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Treating headache recurrence after ED discharge: An RCT of naproxen versus sumatriptan

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Abstract

Background—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 upon discharge from an ED. The aim of this study was to compare the efficacy of oral sumatriptan to naproxen for treatment of post-ED recurrent primary headache.

Methods—This was a randomized, double-blind efficacy trial. We randomized patients to either naproxen 500mg or sumatriptan 100mg for headache recurrence following 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 over the 2-hour period following ingestion of either 500 mg naproxen or 100 mg sumatriptan. This difference was measured on a validated 11-point (0–10) verbal Numerical Rating Scale (NRS). Satisfaction with the medication and side 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. 280 (73%, 95%CI: 68, 77%) reported headache post-ED discharge and 196 (51%, 95%CI: 44, 58%),

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including 88 with migraine, took the investigational medication provided to them. The naproxen group improved by a mean of 4.3 NRS points, while the sumatriptan group improved by 4.1 (95% CI for difference of 0.2: -0.7, 1.1). Findings were virtually identical among the migraine subset (4.3 vs. 4.2 NRS points, 95%CI for difference of 0.1: -1.3, 1.5). 71% (95%CI: 62, 80%) of naproxen patients and 75% (95%CI: 66, 84%) of sumatriptan patients would want to take the same medication the next time. Side effect profiles were also comparable.

Conclusions—In this trial, nearly $\frac{3}{4}$ 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.

Background

The majority of the nearly three million headache patients who present to US emergency departments (ED) annually are suffering an acute exacerbation of a primary headache disorder [1–3]. Primary headache disorders are benign, chronic disorders characterized by episodic exacerbations[4]. In the general population, the two most common primary headache disorders are episodic tension-type headache, with a one-year period prevalence of 38%, [5] and migraine, with a prevalence of 11%[6]. 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 seen 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 seen in the ED[2]. About 25% of all acute primary headaches seen in the ED do not meet criteria for a specific diagnosis[2].

Clinicians use various parenteral therapies to treat acute primary headaches[7]. Despite these interventions, headache recurrence following ED discharge is common [2,8–16]. Management of these post-discharge headaches is variable and rarely studied. The aim of this study was to compare oral naproxen to 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 following parenteral ED treatment for migraine, sumatriptan 100mg will relieve headache better than naproxen 500mg, and 2) in the 48 hour period following parenteral ED treatment for any primary headache, sumatriptan 100mg will relieve headache better than naproxen 500mg.

Methods

Overview

This was a randomized, double-blind comparative efficacy trial of two 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.

Rationale

The International Headache Society recommends the use of the International Classification of Headache Disorders for headache research[17]. This classification scheme divides primary headaches into four major categories— 1) Migraine, 2) Tension-type Headache, 3) Cluster

Headache and the Trigeminal Autonomic Cephalalgias, and 4) Other Primary Headaches—and further subdivides these major categories into multiple subdivisions[18]. However, 25% of primary headaches presenting to the ED cannot be assigned a specific diagnosis because of imprecision in headache description, fewer than five lifetime headaches, and/or duration of headache greater than one week.[19] 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 felt we were most likely to observe a difference in efficacy. Therefore, we identified this subset of patients a priori as a subgroup of interest.

Non-steroidals are first-line, guideline recommended medications for mild-moderate migraine [20]. Since the majority of discharged migraineurs who have headache have mild to moderate pain[2], this is likely to be appropriate medication for many ED patients. Non-steroidals 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 non-steroidal[20]. Naproxen is inexpensive, commonly used and very well tolerated in limited doses. [21,22]

Sumatriptan is considered standard migraine therapy for moderate-severe migraines and for migraines refractory to non-opioid analgesics[20]. Sumatriptan is thought to be efficacious in tension-type headache when the tension-type headache occurs in a patient with underlying migraine disorder[23] and for the treatment of tension-type headache in the ED[24]. We chose a relatively high dose of sumatriptan for this study so that clinical efficacy would not be missed due to insufficient dosing.

Study population

Patients who presented to the ED with an acute headache were included in the study if they were 18 to 64 years old, were treated with parenteral medication in the ED, had a primary headache as determined by the ED attending (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 contra-indication to investigational medication, or daily analgesic medication use.

Study sites

Montefiore Medical Center is in the Bronx, New York, Columbia University Medical Center is in Manhattan, New York, and University of South Alabama is in Mobile, Alabama. All are tertiary medical centers serving predominantly socio-economically 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, seven days per week. At Columbia University and University of South Alabama, volunteer research associates, specifically trained for this study, performed data collection. These volunteers staffed the ED on non-consecutive shifts.

Intervention

We randomized patients to naproxen 500mg or sumatriptan 100mg to be taken orally. At the time of discharge from the ED, we gave patients vials containing one masked gel capsule and instructed them to take the medication if they felt they needed something to treat recurrence of headache following discharge.

Stratification

Two levels of stratification occurred. First, we classified patients as “migraine” or “non-migraine primary headache disorder” using the International Headache Society’s International Classification of Headache Disorders, 2nd edition. The second level of stratification was based on whether or not the patient was administered an anti-emetic dopamine antagonist medication. The goal of this stratification was 1) to address our two primary hypotheses (efficacy for migraine and efficacy for all patients with a primary headache) and 2) to ensure that medication received in the ED did not confound the primary outcome. In order to be classified as migraine, patients had to meet all migraine without aura criteria, including headache duration of four to 72 hours, five similar lifetime headaches, and headache characteristics and associated features listed in Figure 2. Patients who missed one of these criteria (ie, ICHD-2 probable migraine) were classified as “non-migraine primary headache”. We expected the category “non-migraine 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 patients who did not fit any ICHD-2 migraine criteria. Cluster headache was expected to be infrequent.

Randomization and blinding

Randomization occurred in blocks of ten and was determined by a sequence generated at <http://www.randomization.com>. The pharmacist masked the medications by inserting them into unmarked gel capsule. 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.

Protocol

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 migraine or non-migraine 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 over 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 two hours while awake.

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

Measures

1) Numerical Rating Scale for pain- We used an 11-point verbal numerical rating scale 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 ten, with zero being no pain and ten 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[25]. Eleven point pain scales are

commonly used in ED-based headache research and are recommended for use in migraine clinical trials[17].

2) Four point categorical pain intensity scale. As a secondary measure, this trial used the four-point descriptive pain scale recommended for use in migraine research by the International Headache Society[17]. On this scale, patients are asked to characterize their headache as “none, mild, moderate or severe”.

3) Headache-related disability scale. 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)”[17].

Outcomes

Primary—Change in Numerical Rating Scale score between the time of medication ingestion and 2 hours after medication, as described over the telephone 48 hours after ED discharge ($NRS_{\text{time of ingestion}} - NRS_{\text{2 hours later}}$). Patients were asked to consult their headache diaries to recall pain scores accurately.

Secondary—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 emergency room after treatment for headache?” We also asked patients to report their headache-related disability scores, their four point categorical pain intensity scores, and any adverse effects they experienced.

Methodological outcome—Finally, to address the usefulness of making a specific primary headache diagnosis, we assessed the standard deviation of the primary outcome among the group diagnosed with migraine without aura and the group diagnosed with non-migraine primary headache. The purpose of this assessment was to determine if patients diagnosed with migraine were more homogenous in response to our investigational medications than patients lumped together as non-migraine 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.

Analysis

Only patients who suffered headache recurrence and took 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 ($NRS_{\text{time of ingestion}} - NRS_{\text{2 hours later}}$) among patients randomized to sumatriptan was compared to the naproxen group using an independent samples t-test. We performed this analysis for migraine without aura patients and then repeated it for all patients who took the investigational medication regardless of primary headache diagnosis. We report precision of continuous and categorical data and their differences with 95%CI. We used the Levene test for homogeneity of variance to compare standard deviation of the primary outcome between patients with migraine and patients with non-migraine primary headache. Because we performed two overlapping analyses (migraine, all primary headaches) and therefore had two chances to disprove the null hypothesis, we set the α for the primary analyses to 0.025. All analyses were performed using SPSS v.13 (SPSS Inc., Chicago, IL)

Sample size calculation—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 a standard deviation of 3.0 derived from previous ED-based clinical trials[13,26] and an NRS difference of 2.0 (a difference considered to have robust clinical significance[27]), 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 alpha of 0.025 and a power of 0.80. Enrollment continued until 88 patients with migraine without aura who took the investigational medication were successfully followed up at 48 hours.

Results

Enrollment began in March of 2007 and continued for 28 months. We screened one thousand headache patients for eligibility and randomized 410 (Figure 3). We excluded nine randomized patients from the study population because of protocol violations. Specifically, we determined on blinded review of the dataset that these nine did not meet study entry criteria-- five because they did not receive parenteral medication, three because they were admitted to the hospital, and one 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 Table 1 and Table 2.

One hundred three of our 401 patients (27%, 95%CI: 23, 31%) reported no headache after ED discharge, 89 (23%, 95%CI: 19, 27%) reported mild headache, and 191 (50%, 95%CI:45, 55%) reported moderate or severe headache. 196 patients (51%, 95%CI: 46, 56%) took the investigational medication (Figure 3). Similar percentages of patients with migraine without aura and non migraine primary headache reported use of investigational medication: 53% of 166 and 50% of 217, respectively (95%CI for difference of 3%: -7, 13%).

Of the 217 patients with non-migraine 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 >72 hours (76%) and fewer than four 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: -1.3, 1.5). Among all primary headache patients, the naproxen group again improved by a mean of 4.3, while the sumatriptan group improved by a mean of 4.1 (95%CI for difference of 0.2: -0.7, 1.1). Baseline and two 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, 27%) naproxen patients and 26% of 97(95%CI: 18, 36%) sumatriptan patients (95%CI for difference of 7%: -5, 19%). The most common side effects naproxen patients reported were gastrointestinal (7), dizziness/ feeling light headed or weak (5), drowsiness (2), and worsened headache (4). The most common side 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, gender, 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% vs. 43%, 95%CI for difference of 12%: 2, 22%).

We assessed blinding by asking patients if they knew which medication they had received. 86 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 non-migraine primary headache group. The migraineurs improved by a mean of 4.3 (standard deviation 3.3), while the non-migraine group improved by a mean of 4.1 (standard deviation 2.9). When compared statistically, the non-migraine group had less variability than the migraine group ($p=0.05$), with more of the variability in the migraine group coming from heterogeneity in response to sumatriptan.

Limitations

The vast 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 previously 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 post-discharge that patient took the study medication may have impacted the efficacy. We did not assess the efficacy of more than one 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.

In order 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 in an identical manner and data from systematic reviews does not reveal decreased efficacy of sumatriptan associated with re-encapsulation [28].

We did not use a placebo control in this study. Therefore, we cannot conclude based on 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.

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 following ED discharge in patients with 1) migraine without aura and 2) all primary headaches. Because the headache relief obtained with these two medications was so similar (differing by only 0.1–0.2

points on an 11-point scale, with narrow confidence intervals demarcating these differences), we conclude that either agent is a reasonable treatment option. Nearly $\frac{3}{4}$ of patients in this study reported headache recurrence within 48 hours of ED discharge. Unfortunately, about $\frac{1}{4}$ of patients who took the study medications for treatment of headache recurrence following ED discharge continued to suffer moderate or severe headache.

In this study, 50% of all patients reported moderate or severe headache within 48 hours of ED discharge. This is consistent with previously reported data. In an urban ED population, 30% of all headache sufferers 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, 18–87% of migraine patients report recurrent or persistent headaches rated as moderate or severe in intensity 24 hours after discharge [8,11,13,14,16,32]. This widely varying incidence of recurrence is likely related to methodological differences in assessing and defining recurrence. In a Canadian population, 45% of migraine patients reported headache-related functional impairment within 24 hours of ED discharge [12]. In our study, as in others, it was difficult to predict headache recurrence based on features of the history of present illness or past 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 prior to 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, [30,31,39,40] although triptans cannot be used prophylactically to prevent recurrent migraine. [31,41] Sumatriptan 100mg, 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 clinical trials comparing naproxen to sumatriptan for the initial acute migraine attack. In those studies, two hour headache relief rates (defined as headache intensities declining to mild or none from moderate or severe) for sumatriptan 85mg versus naproxen 500mg were reported as 55% versus 44% (Absolute Risk Reduction: 11% [95%CI: 4, 18%]) and 50% versus 43% (Absolute Risk Reduction: 7% [95%CI: 0, 14%]), respectively. [42] In a study of sumatriptan 50mg versus naproxen 500mg, 49% versus 46% reported headache relief at two hours (Absolute Risk Reduction: 3% [95%CI: -6, 12%]). [43] In our study, we did not find a statistically or clinically significant difference between these two 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 anti-emetic dopamine antagonists received by most patients in the ED and oral non-steroidals taken later, a hypothesis which has not yet been tested. There has been a report of decreased responsiveness to triptans after opioid use, [44] though 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 anti-emetic dopamine antagonist to naproxen. In general, opioid use for the primary

headache disorders is not recommended, as it is linked to medication overuse headache[45] and development of chronic migraine. [46]

We were surprised that heterogeneity in response to the investigational medications was greater among the migraine without aura patients. Because this group was homogenous with respect to headache diagnosis and the non-migraine primary headache group was not, this may signal a potential problem 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.[19] It may be that patients report the acute headache differently than an inter-ictal 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 seen among ED patients interferes with accurate headache classification.

In conclusion, nearly ¾ of primary headache patients reported headache recurrence within 48 hours of ED discharge. Naproxen and sumatriptan demonstrate clinically and statistically similar efficacy and side 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, contra-indications, side-effects, and a patient's previous overall experience with the medication.

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Figure 1.
Diagrammatic representation of study protocol

- A. At least 5 attacks fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
 - a. unilateral location
 - b. pulsating quality
 - c. moderate or severe pain intensity
 - d. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache at least one of the following:
 - a. nausea and/or vomiting
 - b. photophobia and phonophobia
 - c. Not attributed to another disorder
- E. No other diagnosis to explain the headache.

Figure 2.

Migraine without aura criteria

Figure 3.
CONSORT flow diagram.

4a.

4b.

4c.

4d.

Figure 4.

Graphical depiction of change in pain scores between time of medication ingestion and two hours later. Larger pain scores signify greater pain

4a. Migraine patients randomized to naproxen

4b. Migraine patients randomized to sumatriptan

4c. Non-migraine patients randomized to naproxen

4d. Non-migraine patients randomized to sumatriptan

Table 1

Baseline characteristics of all patients with MIGRAINE. Reported as number (%) unless otherwise noted

Baseline characteristics	Naproxen		Sumatriptan	
	Used investigational medication n=48	Did not need/ did not take investigational medication n=36	Used investigational medication n=40	Did not need/ did not take investigational medication n=42
Age in years (mean, SD)	35 (9)	37 (11)	35 (9)	36 (9)
Female	45 (94%)	31 (86%)	33 (83%)	35 (83%)
Latino	33 (69%)	24 (67%)	22 (55%)	23 (55%)
Race				
Black/ African American	15 (33%)*	13 (36%)	12 (30%)	15 (35%)
Asian/ Pacific Islander	0	0	0	0
White	12 (26%)	10 (28%)	13 (33%)	13 (30%)
Other	19 (41%)	13 (36%)	15 (38%)	14 (33%)
Headache duration in hours (median, IQR)	26 (15, 48)	27 (11, 48)	30 (8, 48)	24 (13, 72)
Took migraine/ headache medication prior to ED presentation	27 (60%)*	26 (74%)*	29 (73%)	32 (76%)*
Median pain score (0–10) at triage (IQR)	10 (9, 10)	9 (8, 10)	10 (9, 10)	10 (8, 10)
Median pain score (0–10) at discharge	2 (0, 4)	3 (0, 4)	3 (1, 4)	2 (0, 4)
Treated with anti-emetic/ dopamine	47 (98%)	35 (97%)	40 (100%)	40 (95%)

Baseline characteristics	Naproxen		Sumatriptan	
	Used investigational medication n=48	Did not need/ did not take investigational medication n=36	Used Investigational medication n=40	Did not need/ did not take investigational medication n=42
antagonist in ED				
Treated with NSAID in ED	8 (17%)	3 (8%)	11 (28%)	10 (24%)
Treated with opioids in ED	2 (4%)	4 (11%)	4 (10%)	4 (10%)
Treated with triptan in ED	0	0	1 (3%)	0
Treated with corticosteroids in ED	0	0	0	0

* Baseline data missing for some patients

Baseline characteristics of all patients with ANY PRIMARY HEADACHE, including those with migraine. Reported as number (%) unless otherwise noted

Table 2

Baseline characteristics	Naproxen		Sumatriptan	
	Used investigational medication n=98	Did not need/ did not take investigational medication n=92	Used investigational medication n=98	Did not need/ did not take investigational medication n=95
Age in years (mean, SD)	35 (10)	35 (11)	37 (10)	36 (10)
Female	85 (87%)	78 (85%)	82 (84%)	81 (85%)
Latino	66 (67%)*	55 (60%)	60 (61%)	55 (58%)
Race				
Black/ African American	29 (30%)	34 (37%)	30 (31%)	34 (36%)*
Asian/ Pacific Islander	0	0	1 (1%)	0
White	29 (30%)	21 (23%)	28 (29%)	29 (31%)
Other	38 (40%)	37 (40%)	39 (40%)	31 (33%)
Headache duration in hours (median, IQR)	48 (24, 96)	48 (12, 114)	72 (24, 120)	66 (24, 96)
Took migraine/ headache medication prior to ED presentation	66 (67%)*	61 (68%)*	73 (75%)	62 (67%)*
Median pain score (0–10) at triage (IQR)	10 (8, 10)	9 (8, 10)	9 (8, 10)	9 (8, 10)
Median pain score (0–10) at discharge	2 (0, 5)	2 (0, 4)	3 (1, 4)	2 (0, 3)
Treated with anti-emetic/ dopamine	96 (98%)	88 (96%)	95 (97%)	90 (95%)

Baseline characteristics	Naproxen		Sumatriptan	
	Used investigational medication n=98	Did not need/ did not take investigational medication n=92	Used investigational medication n=98	Did not need/ did not take investigational medication n=95
antagonist in ED				
Treated with NSAID in ED	18 (18%)	11 (12%)	24 (25%)	25 (26%)
Treated with opioids in ED	11 (11%)	5 (5%)	6 (6%)	7 (7%)
Treated with triptan in ED	0	0	1 (1%)	0
Treated with corticosteroids in ED	0	0	0	1 (1%)

* Baseline data missing for some patients

Table 3

Headache scores among patients who took the investigational medication

Variable	Subset with migraine		All primary headache patients	
	Naproxen (n=48)	Sumatriptan (n=40)	Naproxen (n=98)	Sumatriptan (n=98)
Median pain score at the time medication was taken, on a scale of 0 to 10 (IQR)	8 (7, 10)	8 (6, 10)	8 (6, 10)	7 (5, 9)
Median pain score 2 hours after medication was taken, on a scale of 0 to 10 (IQR)	2 (2, 6)	3 (0, 6)	2 (0, 6)	3 (0, 5)

Table 4

Secondary outcomes. Reported as n/N (%).

Outcome	Subset with migraine				All primary headache patients			
	Naproxen	Sumatriptan	Difference (95%CI)		Naproxen	Sumatriptan	Difference (95%CI)	
Would take again	31 (67%)	26 (70%)	3% (-17, 22%)		68/ 96 (71%)	69/ 92 (75%)	4% (-9, 17%)	
Functional impairment								
Not impaired	30 (63%)	21 (53%)	Calculated for Not Impaired: 10% (-10, 29%)		61 (63%)	59 (60%)	Calculated for Not Impaired: 3% (-11, 16%)	
Mildly impaired	9 (19%)	11 (28%)			18 (19%)	22 (22%)		
Can't do activities	3 (6%)	5 (13%)			9 (9%)	10 (10%)		
Can't get out of bed	6 (13%)	3 (8%)			9 (9%)	9 (7%)		
Took additional medication for headache	17 (35%)	17 (43%)	8% (-13, 27%)		37/ 97 (38%)	38/ 98 (39%)	1% (-13, 14%)	
Pain level two hours after investigational medication								
None	12 (25%)	12 (30%)	Calculated For Moderate or severe pain: 8% (-11, 26%)		33 (34%)	32 (33%)	Calculated For Moderate or severe pain: 1% (-11, 135)	
Mild	24 (50%)	15 (38%)			38 (39%)	40 (41%)		
Moderate	4 (8%)	9 (23%)			10 (10%)	17 (17%)		
Severe	8 (17%)	4 (10%)			17 (17%)	9 (9%)		