

Combination Treatment for Menstrual Migraine and Dysmenorrhea Using Sumatriptan–Naproxen

Two Randomized Controlled Trials

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OBJECTIVE: To evaluate the efficacy and tolerability of sumatriptan–naproxen during the mild pain phase of a single menstrual migraine attack associated with dysmenorrhea.

METHODS: Two replicate randomized, multicenter, double-blind, placebo-controlled, trials of adults with menstrual migraine and dysmenorrhea were conducted. Participants treated their menstrual migraine attack during the mild pain phase (within 1 hour of onset) with sumatriptan 85 mg and naproxen sodium 500 mg in a single fixed-dose formulation (sumatriptan–naproxen) or placebo. The primary endpoint was 2-hour pain-free response.

RESULTS: Sumatriptan–naproxen was statistically superior to placebo in both studies (n=311, Study 1; n=310, Study 2) for 2-hour and, 2- to 24-hour sustained pain-free response, use of headache and menstrual rescue medications, and several nonpain menstrual symptom categories. Two-hour pain-free rates were Study 1, 42% compared with 23%, and Study 2, 52% compared with 22%, $P<.001$. Two- to 24-hour sustained pain-free rates were Study 1, 29% compared with 18%, $P=.022$; Study 2, 38% compared with 10%, $P<.001$. Headache and menstrual medication rates were Study 1, 37% compared with 53%, $P=.005$; Study 2, 31% compared with 69%, $P<.001$. Women treated with sumatriptan–naproxen continued to be pain free through 48 hours compared with placebo: Study 1, 26% compared with 17%, $P=.040$; Study 2, 28% compared with 8%, $P<.001$. No serious adverse events were reported in either study; nausea and dizziness were the most frequently reported adverse events.

CONCLUSION: Sumatriptan–naproxen provided an effective pain-free response at 2 hours, which was maintained up to 48 hours in menstrual migraineurs with dysmenorrhea. Sumatriptan–naproxen was well-tolerated and resulted in decreased rescue medication use and relief of nonpainful menstrual symptoms.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00329459 and NCT00329355 (Obstet Gynecol 2009;114:106–13)

LEVEL OF EVIDENCE: I



Menstrual migraine (migraines occurring 2 days before to 3 days after the onset of menses) afflicts 40–70% of women experiencing migraine headaches. Menstrual migraines have been associated with significantly longer attack duration, greater work disability, and reduced pharmacologic response compared with nonmenstrual migraine attacks.¹

Dysmenorrhea (menstrual cramps and other menstruation-associated symptoms) is the most common gynecologic complaint and the leading cause of recurrent short-term school or work absenteeism among female adolescents and young adults.² Dysmenorrheic symptoms typically reported in primary dysmenorrheal clinical trials are headache, abdominal cramps, nausea, backache, and tiredness.³ Although the co-occurrence of dysmenorrheic symptoms with menstrual migraine and the effect of dysmenorrhea on the severity of migraine are unknown, both dysmenorrhea and menstrual migraine are common among menstruating women.⁴

Increased prostaglandin production has been associated with both dysmenorrhea and migraine; addressing this may provide additional benefit for individuals experiencing both conditions concurrently.^{4,5} Clinical studies evaluating medications in menstrual migraine with dysmenorrhea have not been conducted. These replicate studies evaluate the efficacy and safety of sumatriptan–naproxen administered during the mild pain phase of a single menstrual migraine attack associated with dysmenorrhea. The objective of these studies was to evaluate the efficacy and tolerability of sumatriptan–naproxen during the mild pain phase of a single menstrual migraine attack associated with dysmenorrhea.

MATERIALS AND METHODS

Women aged 18 years and older were eligible if they had a 6-month minimal history of migraine with or without aura according to International Headache Society criteria and with an average frequency of one to six migraine attacks per month in the past 3 months. Participants typically experienced moderate-to-severe migraine preceded by an identifiable mild headache phase and were able to distinguish between mild headache of migraine pain and tension-type headache. Participants needed a minimum 6-month history of menstrual migraine with attacks in at least two of the three perimenstrual periods before screening. Dysmenorrhea at the onset of menstruation in at least two of 3 months before screening was also required. Participants who were in good health and were appropriate candidates consistent with currently ap-

proved labels for sumatriptan/naproxen sodium and naproxen sodium alone were included in the study.^{6,7}

Medications that could confound the evaluation of study treatment were prohibited and included regular use (an average of 4 or more days per month over the last 6 months) of opioids or barbiturates, migraine or menstrual prophylactic medications that were not stabilized (ie, a change in medication dose within the past 2 months) or were used for intermittent prophylaxis, and daily use of nonsteroidal medications. Participants with hypersensitivity, intolerance, or contraindication to the use of sumatriptan or naproxen sodium or any of their components, aspirin, or any other 5HT₁ receptor agonist were excluded.

Two replicate multicenter, randomized, double-blind, placebo-controlled studies were conducted at 64 sites (30 centers in study 1; 34 centers in Study 2) in the United States from May to November 2006 (48% primary care physicians; 37% headache specialists or neurologists; 16% obstetric or gynecologic specialists). An institutional review board approved the study protocol at each site and all participants signed a written consent document before enrollment. Participants had a baseline safety assessment performed at the screening visit, including a review of the medical history, review of migraine and menstrual treatment history, physical examination, clinical laboratory tests, electrocardiogram, and a pregnancy test for women of child-bearing potential. Double-blind study medication and study diaries were dispensed to eligible participants at the end of the screening visit. Participants were randomly assigned by a computer-generated code. When a participant became eligible for assignment, the investigator (or designee) called the Registration and Medication Ordering System for a randomization and container number, which were created using a computer-generated randomization code before packaging of investigational product. No participant was unblinded in either study. In an emergency, the investigator may have unblinded the participant's treatment assignment by contacting Registration and Medication Ordering System. However, it was recommended that before unblinding, the medical monitor was contacted to ensure that this action was appropriate. If unblinding had occurred, the date and reason would have been recorded.

Participants were instructed to treat their next menstrual migraine attack during the mild pain phase (within 1 hour of onset) with a single fixed-dose tablet of sumatriptan–naproxen sodium (sumatriptan, 85 mg, as the succinate salt, formulated with RT technology, and naproxen sodium, 500 mg; TREXIMET [sumatriptan and naproxen sodium], GlaxoSmithKline,



Research Triangle Park, NC) or placebo. Participants were required to wait a minimum of 2 hours before taking any additional medication, including headache or menstrual symptom rescue medication. If the first dose did not provide adequate pain relief, participants could take rescue medication including sumatriptan-naproxen sodium, naproxen sodium, or sumatriptan succinate.

The primary efficacy endpoint was the percentage of participants who became headache pain free 2 hours after treatment. A headache pain-free response was defined as posttreatment headache pain severity of none (0) in participants who had not used rescue medication through the assessment time point. A sustained headache pain-free response was defined as being headache pain free at 2 hours with no return of headache pain or use of rescue medication during the 24 or 48 hour postdose period. Menstrual symptom relief was defined as at least a 1 point decrease in severity on a scale of 0 to 3 (0=pain free; 1=mild; 2=moderate; 3=severe). The sum of pain intensity differences measurement for menstrual symptoms was defined as differences from baseline across each planned assessment time.

Approximately 320 participants were planned for randomization to obtain 240 menstrual migraine participants in the primary analysis population. It was assumed that 75% of assigned participants would treat a menstrual migraine attack within the protocol-specified 12 weeks and that the difference in 2-hour headache pain-free and sustained headache pain-free rates between sumatriptan-naproxen and placebo would be approximately 25% and 20%, respectively, that is, 20% compared with 45% for 2-hour headache pain free, and 10% compared with 30% for sustained headache pain free. Using a two-tailed 5% type I error rate, a trial with 240 participants had greater than 90% power to detect a difference in 2-hour headache pain (primary endpoint) and at least 80% power to detect a difference in sustained headache pain-free rates between sumatriptan-naproxen and placebo.

The population used for the primary efficacy analysis was the intent-to-treat population. The intent-to-treat population was composed of participants in the safety population who provided an evaluation of their randomized treatment. The safety population was composed of all participants who were treated with investigational product.

The primary endpoint was the percentage of participants in the intent-to-treat population who were headache pain free (on a 0 to 3 scale, with 0=none, 1=mild, 2=moderate, and 3=severe) at 2 hours after treatment with sumatriptan-naproxen compared with

placebo and adjusted for rescue medication use. The secondary endpoints were evaluated if a significant difference between sumatriptan-naproxen compared with placebo at 2 hours was detected. Secondary endpoints were evaluated statistically using a hierarchical step-down method to control the Type I error rate for multiplicity, except for the exploratory endpoint 2–48 hours sustained pain free.⁸ The following prespecified method was used to control for multiplicity. Endpoints were grouped into families (ie, eight endpoint comparisons), and the families were ordered sequentially. Testing of a family could take place only if the first endpoint on the prior family tested was significant. Testing of members within a family utilized the Holm method.⁹ The significance level $\alpha=0.05$ was used for comparisons.

Comparisons of percentages between treatment groups were made using Cochran-Mantel-Haenszel tests. Tests of treatment effects for quantitative variables were made using analysis of variance.

RESULTS

Almost all participants who were randomly assigned and treated with study drug (safety population Study 1, $n=312$; Study 2, $n=311$) provided evaluable data (intent-to-treat population Study 1, $n=311$; Study 2, $n=310$). The disposition of participants is reported in Figure 1. The demographics of the study population and the acute migraine medication history from the previous 3 months are described in Table 1.

The majority of participants had a diagnosis of migraine without aura; slightly more participants had this diagnosis in Study 1 (74%) than in Study 2 (60%). The median age of onset of menstrual migraine was 21 years in Study 1 and 22 years in Study 2. Participants had a median of three migraines and five headache days per month. The mean duration of a migraine attack ranged from 24 hours to greater than 72 hours for 57–61% of participants. The median age of onset of menstruation was 13 years in both studies. The median age of onset of dysmenorrhea was 14 years in Study 1 and 15 years in Study 2. The majority of participants were diagnosed with primary (compared with secondary or unknown) dysmenorrhea (Study 1, 77%; Study 2, 92%). Baseline migraine and menstrual symptoms are reported in Table 2. The efficacy results presented here were replicated across the two studies.

A significantly greater percentage of participants treated with sumatriptan-naproxen were headache pain free 2 hours after treatment compared with participants treated with placebo. The therapeutic



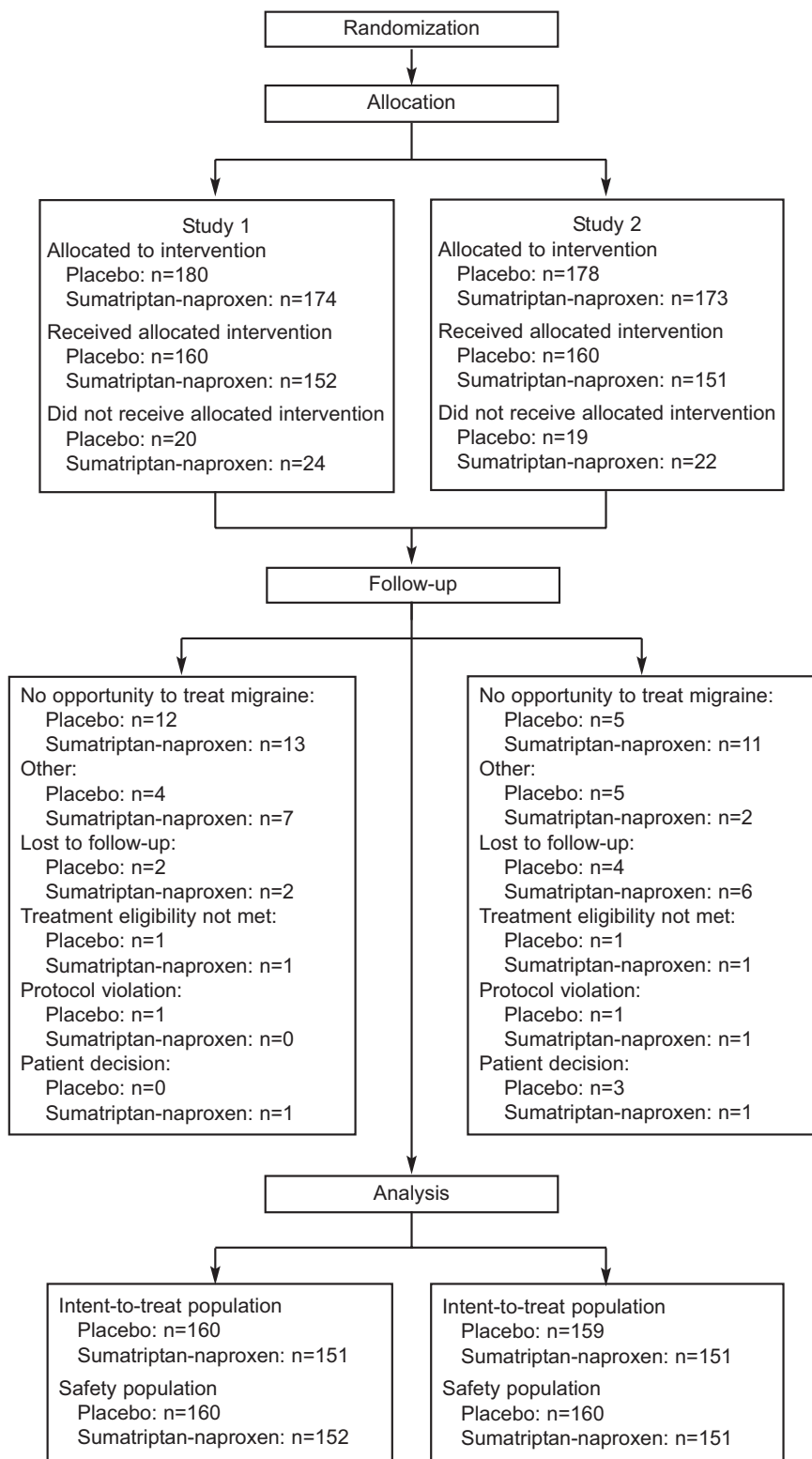


Fig. 1. Disposition of women in the two studies.

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gain (ie, the difference between treatment groups) was 19% in Study 1 and 30% in Study 2 (Study 1, 42% compared with 23%, $P<.001$; Study 2, 52% compared

with 22%, $P<.001$). Figure 2 displays the percentage of participants who were pain free 0.5 hours, 1 hour, 2 hours, and 4 hours after treatment.



Table 1. Demographics and Medication Use for Acute Migraine in Previous 3 Months

Safety Population	Study 1			Study 2		
	Sumatriptan–Naproxen (n=160)	Placebo (n=152)	Total (N=312)	Sumatriptan–Naproxen (n=151)	Placebo (n=160)	Total (N=311)
Age (y)	36±9	36±8	36±8	37±8	38±9	37±9
White	134 (88)	147 (92)	281 (90)	127 (84)	141 (88)	268 (86)
Child-bearing potential	122 (80)	140 (88)	262 (84)	132 (87)	138 (86)	270 (87)
Oral contraceptive	48 (32)	47 (29)	95 (30)	45 (30)	46 (29)	91 (29)
Triptans	80 (53)	81 (51)	161 (52)	98 (62)	85 (56)	183 (59)
Sumatriptan	45 (30)	36 (23)	81 (26)	43 (28)	59 (37)	102 (33)
NSAIDs	62 (41)	69 (43)	131 (42)	60 (40)	76 (48)	136 (44)
Over-the-counter naproxen	12 (8)	19 (12)	31 (10)	23 (15)	35 (22)	58 (19)

NSAID, nonsteroidal anti-inflammatory drug.
Data are mean±standard deviation or n (%).

A significantly greater percentage of participants treated with sumatriptan–naproxen were pain free 4 hours after treatment compared with placebo. The therapeutic gain was 25% in Study 1 and 37% in Study 2 (Study 1, 60% compared with 36%, $P<.001$; Study 2, 66% compared with 30%, $P<.001$). Significantly more participants treated with sumatriptan–naproxen had a sustained pain-free response (2 to 24 hours) compared with placebo-treated participants (Study 1, 29% compared with 18%, 11% difference, $P=.022$; Study 2, 38% compared with 10%, 28% difference, $P<.001$; Fig. 3).

The rate of sustained pain-free response from 2 to 48 hours postdose was significantly higher among participants treated with sumatriptan–naproxen than in placebo-treated participants (Study 1, 26% compared with 17%, 10% difference, $P=.040$; Study 2, 28% compared with 8%, 21% difference, $P<.001$; Fig. 3). Sumatriptan–naproxen was statistically superior to

placebo in both studies ($P<.05$) for overall use of rescue medications (headache or menstrual symptoms) as well as for use of rescue medication for headache. A significantly lower percentage of participants treated with sumatriptan–naproxen used rescue medications for headache or menstrual symptoms compared with placebo-treated participants (Study 1, 37% compared with 53%, 16% difference, $P=.005$; Study 2, 31% compared with 69%, 37% difference, $P<.001$). The majority of participants attributed their rescue medication use to their headaches, as opposed to menstrual, symptoms.

Statistically significant differences between treatment groups favored sumatriptan–naproxen in both studies in the following *nonpain* menstrual symptom categories (bloating, tiredness, irritability): overall composite sum of pain intensity differences (30 minutes to 4 hours, $P\leq.016$), composite nonpain relief (2

Table 2. Baseline Migraine and Menstrual Symptoms

Intent-to-Treat Population	Study 1		Study 2	
	Sumatriptan–Naproxen (n=151)	Placebo (n=160)	Sumatriptan–Naproxen (n=151)	Placebo (n=159)
Migraine symptoms at time of treatment				
Aura present	22 (15)	29 (19)	41 (28)	29 (18)
Median time to treat (min)	30	30	20	30
Mild pain	142 (94)	144 (91)	129 (86)	138 (87)
Nausea	46 (30)	56 (35)	53 (36)	59 (37)
Photophobia	115 (77)	115 (73)	115 (77)	121 (78)
Phonophobia	104 (69)	101 (64)	101 (67)	107 (69)
Menstrual symptoms 30 min after treating				
Abdominal pain	84 (57)	93 (58)	83 (56)	96 (61)
Back pain	79 (53)	82 (52)	73 (49)	81 (52)
Overall pain	139 (94)	143 (91)	131 (89)	139 (89)
Bloating	96 (65)	116 (72)	101 (69)	99 (64)
Tiredness	131 (88)	133 (84)	132 (89)	129 (83)
Irritability	122 (82)	131 (82)	119 (80)	126 (81)

Data are n (%) except where otherwise specified.
Slight variations in calculation of percentages are due to missing data by symptom.



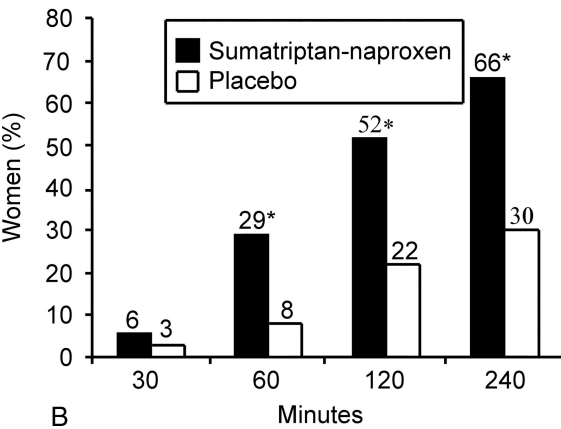
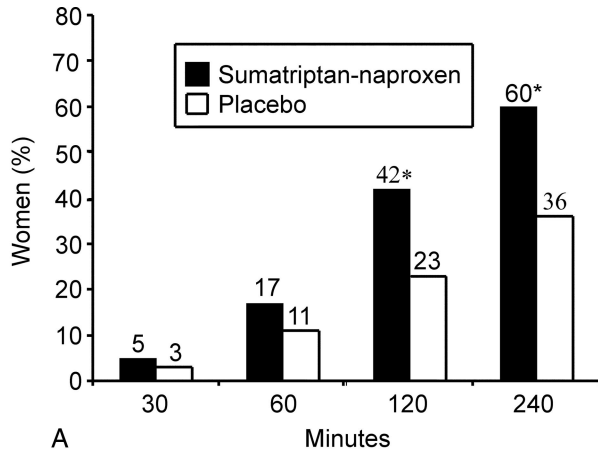


Fig. 2. Pain-free response rates over time (0.5, 1, 2, and 4 hours). **A.** Study 1. **B.** Study 2. [†] $P < .001$.

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and 4 hours, $P \leq .017$), irritability sum of pain intensity differences ($P < .001$), and irritability relief (1, 2, and 4 hours, $P \leq .005$). No significant differences were noted between treatment groups with menstrual *pain* symptoms. There was no statistically significant difference between treatment groups in the sustained composite endpoint (sustained headache pain free, migraine-associated symptom-free, and menstrual symptom relief from 2 to 24 hours postdose).

The post-hoc analysis of 2-hour pain-free response stratified by participants with or without at least one moderate or severe menstrual symptom at baseline demonstrated that participants with at least one moderate or severe menstrual symptom (compared with those without) were less likely to be pain free at 2 hours. The percentage of participants in the sumatriptan-naproxen group with no moderate or severe menstrual symptoms at baseline who were pain free after 2 hours was 61%. In contrast, the percentages

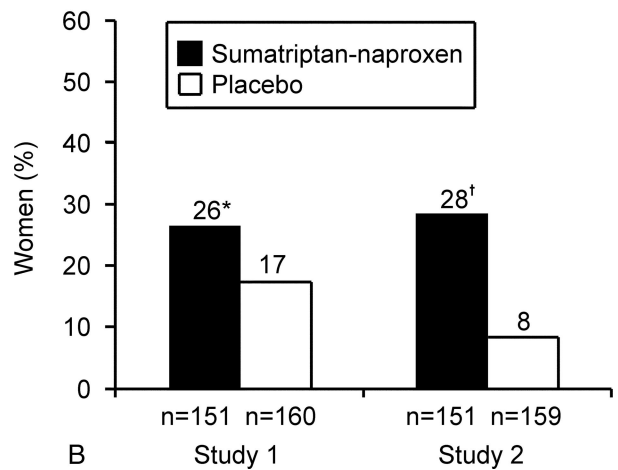
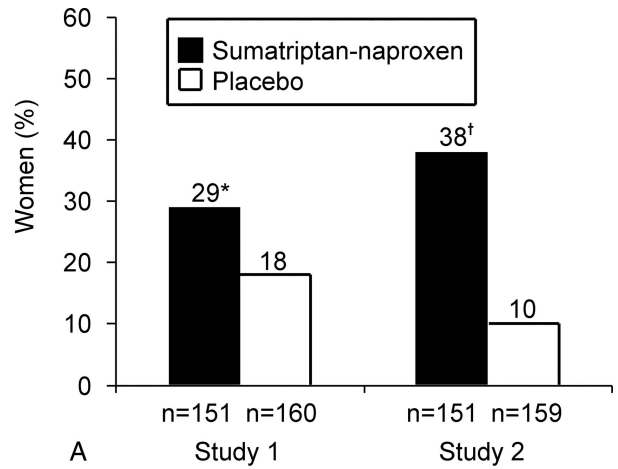


Fig. 3. Sustained pain-free response rates, 2–24 hours (**A**) and 2–48 hours (**B**) sustained pain free (pain free at 2 hours and maintained at 24 hours and 48 hours, without use of rescue medication). Statistical analysis did not control for multiplicity for the 2–48 hours exploratory endpoint. * $P < .05$; [†] $P < .001$.

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of participants with one or more moderate or severe menstrual symptoms at baseline and who were pain free after 2 hours ranged from 21–32%. After treatment with sumatriptan-naproxen, the therapeutic gain for a 2-hour pain-free response was higher in participants with no or mild menstrual symptoms at baseline (Study 1, 61%; Study 2, 69%) compared with participants with at least one moderate or severe baseline menstrual symptom (Study 1, 32%; Study 2, 42%).

There were no serious adverse events reported in either study, nor were there any premature withdrawals due to an adverse event. The adverse events reported were consistent with the known safety pro-



file of the two drugs. No new or unexpected adverse events were reported.

The most commonly reported adverse events were nausea, dizziness, and dry mouth. Adverse events considered by the investigator to be related to study drug occurred at a frequency of less than 1% in Study 1. In Study 2, the drug-related adverse events that occurred more frequently than placebo were dizziness (5% compared with 2%), nausea (4% compared with less than 1%), dry mouth (2% compared with less than 1%), and paresthesia (2% compared with 0).

DISCUSSION

We found that sumatriptan–naproxen provided an effective pain-free response at 2 hours, which was maintained up to 48 hours in menstrual migraineurs with dysmenorrhea. Although similarly designed trials have demonstrated the efficacy of sumatriptan tablets in menstrual migraine, those studies did not specifically enroll participants with dysmenorrhea, nor was the effect on menstrual symptoms evaluated.^{10,11} These data suggest that sumatriptan–naproxen provides both an early (2 hour) and sustained (through 48 hours) pain-free status in at least one fourth of menstrual migraine participants with two comorbid pain conditions, menstrual migraine and dysmenorrhea.

It was unknown whether the overall incidence of rescue medications would be higher because of the co-occurrence of two painful conditions in the study populations. Although significantly fewer female participants treating with sumatriptan–naproxen used rescue medication compared with placebo in this study, the overall incidence of rescue medication was higher than that reported previously in early intervention studies that included both men and women.^{12,13} Although the majority of participants in the current studies attributed their use of rescue medication to “migraine,” the coexistence of menstrual pain may influence the use of pain medication.

In these studies, more participants had a reduction in a composite of menstrual nonpain symptoms (bloating, tiredness, irritability) and irritability alone after treatment with sumatriptan–naproxen compared with placebo. These findings were initially unexpected with respect to the basic mechanisms of a triptan and a nonsteroidal antiinflammatory drug. However, it is noteworthy that irritability and tiredness, although not recognized by the International Headache Society, have been previously reported as migraine symptoms.¹⁴

In this population, responsiveness of menstrual migraine pain seems to be correlated with the severity of dysmenorrhea. Because pain thresholds in migraineurs

and in women with dysmenorrhea may be affected by these conditions, it was unknown whether co-occurrence of migraine and dysmenorrhea decrease migraine responsiveness to treatment to a greater degree than migraine alone.¹⁵ Post-hoc analyses of 2-hour pain-free responses demonstrated a therapeutic gain that was higher in participants with mild or no baseline menstrual symptoms compared with those with one or more moderate or severe menstrual symptoms at baseline. These data suggest that the co-occurrence of dysmenorrhea with menstrual migraine lowers pain thresholds in an additive fashion. Consequently, this observation precludes any direct comparison between the data in this trial to previously conducted trials.

After treatment with sumatriptan–naproxen, the composite endpoint of menstrual pain (overall pain, abdominal pain, back pain) did not differ significantly from placebo, therefore, additional statistical testing in the “pain family” was not controlled for multiplicity. Limitations in study design may have confounded these results: First, because baseline menstrual symptoms were not collected, the 30-minute time point was used. Without a true baseline assessment, the sensitivity to detect a difference between an active treatment compared with placebo may have been compromised. Second, the sum of pain intensity differences measurement (0 to 8 hours) is a commonly used endpoint in clinical trials evaluating dysmenorrhea; however, the assay sensitivity of this endpoint was unknown a priori, and in the current studies only included to 4 hours. Third, the distinct pharmacokinetic profile of naproxen when administered as sumatriptan–naproxen sodium has a blunted and delayed maximal plasma concentration,⁷ which may have affected the therapeutic window for menstrual symptom relief up to 4 hours.

Despite the limitations of these studies, an early (2 hour) and sustained (to 48 hours) headache pain-free status was achieved after treatment with sumatriptan–naproxen in this unique population. An explanation of the sustained effect of sumatriptan–naproxen observed in these studies may be the enhanced antinociceptive and antiinflammatory properties of combination therapy as compared with triptan monotherapy. Sumatriptan–naproxen may be targeting pathophysiologic mechanisms inherent both to migraine and dysmenorrhea. In menstrual migraine, there are several processes that lead to the generation of pain, including vasodilation, inflammation, edema, and nociception. Menstrual migraine and dysmenorrhea may be mechanistically linked by the arachidonic acid cascade and the subsequent production of prostaglandins, with prostaglandins playing a pivotal role in the pathogenesis of both migraine and dysmenorrhea.



The tolerability and safety of sumatriptan-naproxen in this study was consistent with the known safety profile of this product. The most commonly reported adverse events were nausea and dizziness, both of which are commonly reported in migraineurs as well as in previous studies of sumatriptan-naproxen. Therefore, sumatriptan-naproxen was generally well-tolerated in this population.

In summary, despite evidence that participants with co-occurring pain conditions may be more refractory, sumatriptan-naproxen provided an effective headache pain-free response at 2 hours, which was maintained up to 48 hours in participants with comorbid conditions of menstrual migraine and dysmenorrhea. Additionally, treatment with sumatriptan-naproxen was well-tolerated and resulted in decreased rescue medication use and relief of nonpainful menstrual symptoms.

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