Treating Headache Recurrence After Emergency Department Discharge: A Randomized Controlled Trial of Naproxen Versus Sumatriptan

Benjamin W. Friedman, MD, MS
Clemencia Solorzano, RPh
David Esses, MD
Shujun Xia, MD, PhD
Michael Hochberg, MD
Niels Dua, MD, MS
Alan Heins, MD, MPH
Paul Sasso, MD
Polly E. Bijur, PhD
Richard B. Lipton, MD
E. John Gallagher, MD

From the Department of Emergency Medicine (Friedman, Esses, Xia, Hochberg, Bijur, Gallagher), Department of Epidemiology and Population Health, (Bijur, Lipton, Gallagher), and Department of Neurology (Lipton), Albert Einstein College of Medicine, Bronx, NY; the Pharmacy Department, Montefiore Medical Center, Bronx, NY (Solorzano); the Division of Emergency Medicine, Columbia University Medical Center, New York, NY (Dua, Sasso); and the Department of Emergency Medicine, University of South Alabama College of Medicine, Mobile, AL (Heins).

**Study objective:** Multiple parenteral medications are used to treat migraine and other acute primary headaches in the emergency department (ED). Regardless of specific headache diagnosis, no medication eliminates the frequent recurrence of primary headache after ED discharge. It is uncertain which medication primary headache patients should be given on discharge from an ED. The aim of this study is to compare the efficacy of oral sumatriptan with naproxen for treatment of post-ED recurrent primary headache.

**Methods:** This was a randomized, double-blind efficacy trial. We randomized patients to either naproxen 500 mg or sumatriptan 100 mg for headache recurrence after ED discharge. Patients were eligible if they received parenteral therapy for an acute exacerbation of a primary headache in the ED. Patients who met established criteria for migraine without aura were designated a priori as a homogenous subgroup of interest. We followed all patients by telephone 48 hours after ED discharge. The primary endpoint was the between-group difference in change in pain intensity during the 2-hour period after ingestion of either 500 mg naproxen or 100 mg sumatriptan. This difference was measured on a validated 11-point (0 to 10) verbal numeric rating scale (NRS). Satisfaction with the medication and adverse effects were also assessed. Patients who met criteria for migraine without aura were analyzed twice according to a priori design: once as a homogenous subgroup and then again combined with all other primary headaches.

**Results:** Of 410 patients randomized, 383 (93%) had outcome data available for analysis. Two hundred eighty (73%; 95% confidence interval [CI] 68% to 77%) reported headache post-ED discharge and 196 (51%; 95% CI 44% to 58%), including 88 with migraine, took the investigational medication provided to them. The naproxen group improved by a mean of 4.3 NRS points, whereas the sumatriptan group improved by 4.1 points (95% CI for difference of 0.2 points: −0.7 to 1.1 points). Findings were virtually identical among the migraine subset (4.3 versus 4.2 NRS points; 95% CI for difference of 0.1 points: −1.3 to 1.5 points). Seventy-one percent (95% CI 62% to 80%) of naproxen patients and 75% (95% CI 66% to 84%) of sumatriptan patients would want to take the same medication the next time. Adverse effect profiles were also comparable.

**Conclusion:** In this trial, nearly three quarters of patients reported headache recurrence within 48 hours of ED discharge. Naproxen 500 mg and sumatriptan 100 mg taken orally relieve post-ED recurrent primary headache and migraine comparably. Clinicians should be guided by medication costs, contraindications, and a patient’s previous experience with the medication. [Ann Emerg Med. 2010;xx:xxx.]

Please see page XX for the Editor’s Capsule Summary of this article.
EDITOR’S CAPSULE SUMMARY

What is already known on this topic
Headache recurrence after emergency department (ED) therapy for acute migraine or other primary headache is common.

What question this study addressed
Is oral naproxen or sumatriptan a better choice to lessen the intensity of recurrent headache within 48 hours of ED care and discharge?

What this study adds to our knowledge
In this double-blind randomized trial, 73% of the 383 patients had postdischarge headache recurrence within 48 hours, including 51% of those receiving a diagnosis of migraine. The study drugs did not differ in altering headache intensity or adverse effect frequency.

How this might change clinical practice
Clinicians should prepare patients for post-ED discharge headaches. Naproxen and sumatriptan were equivalent in efficacy and can be chosen according to cost, adverse effects, and previous patient experience.

INTRODUCTION

Background
The majority of the nearly 3 million headache patients who present to US emergency departments (EDs) annually are experiencing an acute exacerbation of a primary headache disorder. Primary headache disorders are benign, chronic disorders characterized by episodic exacerbations. In the general population, the 2 most common primary headache disorders are episodic tension-type headache, with a 1-year prevalence of 38%, and migraine, with a prevalence of 11%. The distribution of diagnoses in the ED differs from the distribution in the population because most patients with tension-type headache do not need to go to the ED. Migraine is the primary headache type observed most commonly in the ED, accounting for 60% of all primary headache visits. Episodic tension-type headache represents only about 10% of all primary headaches observed in the ED. About 25% of all acute primary headaches observed in the ED do not meet criteria for a specific diagnosis.

Clinicians use various parenteral therapies to treat acute primary headaches. Despite these interventions, headache recurrence after ED discharge is common. Management of these postdischarge headaches is variable and rarely studied. The aim of this study was to compare oral naproxen with oral sumatriptan to determine which agent relieves post-ED recurrent headache more efficaciously. Our primary hypotheses were as follows: (1) in the 48-hour period after parenteral ED treatment for migraine, sumatriptan 100 mg will relieve headache better than naproxen 500 mg, and (2) in the 48-hour period after parenteral ED treatment for any primary headache, sumatriptan 100 mg will relieve headache better than naproxen 500 mg.

MATERIALS AND METHODS

This was a randomized, double-blind, comparative efficacy trial of 2 active oral medications in a population of patients discharged from the ED after treatment for an acute primary headache. To maintain a homogenous study population, we included patients only if they received parenteral medication for their headache in the ED and if secondary or organic headache was not being considered. We followed all patients by telephone 48 hours after ED discharge, but by design, we included in the primary efficacy analysis only those patients who took their medication (Figure 1). This trial was registered at http://www.clinicaltrials.gov and approved by the institutional review boards of Montefiore Medical Center, Columbia University, and the University of South Alabama.

The International Headache Society recommends the use of the International Classification of Headache Disorders for headache research. This classification scheme divides primary headaches into 4 major categories: migraine, tension-type headache, cluster headache and the trigeminal autonomic cephalalgias, and other primary headaches—and further subdivides these major categories into multiple subdivisions. However, 25% of patients presenting to the ED with primary headaches cannot be assigned a specific diagnosis because of imprecision in headache description, fewer than 5 lifetime headaches, or duration of headache greater than 1 week. Because current evidence-based treatment of primary headache is usually contingent on the diagnostic classification of the acute headache attack, emergency clinicians are often left with uncertainty about how best to treat a significant proportion of headache patients. In this study, we included the full spectrum of primary headache patients, including those with “unclassifiable” primary headache. However, patients with acute migraine without aura represent a homogenous, readily identifiable group, and one in which we thought we were most likely to observe a difference in efficacy. Therefore, we identified this subset of patients a priori as a subgroup of interest.

Nonsteroidals are first-line, guideline-recommended medications for mild to moderate migraine. Because the majority of discharged migraineurs who have headache have mild to moderate pain, this is likely to be appropriate medication for many ED patients. Nonsteroidals are also recommended as first-line therapy for tension-type headaches. Naproxen is recommended as category A by the US Headache Consortium with as much clinical effect as any other nonsteroidal. Naproxen is inexpensive, commonly used, and very well tolerated in limited doses.

Sumatriptan is considered standard migraine therapy for moderate to severe migraines and for migraines refractory to...
nonopioid analgesics. Sumatriptan is thought to be efficacious in tension-type headache when the tension-type headache occurs in a patient with underlying migraine disorder and for the treatment of tension-type headache in the ED. We chose a relatively high dose of sumatriptan for this study so that clinical efficacy would not be missed because of insufficient dosing.

**Selection of Participants**

Patients who presented to the ED with an acute headache were included in the study if they were aged 18 to 64 years, were treated with parenteral medication in the ED, had a primary headache as determined by the ED attending physician (defined as an acute exacerbation of an underlying recurrent headache disorder), and were to be discharged home from the ED. We excluded patients for clinical suspicion of a secondary or organic cause of headache; performance of a lumbar puncture; pregnancy; allergy, intolerance, or contraindication to investigational medication; or daily analgesic medication use.

**Setting**

Montefiore Medical Center is in the Bronx, NY; Columbia University Medical Center is in Manhattan, NY; and the University of South Alabama is in Mobile, AL. All are tertiary medical centers serving predominantly socioeconomically depressed populations. At Montefiore Medical Center, salaried research associates performed data collection. These are trained, bilingual (Spanish and English), patient care technician–level employees, who staff the ED 24 hours per day, 7 days per week. At Columbia University and the University of South Alabama, volunteer research associates specifically trained for this study performed data collection. These volunteers staffed the ED on nonconsecutive shifts.
migraine) were classified as having nonmigraine primary headache. We expected the category “nonmigraine primary headache” to consist of a heterogeneous group of headache diagnoses, including probable migraine, episodic tension-type headache, probable tension-type headache, other primary headache, and headaches that did not fit any International Classification of Headache Disorders, 2nd Edition migraine criteria. Cluster headache was expected to be infrequent.

Randomization occurred in blocks of 10 and was determined by a sequence generated at http://www.randomization.com. The pharmacist masked the medications by inserting them into unmarked gel capsules. Surplus space in the capsule was filled with scant amounts of lactose. The pharmacist randomized and blinded the medication in a location removed from the ED and inaccessible to ED personnel. ED personnel were presented with the unmarked gel capsules, which were dispensed to patients in the order determined by randomization.

We approached patients for participation in the study in the ED after their pain had been controlled with parenteral medication and they were ready to be discharged. At this point, we obtained informed consent and collected baseline demographic information, headache history, and pain intensity scores. Using the study questionnaire as a guide, we classified the patient as having migraine or nonmigraine primary headache.

The study medication, consisting of one gel capsule placed within a medication vial, was taken from the medication storage cabinet and given to the patient. Research associates also gave the patient a discharge instruction sheet, which provided information about headache diagnosis and management and a headache diary to track headache intensity levels during the 48 hours after discharge. Research associates instructed study patients in the use of the headache diary and asked them to record headache intensity levels every 2 hours while awake.

Forty-eight hours after ED discharge, the research associates conducted follow-up interviews with the patient by telephone. If contact could not be established, follow-up telephone calls were made every 8 hours until contact was established or the telephone follow-up was deemed futile. Failing telephone follow-up, we attempted to complete follow-up with express courier or home visit by the principal investigator.

**Outcome Measures**

We used an 11-point verbal numeric rating scale (NRS) for pain as the primary measurement tool for this trial. On this scale, patients are asked to describe their pain as a number between zero and 10, with zero being no pain and 10 being the worst pain imaginable. This scale has been shown to be both valid and reliable and to perform comparably to a visual analog scale while being easier to administer. Eleven-point pain scales are commonly used in ED-based headache research and are recommended for use in migraine clinical trials.

As a secondary measure, this trial used the 4-point descriptive pain scale recommended for use in migraine research by the International Headache Society. On this scale, patients are asked to characterize their headache as “none,” “mild,” “moderate,” or “severe.”

We used a descriptive categorical scale to characterize the patient’s headache-related disability. On this scale, patients describe their disability as “1) none; 2) mildly impaired (having a little bit of difficulty doing what I usually do); 3) moderately impaired (having a great deal of difficulty doing what I usually do and can only do very minor activities); or 4) severely impaired (requiring bed rest).”

The primary outcome measure was the change in NRS score between medication ingestion and 2 hours after medication, as described over the telephone 48 hours after ED discharge \( \left( NRS_{\text{time of ingestion}} - NRS_{\text{2 hours later}} \right) \). Patients were asked to consult their headache diaries to recall pain scores accurately.

The secondary outcome measure was the percentage of patients who answered the following question affirmatively: “Do you want to receive the same medication the next time you are discharged from the ED after treatment for headache?” We also asked patients to report their headache-related disability scores, their 4-point categorical pain intensity scores, and any adverse effects they experienced.

Finally, to address the usefulness of making a specific primary headache diagnosis, we assessed the standard deviation (SD) of the primary outcome among the group receiving a diagnosis of migraine without aura and the group receiving a diagnosis of nonmigraine primary headache. The purpose of this assessment was to determine whether patients receiving a diagnosis of migraine were more homogenous in response to our investigational medications than patients lumped together as receiving a nonmigraine primary headache diagnosis. Homogeneity in response among patients with a diagnosis in common would support the validity of separating primary headache disorders as the International Classification of Headache Disorders recommends.

**Primary Data Analysis**

Only patients who experienced headache recurrence and received the study medication were included in the efficacy analyses. We excluded patients lost to follow-up from the primary analysis because no assumptions could be made about these data. Mean change in NRS \( \left( NRS_{\text{time of ingestion}} - NRS_{\text{2 hours later}} \right) \) among patients randomized to sumatriptan was compared with that of the naproxen group, using an independent-samples t test. We performed this analysis for patients with migraine without aura and then repeated it for all patients who received the investigational medication regardless of primary headache diagnosis. We report precision of continuous and categorical data and their differences with 95% confidence interval (CI). We used the Levene test for homogeneity of variance to compare SD of the primary outcome between patients with migraine and patients with nonmigraine primary headache. Because we performed 2 overlapping analyses (migraine, all primary headaches) and therefore had 2 chances to disprove the null hypothesis, we set the \( \alpha \) for the primary analyses to .025.
All analyses were performed using SPSS (version 13; SPSS, Inc., Chicago, IL).

We based the sample size calculation on finding a clinically important difference in those patients who met criteria for migraine without aura. This stratum was of greatest interest because it represents a homogenous group of patients with the headache type encountered most commonly in the ED. Using an SD of 3.0 derived from previous ED-based clinical trials and an NRS difference of 2.0 (a difference considered to have robust clinical significance), a sample size calculation revealed the need for 44 patients with migraine without aura in each group, for a total of 88 patients, using a conservative and a power of 0.80. Enrollment continued until 88 patients with migraine without aura who received the investigational medication were successfully followed up at 48 hours.

RESULTS

Enrollment began in March 2007 and continued for 28 months. We screened 1,000 headache patients for eligibility and randomized 410 (Figure 3). We excluded 9 randomized patients from the study population because of protocol violations. Specifically, we determined on blinded review of the data set that these 9 did not meet study entry criteria, 5 because they did not receive parenteral medication, 3 because they were admitted to the hospital, and 1 because of performance of a lumbar puncture. Among the 401 primary headache patients who were randomized and eligible, 166 specifically met the International Headache Society’s migraine without aura criteria. We obtained outcome data on 95.5% of randomized and eligible patients. Baseline characteristics of these patients are listed in Tables 1 and 2.

One hundred three of our 401 patients (27%; 95% CI 23% to 31%) reported no headache after ED discharge, 89 (23%; 95% CI 19% to 27%) reported mild headache, and 191 (50%; 95% CI 45% to 55%) reported moderate or severe headache. One hundred ninety-six patients (51%; 95% CI 46% to 56%) took the investigational medication (Figure 3). Similar percentages of patients with migraine without aura and nonmigraine primary headache reported use of investigational
medication: 53% of 166 and 50% of 217, respectively (95% CI for difference of 3%: −7% to 13%).

Of the 217 patients with nonmigraine primary headache who were available for follow-up, 117 met criteria for probable migraine. Only 2 patients met International Headache Society criteria for episodic tension-type headache and 15 met criteria for probable tension-type headache. The remaining 83 patients could not readily be assigned an International Classification of Headache Disorders diagnosis. Barriers to classification in these 83 patients were duration of headache greater than 72 hours (76%) and fewer than 4 previous similar headaches (50%).

Within the subset of patients with migraine without aura, the naproxen group had a mean pain improvement over 2 hours of 4.3 NRS points and the sumatriptan had a mean improvement of 4.2 (95% CI for a difference of 0.1: −0.7 to 1.1). Among all primary headache patients, the naproxen group again improved by a mean of 4.3, whereas the sumatriptan group improved by a mean of 4.1 (95% CI for difference of 0.2: −0.7 to 1.1). Baseline and 2-hour pain scores are listed in Table 3 and depicted in Figure 4. Secondary outcomes are listed in Table 4.

Adverse medication effects were reported by 19% of 97 (95% CI 11% to 27%) naproxen patients and 26% of 97 (95% CI 18% to 36%) sumatriptan patients (95% CI for a difference of 7%: −5% to 19%). The most common adverse effects naproxen patients reported were gastrointestinal (7), dizziness/feeling lightheaded or weak (5), drowsiness (2), and worsened headache (4). The most common adverse effects sumatriptan patients reported were gastrointestinal (9), dizziness/feeling lightheaded or weak (2), and drowsiness (2).

Use of investigational medication was not associated with duration of headache, sex, age, triage pain scores, or discharge pain scores. Patients who reported at baseline that their headache sometimes, usually, or always recurred after initial treatment were more likely to use the investigational medication than patients who reported their headache never or rarely recurred (55% versus 43%; 95% CI for difference of 12%: 2% to 22%).

We assessed blinding by asking patients whether they knew which medication they had received. Eighty-six of 95 patients (91%) in the naproxen arm did not know they received naproxen, stating that they did not know which medication they were given or that they believed they were given sumatriptan. Similarly, 89 of 94 (95%) in the sumatriptan arm did not know they had received sumatriptan.

To help determine the utility of making a specific primary headache diagnosis, we compared variability in response to the medications between the 88 patients in the migraine without aura group and the 108 patients in the nonmigraine primary headache group. The migraineurs improved by a mean of 4.3 (SD 3.3), whereas the nonmigraine group improved by a mean of 4.1 (SD 2.9). When compared statistically, the nonmigraine group had less variability than the migraine group (P=0.05).

### Table 1. Baseline characteristics of all patients with migraine (reported as number [%] unless otherwise noted).

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Naproxen Used Investigational Medication (n=48)</th>
<th>Did Not Need/Did Not Take Investigational Medication (n=36)</th>
<th>Sumatriptan Used Investigational Medication (n=40)</th>
<th>Did Not Need/Did Not Take Investigational Medication (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>35 (9)</td>
<td>37 (11)</td>
<td>35 (9)</td>
<td>36 (9)</td>
</tr>
<tr>
<td>Female</td>
<td>45 (94)</td>
<td>31 (86)</td>
<td>33 (83)</td>
<td>35 (83)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>33 (69)</td>
<td>24 (67)</td>
<td>22 (55)</td>
<td>23 (55)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15 (33)*</td>
<td>13 (36)</td>
<td>12 (30)</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>12 (26)</td>
<td>10 (28)</td>
<td>13 (33)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (41)</td>
<td>13 (36)</td>
<td>15 (38)</td>
<td>14 (33)</td>
</tr>
<tr>
<td><strong>Headache duration, h, median (IQR)</strong></td>
<td>26 (15, 48)</td>
<td>27 (11, 48)</td>
<td>30 (8, 48)</td>
<td>24 (13, 72)</td>
</tr>
<tr>
<td><strong>Took migraine/headache medication before ED presentation</strong></td>
<td>27 (60)*</td>
<td>26 (74)*</td>
<td>29 (73)</td>
<td>32 (76)*</td>
</tr>
<tr>
<td><strong>Median pain score (0–10) at triage (IQR)</strong></td>
<td>10 (9, 10)</td>
<td>9 (8, 10)</td>
<td>10 (9, 10)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td><strong>Median pain score (0–10) at discharge (IQR)</strong></td>
<td>2 (0, 4)</td>
<td>3 (0, 4)</td>
<td>3 (1, 4)</td>
<td>2 (0, 4)</td>
</tr>
<tr>
<td><strong>Treated with antiemetic/dopamine antagonist in ED</strong></td>
<td>47 (98)</td>
<td>35 (97)</td>
<td>40 (100)</td>
<td>40 (95)</td>
</tr>
<tr>
<td><strong>Treated with nonsteroidal anti-inflammatory drug in ED</strong></td>
<td>8 (17)</td>
<td>3 (8)</td>
<td>11 (28)</td>
<td>10 (24)</td>
</tr>
<tr>
<td><strong>Treated with opioids in ED</strong></td>
<td>2 (4)</td>
<td>4 (11)</td>
<td>4 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td><strong>Treated with triptan in ED</strong></td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Treated with corticosteroids in ED</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

IQR, Interquartile range. *Baseline data missing for some patients.
with more of the variability in the migraine group coming from heterogeneity in response to sumatriptan.

**LIMITATIONS**

The majority of patients in this study received a parenteral dopamine antagonist as initial ED treatment for their headache. Thus, the generalizability of this study to other types of ED treatment may be limited.

We based specific primary headache diagnosis on data obtained during the ED visit and not headache diaries or a more thorough headache history. Thus, the accuracy of these diagnoses was not verified against a criterion standard, although the methodology we used has been shown to be reliable.19

We did not control the variability to time that the study medication was taken or record this information. The time postdischarge that the patient received the study medication may have affected the efficacy. We did not assess the efficacy of more than 1 dose of study medication. A subsequent dose of either of these medications may have improved overall efficacy. We did not measure our patients’ compliance with the headache diary.

To obtain successful double blinding, it was necessary for us to encapsulate the medications, which may have altered absorption kinetics of either or both agents. However, a trained pharmacist prepared both medications identically, and data from systematic reviews do not reveal decreased efficacy of sumatriptan associated with reencapsulation.28

We did not use a placebo control in this study. Therefore, we cannot conclude according to these data that these medications are more effective than placebo. However, both of the investigational medications used in this study have previously demonstrated superiority to placebo in studies targeted at the initial treatment of headache,21,22,29 and sumatriptan has been shown to be superior to placebo for treatment of migraine recurrence.30,31 Additionally, there is a sound ethical rationale for not performing headache trials with a placebo control.

**Table 2.** Baseline characteristics of all patients with any primary headache, including those with migraine (reported as number [%] unless otherwise noted).

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Naproxen (n=98)</th>
<th>Did Not Need/Did Not Take Investigational Medication (n=92)</th>
<th>Sumatriptan (n=95)</th>
<th>Did Not Need/Did Not Take Investigational Medication (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>35 (10)</td>
<td>35 (11)</td>
<td>37 (10)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Female</td>
<td>85 (87)</td>
<td>78 (85)</td>
<td>82 (84)</td>
<td>81 (85)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>66 (67)*</td>
<td>55 (60)</td>
<td>60 (61)</td>
<td>55 (58)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>29 (30)</td>
<td>34 (37)</td>
<td>30 (31)</td>
<td>34 (36)*</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>White</td>
<td>29 (30)</td>
<td>21 (23)</td>
<td>28 (29)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Other</td>
<td>38 (40)</td>
<td>37 (40)</td>
<td>39 (40)</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Headache duration, h, median (IQR)</td>
<td>48 (24, 96)</td>
<td>48 (12, 114)</td>
<td>72 (24, 120)</td>
<td>66 (24, 96)</td>
</tr>
<tr>
<td>Took migraine/headache medication before ED presentation</td>
<td>66 (67)*</td>
<td>61 (68)*</td>
<td>73 (75)</td>
<td>62 (67)*</td>
</tr>
<tr>
<td>Median pain score (0–10) at triage (IQR)</td>
<td>10 (8, 10)</td>
<td>9 (8, 10)</td>
<td>9 (8, 10)</td>
<td>9 (8, 10)</td>
</tr>
<tr>
<td>Median pain score (0–10) at discharge</td>
<td>2 (0, 5)</td>
<td>2 (0, 4)</td>
<td>3 (1, 4)</td>
<td>2 (0, 3)</td>
</tr>
<tr>
<td>Treated with antiemetic/dopamine antagonist in ED</td>
<td>96 (98)</td>
<td>88 (96)</td>
<td>95 (97)</td>
<td>90 (95)</td>
</tr>
<tr>
<td>Treated with nonsteroidal anti-inflammatory drug in ED</td>
<td>18 (18)</td>
<td>11 (12)</td>
<td>24 (25)</td>
<td>25 (26)</td>
</tr>
<tr>
<td>Treated with opioids in ED</td>
<td>11 (11)</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Treated with triptan in ED</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Treated with corticosteroids in ED</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Baseline data missing for some patients.

**Table 3.** Headache scores among patients who took the investigational medication.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subset With Migraine</th>
<th>All Primary Headache Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median pain score when medication was ingested, on a scale of 0 to 10 (IQR)</td>
<td>Naproxen (n=48)</td>
<td>Sumatriptan (n=40)</td>
</tr>
<tr>
<td></td>
<td>8 (7, 10)</td>
<td>8 (6, 10)</td>
</tr>
<tr>
<td>Median pain score 2 h after medication was ingested, on a scale of 0 to 10 (IQR)</td>
<td>Naproxen (n=98)</td>
<td>Sumatriptan (n=98)</td>
</tr>
<tr>
<td></td>
<td>2 (0, 6)</td>
<td>3 (0, 6)</td>
</tr>
</tbody>
</table>
DISCUSSION

In this randomized clinical trial, we compared the efficacy of 500 mg naproxen to 100 mg sumatriptan taken orally for treatment of short-term recurrence of headache after ED discharge in patients with migraine without aura and all primary headaches. Because the headache relief obtained with these 2 medications was similar (differing by only 0.1 to 0.2 points on an 11-point scale, with narrow CIs demarcating these differences), we conclude that either agent is a reasonable treatment option. Nearly three quarters of patients in this study reported headache recurrence within 48 hours of ED discharge. Unfortunately, approximately one quarter of patients who took the study medications for treatment of headache recurrence after ED discharge continued to experience moderate or severe headache.

Figure 4. Graphic depiction of change in pain scores between time of medication ingestion and 2 hours later. Larger pain scores signify greater pain. A, Migraine patients randomized to naproxen. B, Migraine patients randomized to sumatriptan. C, Nonmigraine patients randomized to naproxen. D, Nonmigraine patients randomized to sumatriptan.
In this study, 50% of all patients reported moderate or severe headache within 48 hours of ED discharge, which is consistent with previously reported data. In an urban ED population, 30% of those experiencing headache reported moderate or severe headaches after discharge, and 46% reported headache-related functional impairment.2,12 These outcomes were not statistically different when those who met criteria for migraine were compared with those who did not. In ED-based clinical trials, 18% to 87% of migraine patients report recurrent or persistent headache recurrence within 24 hours after discharge.8,11,13,14,16,32 This widely varying incidence of headache recurrence is likely related to methodological differences in assessing and defining recurrence. In a Canadian population, 45% of migraine patients reported headache recurrence after ED discharge; and 46% reported headache-related functional impairment.12 In our study, as in others, it was difficult to predict headache recurrence according to features of the history of present illness or headache history.33-35 These data suggest that emergency physicians should address the possibility of recurrence when discharging all of their primary headache patients.

We were unable to identify any ED-based clinical trials that addressed treatment of headache recurrence. Dexamethasone has a number needed to treat of 9 to 10 when used prophylactically before ED discharge to prevent development of headache recurrence.36,37 Naproxen, when used prophylactically in the outpatient setting to prevent migraine recurrence, has a number needed to treat of 3.38 Several clinical trials have found that triptans effectively treat the recurrent migraine in patients initially treated with the same triptan,30,31,35,40 although triptans cannot be used prophylactically to prevent recurrent migraine.31,41 Sumatriptan 100 mg, when used to treat headache recurrence in the outpatient setting after initial treatment with oral or subcutaneous sumatriptan, has a number needed to treat of 3 to 4.30,31

Our results differ somewhat from those of clinical trials comparing naproxen with sumatriptan for the initial acute migraine attack. In those studies, 2-hour headache relief rates (defined as headache intensities decreasing to mild or none from moderate or severe) for sumatriptan 85 mg versus naproxen 500 mg were reported as 55% versus 44% (absolute risk reduction 11% [95% CI 4% to 18%]) and 50% versus 43% (absolute risk reduction 7% [95% CI 0% to 14%]), respectively.42 In a study of sumatriptan 50 mg versus naproxen 500 mg, 49% versus 46% reported headache relief at 2 hours (absolute risk reduction 3% [95% CI −6% to 12%]).43 In our study, we did not find a statistically or clinically significant difference between these 2 medications, despite using a larger dose of sumatriptan. This finding may be due to a greater susceptibility to treatment in the recurrent attack or to a synergy between the parenteral antiemetic dopamine antagonists received by most patients in the ED and oral nonsteroidal received later, a hypothesis that has not yet been tested. There has been a report of decreased responsiveness to triptans after opioid use,34 although this effect is modest and most patients in our study did not receive opioids.

Although naproxen or sumatriptan, taken once the recurrent headache develops, may help some patients with post-ED headache recurrence, many will not benefit from these interventions. A reasonable therapeutic option for patients with unrelieved recurrent headache may be to combine sumatriptan with naproxen, a strategy shown to be more effective than either medication alone in initial treatment of acute migraine.42 Alternatively, it is reasonable to add an oral antiemetic dopamine antagonist to naproxen. In general, opioid use for the primary headache disorders is not recommended, because it is linked to medication overuse headache and development of chronic migraine.

We were surprised that heterogeneity in response to the investigational medications was greater among the migraine without aura patients. Because this group was homogeneous with respect to headache diagnosis and the nonmigraine primary headache group was not, this may signal a potential problem

Table 4. Secondary outcomes (reported as n/N [%]).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subset With Migraine</th>
<th>All Primary Headache Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naproxen</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Would take again</td>
<td>31/46 (67)</td>
<td>26/37 (70)</td>
</tr>
<tr>
<td>Functional impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not impaired</td>
<td>30 (63)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>9 (19)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Cannot do activities</td>
<td>3 (6)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Cannot get out of bed</td>
<td>6 (13)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Took additional medication for headache</td>
<td>17/48 (35)</td>
<td>17/40 (43)</td>
</tr>
</tbody>
</table>
with the International Classification of Headache Disorders when applied in the ED setting. Classification schemes that do not predict response to treatment or prognosis are of little value to clinicians. It is not clear why the International Classification of Headache Disorders did not perform well in this study, although this has been reported previously in the ED setting. It may be that patients report the acute headache differently than an interictal recounting of a full headache history, particularly with respect to similarity of any single acute headache to previous headaches. It may also be that the prolonged duration of headache observed among ED patients interferes with accurate headache classification.

In conclusion, nearly three quarters of primary headache patients reported headache recurrence within 48 hours of ED discharge. Naproxen and sumatriptan demonstrate clinically and statistically similar efficacy and adverse effect profile for the post-ED treatment of recurrence of all primary headaches and migraine without aura. Clinicians deciding which medication to prescribe for recurrence can therefore be guided by considerations such as costs, contraindications, adverse effects, and a patient’s previous overall experience with the medication.

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**Author contributions:** BWF, CS, DE, ND, AH, PEB, and EJG conceived the study and designed the trial. BWF, DE, ND, AH, and PS supervised the conduct of the trial and data collection. BWF, DE, ND, and AH undertook recruitment of participating centers and patients and managed the data, including quality control. PEB, RBL, and EJG provided statistical advice on study design. BWF analyzed the data. BWF drafted the article, and all authors contributed substantially to its revision. BWF takes responsibility for the paper as a whole.

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**Address for correspondence:** Benjamin W. Friedman, MD, MS, Department of Emergency Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210th St, Bronx, NY 10467; 718-920-6626, fax 718-798-0730; E-mail befriedm@montefiore.org.

**REFERENCES**


20. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the...


27. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med. 1998;5:1086-1090.


Editor's Capsule Summary: What question this study addressed: Is oral naproxen or sumatriptan a better choice to lessen the intensity of recurrent headache within 48 hours of ED care and discharge? What this study adds to our knowledge: In this double-blind randomized trial, 73% of the 383 patients had postdischarge headache recurrence within 48 hours, including 51% of those receiving a diagnosis of migraine. The study drugs did not differ in altering headache intensity or adverse effect frequency.