Metoclopramide + Placebo	Difference (95% CI)
Improvement in 0–10 pain score between baseline and 1 h	5.1 (n=104)	4.8 (n=101) <sup>*</sup>	0.3 (–0.6 to 1.1)
Required rescue medication in ED (%)	31/104 (30)	40/104 (38)	9% (–4 to 21%)
Sustained headache freedom (%) <sup>†</sup>	17/101 (17)	14/102 (14)	3% (–7 to 13%)
Want same medication again (%) <sup>‡</sup>	84/99 (85)	77/102 (76)	9% (–2 to 20%)
Functional impairment at 1 h; unable to perform usual activities (%) <sup>§</sup>	27/103 (26) <sup>*</sup>	30/98 (31) <sup>*</sup>	4% (–8 to 17%)

Data are presented as n/No. (%) unless indicated otherwise.

<sup>\*</sup>Missing data when patient did not/could not answer the question.

<sup>†</sup>Achieved a headache level of “none” in the ED and maintained a level of “none” without the use of rescue medication for 48 hours. Patients who required rescue medication were considered to have had outcome failures.

<sup>‡</sup>At the 48-hour follow-up telephone call, patients were asked whether they wished to receive the same medication during a subsequent migraine visit to the ED.

<sup>§</sup>Patients who responded “I can’t get out of bed” and “I’d have a great deal of difficulty doing what I usually do” are included in the numerator. Patients who responded “I can do my normal activities” and “I’d have a little bit of difficulty doing what I usually do” are not included in the numerator.

**Table 3.** Adverse events.

Adverse Event	Metoclopramide + Diphenhydramine, n/No. (%)	Metoclopramide + Placebo, n/No. (%)	Difference (95% CI)
Very restless after receiving study medications*	8/99 (8)	7/102 (7)	1% (-6 to 8%)
Required rescue dose of diphenhydramine to treat symptoms of acute akathisia	5/104 (5)	8/103 (8)	3% (-4 to 10%)
Very drowsy after receiving study medications*	17/99 (17)	14/102 (14)	3% (-7 to 13%)

\*At the 48-hour follow-up telephone call, study participants were asked to recall whether they experienced restlessness or drowsiness after receiving the investigational medication. Participants were forced to choose among the following options: "no," "a little bit," or "a lot."

combination during a subsequent ED visit, whereas only 76% of those who received placebo would want the same medication combination again. The changes in pain score from baseline to 1 hour are depicted by group and individually in [Figure 2](#).

Outcome measures in the allergic subgroup were less encouraging about the potential for smaller but plausibly important effects. However, symptoms of allergy at baseline were relatively uncommon in this cohort. Less than 15% of all study participants were rated as allergic with a validated instrument, which limits our ability to comment on the efficacy of diphenhydramine within this population. Our data do not preclude the possibility of benefit, particularly because more patients who received diphenhydramine would want the same medication combination during a subsequent migraine attack. However, the point estimate of the primary outcome favored placebo, as did need for rescue medication. The improvement in 0 to 10 pain score between baseline and 1 hour was comparable.

In accordance with a stopping rule established before this study began, the data and safety monitoring board recommended halting the study after 208 patients were enrolled, slightly past the halfway point of the trial. It is possible that the findings in the first half of the sample were not representative and continued data collection would have revealed a clinically significant difference between groups, but that is extremely unlikely, given the large size of the interim sample and the small difference between groups.

**Table 4.** Outcomes among patients deemed allergic.

Variable	Metoclopramide + Diphenhydramine	Metoclopramide + Placebo	Difference (95% CI)
Improvement in 0–10 pain score between baseline and 1 h	3.8 (n=15)	3.7 (n=12)*	0.1 (-2.1 to 2.3)
Required rescue medication	6/15 (40)	3/14 (21)	19% (-14 to 51%)
Sustained headache freedom <sup>†</sup>	3/15 (20)	1/13 (8)	12% (-13 to 37%)
Want same medication again <sup>‡</sup>	14/15 (93)	7/13 (54)	39% (10 to 69%)

n/No. (%) unless otherwise indicated.

\*Two patients did not provide an answer to this question.

<sup>†</sup>Achieved a headache level of "none" in the ED and maintained a level of "none" without the use of rescue medication for 48 hours. Patients who required rescue medication were considered to have had outcome failures.

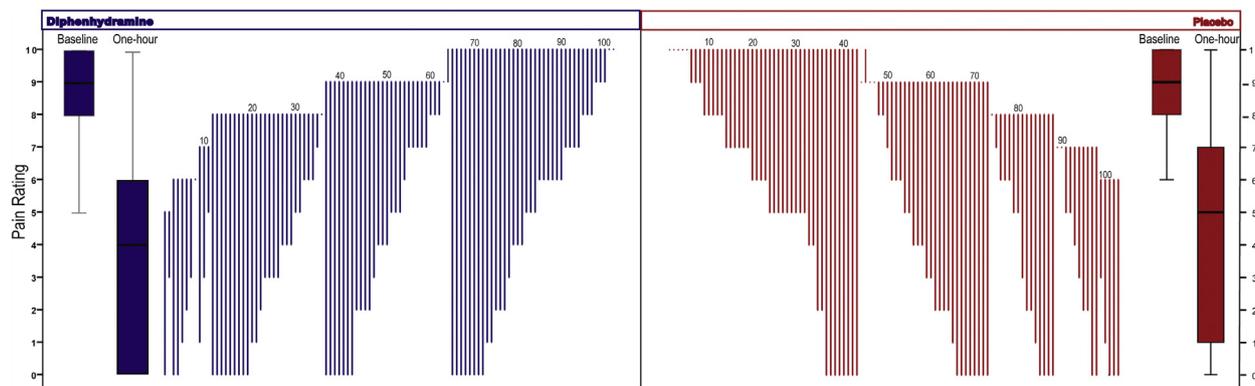
<sup>‡</sup>At the 48-hour follow-up telephone call, patients were asked whether they wished to receive the same medication during a subsequent migraine visit to the ED.

## DISCUSSION

In this ED-based, double-blind, randomized, clinical trial of treatment for acute migraine, we found that adding 50 mg of intravenous diphenhydramine to metoclopramide 10 mg did not improve outcomes compared with metoclopramide alone. Diphenhydramine also did not decrease the rate of akathisia. Our results are generally in keeping with those of other ED-based acute migraine clinical trials, which have shown that although substantial initial relief is generally obtainable regardless of which parenteral intervention is used, sustained relief for 48 hours beyond the ED visit is more difficult to achieve.<sup>12-17</sup>

Given the frequency with which antihistamines are used to treat acute migraine, there is a surprising paucity of experimental data on this topic. Existing data come from small clinical trials<sup>18</sup> or nonexperimental designs,<sup>19</sup> which have reached different conclusions. To our knowledge, this is the first adequately powered randomized clinical trial to demonstrate that diphenhydramine does not improve outcomes in an unselected population of ED patients presenting with acute moderate to severe migraine.

Theories of an allergic basis of migraine date back nearly 100 years.<sup>20,21</sup> Food allergy in particular has been linked to migraine, and food elimination diets have purportedly cured migraine.<sup>22</sup> Experimentally designed studies have reached differing conclusions but suggest that targeted food elimination diets may be of mild to modest benefit for selected patients with allergic migraine.<sup>23-26</sup> Among our



**Figure 2.** Baseline and one hour pain scores for each participant.

migraine patients with concomitant symptoms of allergic rhinitis, diphenhydramine did not appear to confer any benefit over metoclopramide alone.

Diphenhydramine is often administered prophylactically to blunt extrapyramidal adverse effects (mostly akathisia) of intravenous antidopaminergics. Although this is an evidence-based strategy for patients receiving intravenous prochlorperazine,<sup>10,27</sup> existing data do not support the use of diphenhydramine in this role for patients receiving intravenous metoclopramide.<sup>11,28</sup> Similarly, in this study, the rate of akathisia was comparable regardless of whether patients received 50 mg intravenous diphenhydramine or placebo. Although only 8% of patients who received metoclopramide+placebo experienced akathisia, this is frequent enough that physicians should caution patients that this adverse effect may occur with this medication.

Other extrapyramidal adverse effects were uncommon. As far as we could determine using structured telephone follow-up at 48 hours, there were no occurrences of other dystonic reactions or tardive dyskinesia in either study arm. Tardive dyskinesia in particular is a rare extrapyramidal adverse effect, typically associated with longer exposure to antidopaminergic agents. Nonetheless, this study of only 208 patients is ill suited to comment on the incidence of this rare irreversible motor disorder. To the best of our knowledge, tardive dyskinesia has never occurred after a single dose of intravenous metoclopramide.<sup>29</sup>

We were somewhat surprised to discover that length of stay in the ED was not greater among patients who received 50 mg of intravenous diphenhydramine. Drowsiness is a known adverse effect of diphenhydramine. It is therefore unclear why study participants who received diphenhydramine did not have longer ED dwell times or report more functional impairment at 2 hours than those allocated to placebo. Our findings, however, are consistent with those of other studies of centrally acting

antidopaminergics combined with diphenhydramine, in which drowsiness or functional impairment at ED discharge among patients who received the centrally acting agents was no greater than among those who received sumatriptan, a medication not expected to cause drowsiness.<sup>13,30</sup>

In conclusion, there is no reason to coadminister intravenous diphenhydramine with metoclopramide routinely for ED patients with acute migraine.

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**APPENDIX E1****Congestion Quantifier 5 instrument<sup>1</sup>**

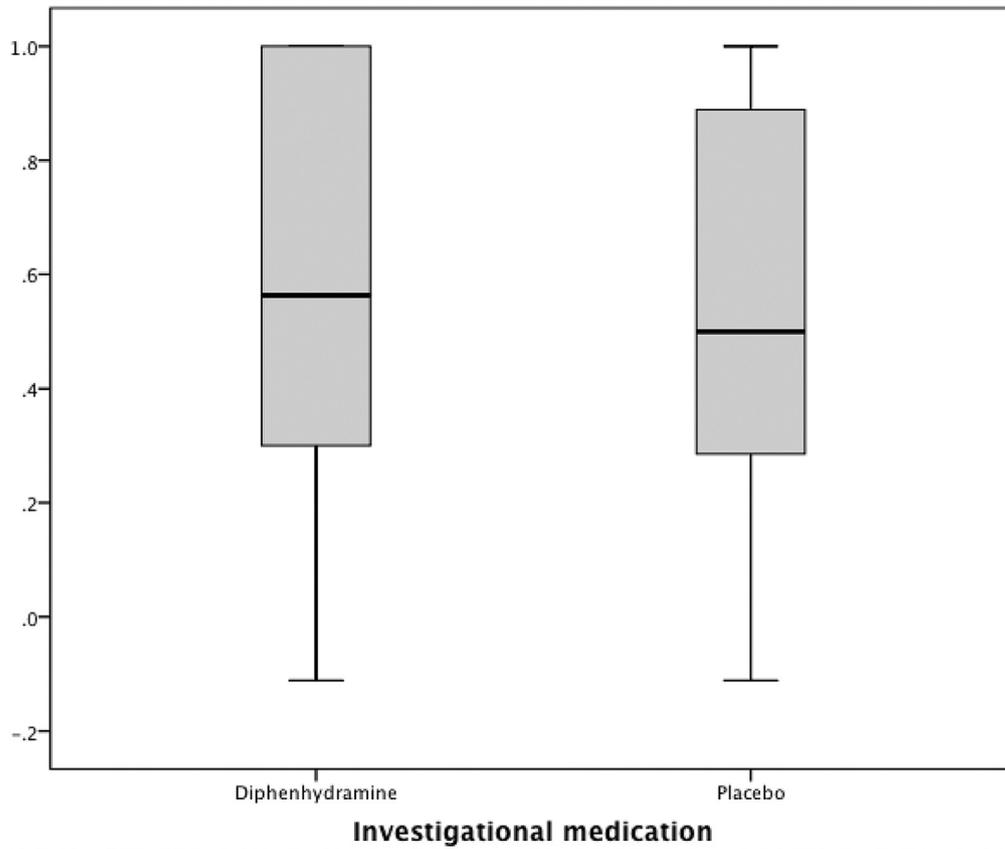
During the past week, how often....

- 1) Did you have nasal stuffiness, blockage, or congestion
- 2) Did you have to breathe through your mouth because you couldn't breathe through your nose
- 3) Did you have difficulty completely clearing your nose even after repeated blowing
- 4) Did you awaken in the morning with nasal stuffiness, blockage, or congestion

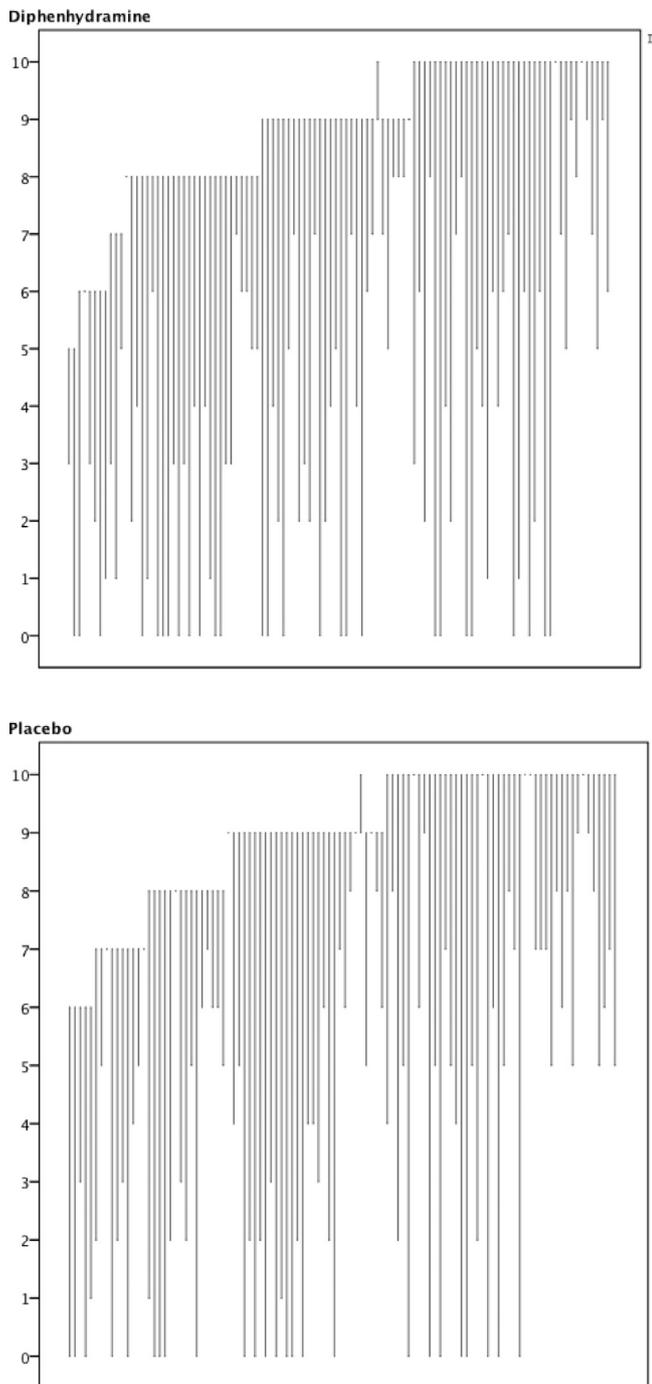
- 5) Was your sleep affected by nasal stuffiness, blockage, or congestion  
None of the time=0  
A little of the time=1  
Some of the time=2  
Most of the time=3  
All of the time=4  
Score of >6=positive

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**Figure E1.** Box and whiskers plot of the percentage improvement in 0 to 10 pain score between baseline and 1 hour (improvement in 0 to 10 score/baseline score). 1.0 Signifies complete improvement. 0 Signifies no improvement. Negative score indicate worsening.



**Figure E2.** Line graph representing each participant's experience at baseline and 1 hour later. The origin of the line depicts the 0 to 10 pain score at baseline. The terminus of the line depicts the 0 to 10 pain score at 1 hour. The graphs are sorted by baseline pain score. Thus, lines that rise unexpectedly depict participants whose pain worsened during the study period.