Sumatriptan–naproxen fixed combination for acute treatment of migraine: a critical appraisal

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Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen and naproxen sodium, are effective yet nonspecific analgesic and anti-inflammatory drugs, which work for a variety of pain and inflammatory syndromes, including migraine. In migraine, their analgesic effect helps relieve the headache, while their anti-inflammatory effect decreases the neurogenic inflammation in the trigeminal ganglion. This is the hypothesized mechanism by which they prevent the development of central sensitization. Triptans, including sumatriptan, work early in the migraine process at the trigeminovascular unit as agonists of the serotonin receptors (5-HT receptors) 1B and 1D. They block vasoconstriction and block transmission of signals to the trigeminal nucleus and thus prevent peripheral sensitization. Therefore, combining these two drugs is an attractive modality for the abortive treatment of migraine. Sumatriptan–naproxen fixed combination tablet (Treximet® [sumatriptan–naproxen]) proves to be an effective and well tolerated drug that combines these two mechanisms; yet is far from being the ultimate in migraine abortive therapy, and further research remains essential.

Keywords: Treximet®, sumatriptan–naproxen, migraine, treatment

Introduction to management of acute migraine

The lifetime prevalence of headache is over 90%. Tension type headache is the most common of the primary headache disorders, with a prevalence of 42% to 78%. Migraines on the other hand occur at a frequency of 18% to 33% in females vs 7% to 13% males. It is estimated however that over half of migraineurs remain undiagnosed!

The burden of migraine is not negligible. Around a quarter of migraineurs lose 6 or more days of work per year, resulting in $300 to $570 per month of lost labor per patient and over $1,600 per year in individual medical cost. This amounts to a total societal cost of $5 to $17 billion per year. In a more recent large population-based study, 2/3 of migraineurs experienced one or more attacks every month. Nonetheless, until recently, research in migraine management has lagged behind other fields of medicine.

In formulating a treatment strategy for migraine, it is recommended that the approach be multidimensional, including: a) Nonpharmacologic approaches and physical techniques, such as behavioral medicine techniques, manipulation, acupuncture, and physical therapy; b) Abortive therapy; c) Prophylactic therapy; d) Adjunctive therapies in migraine (vitamins, minerals, supplements, herbs), eg, vitamin B-2, Mg, feverfew, petasites, melatonin, coenzyme Q10.
A recent guideline published by the European Federation of Neurologic Societies (EFNS) lists the following symptomatic treatments for individual headache attacks or abortive therapy (organized between specific and nonspecific treatments):

a) nonspecific therapy with medications that relieve pain, including: i) NSAIDs: aspirin, ibuprofen, naproxen, diclofenac, paracetamol, other NSAIDs and NSAIDs combined with nonNSAID analgesics, ii) nonnarcotic pain medication: caffeine, tramadol; iii) narcotics, noting that these are only of minor efficacy; iv) antiemetics: metoclopramide, domperidon; v) corticosteroids; vi) intravenous valproate; vii) semi-specific medications: isometheptene, butalbital (not in the EFNS guideline).

b) specific abortive medications: i) triptans, ii) ergot derivatives: ergotamine, dihydroergotamine (DHE).

Prophylactic anti-migraine therapy (PAMT) includes a multitude of agents with varying degrees of data to support them: a) agents with a level A recommendation: i) certain beta-adrenergic blockers (metoprolol, propranolol); ii) flunarizine, certain anticonvulsants (topiramate, valproate). b) agents with less supportive data: i) tricyclic antidepressants, especially amitriptyline; ii) NSAIDs (naproxen, aspirin); iii) petasites; iv) other beta-adrenergic blockers (bisoprolol); v) other anticonvulsants (gabapentin), neutraceuticals: magnesium, feverfew (Tenacetum parthenium), riboflavin, coenzyme Q10, vi) angiotensin converting enzyme (ACE) inhibitors (lisinopril and angiotensin-receptor blockers (ARB) (candesartan), vii) methysergide, viii) calcium-channel blockers other than flunarizine, ix) other antidepressants, especially serotonin-norepinephrine reuptake inhibitors (SNRI) (such as venlafaxine), x) botulinum toxin A, possibly in chronic migraineurs naïve to other prophylactic treatments.

A holistic approach is therefore advantageous, as the combination of different treatments may be synergistic, especially if combining therapeutic categories. This also allows the addressing of migraine comorbidities.

The role of prophylaxis is to decrease the burden of headache by decreasing the frequency and severity of the headache. Prophylaxis may also enhance the efficacy of abortive therapies. In choosing a prophylactic medication, one should assess the burden of disability from migraine, assess triggers (sleep, diet, or hormones), set reasonable expectations, and respect patient tolerance in terms of speed of action of the medicine versus the tolerance of side effects.

There are no clear guidelines for recommending prophylactic treatment. This is a multidimensional assessment, and considerations include: a) More than 2 attacks a month; b) Inadequate relief from or contraindication to abortive treatment; c) Prolonged, poorly responsive menstrual migraine; d) Degree of disability due to migraine.

Once prophylactic medications are started, the treating physician should monitor the patient for side effects, and reassess efficacy, keeping in mind that it often takes more than 6 weeks for efficacy to be perceived.

 Abortive therapy should be individually tailored, taking into consideration the medication class, route of administration, dosing, contraindications, development of tachyphylaxis, and side effects. Effectiveness may vary from subject to subject. Maximum tolerated doses should be tried before concluding a drug is ineffective. Often abortive treatments may need to be varied over time, as some patients appear to develop tachyphylaxis.

**Overview of mode of action of sumatriptan–naproxen**

Since migraine has multiple pathogenic mechanisms at play, using combination therapy is an attractive modality. The combination tablet contains 85 mg sumatriptan and 500 mg naproxen.

Naproxen is a NSAID that is available in the US either as a propionic acid (naproxen) or its sodium salt (naproxen sodium). 200 mg naproxen base is equivalent to 220 mg naproxen sodium. It possesses analgesic, anti-inflammatory and antipyretic properties by decreasing the formation of prostaglandin precursors. This is mediated through reversible inhibition of the cyclooxygenase-1 and 2 (COX-1 and 2) enzymes. Its desired effects are thought to be mediated through the inhibition of COX-2 while its undesirable side effects are mediated through inhibition of COX-1. It is labeled for use in the management of arthritis (ankylosing spondylitis, osteoarthritis, rheumatoid disorders, and gout), mild-to-moderate pain, tendonitis, bursitis, dysmenorrhea, fever, and for the management of dental pain and swelling. The use of naproxen in migraine is based on its recommended use for the treatment of mild to moderate pain. It is therefore a nonspecific symptomatic treatment in migraine which remains an unlabeled use in the United States. The recommended initial dosing in migraine therapy is 500–750 mg, with additional doses of 250–500 mg given as needed up to a maximum daily dose of 1250 mg. Enteric-coated formulations of naproxen are not recommended for the treatment of acute
migraine attacks.\textsuperscript{27–29} Naproxen and naproxen-sodium have been tested for migraine prophylaxis with modest results.\textsuperscript{30}

Sumatriptan was the first approved antimigraine agent in the United States by the Food and Drug administration (FDA) in 1991. It was initially thought to act as an agonist at the 5-HT\textsubscript{1b} receptor causing vasoconstriction and pain relief. However, no temporal correlation was identified between the vasoconstriction and pain relief, so other receptors were sought. These were shown to be the 5-HT\textsubscript{1d} receptors, which are densely localized in humans on tissues known to be involved in the pathogenesis of migraine, such as the carotid artery, the circle of Willis, and meninges. They co-localize to nerve endings that also show immunoreactivity to the calcitonin gene related peptide (CGRP) and tyrosine hydroxylase, implicating them in the inhibition of neurogenic inflammation.\textsuperscript{31} Therefore, triptans are now known to be selective 5-HT\textsubscript{1b,1d} receptor agonists. Both the 5-HT\textsubscript{1b} and 5-HT\textsubscript{1d} receptors belong to the 5-HT\textsubscript{1d} receptor subfamily and are expressed in the trigeminal ganglion, substantia nigra and basal ganglia, where triptans exert their central effect, regulating the firing rate of dopaminergic neurons. Peripherally, 5-HT\textsubscript{1b} receptor is expressed on cranial blood vessels and mediates vasoconstriction while the 5-HT\textsubscript{1d} receptor is expressed on trigeminal nerve endings. There, it functions as an autoreceptor, inhibiting serotonin release and decreasing neurogenic inflammation.\textsuperscript{32}

Triptans are preferred to ergotamine and ergotamine derivatives, because they are at least as potent, with better tolerability and fewer side effects. While triptans are direct agonists at the 5-HT\textsubscript{1b,1d} receptors, ergotamine has nonspecific partial activity at the tryptaminergic, dopaminergic, and alpha-adrenergic receptors. This leads to vasoconstriction both peripherally and intracranially as well as depression of the central vasomotor centers, which accounts for their increased risk of peripheral vascular, cardiovascular, and cerebrovascular complications.\textsuperscript{33}

The advantage of triptans over other analgesics is the fact that triptans not only control pain, but also the non-headache symptoms of migraine, such as nausea, vomiting, photophobia and phonophobia.\textsuperscript{34,35}

Sumatriptan may exert a positive effect in diminishing the migraine any time during the headache in some patients. In others it works primarily if given early in the headache, but not in the aura or prodrome period. Burstein and Jakubowski developed an animal model for neurogenic inflammation in the mouse, by bathing the dura with an “inflammatory soup”, the contents of which approximated the extracellular fluid produced at the dura by stimulating the trigeminal ganglion. They demonstrated that in animals exposed to inflammatory soup, there was sensitization at the trigeminal ganglion cells within 20 minutes of exposure. Sumatriptan given before 20 minutes blocked this response. Sumatriptan given after 20 minutes was ineffective.\textsuperscript{36} In a small patient sample, Burstein, Collins and Jakubowski showed that two-thirds of subjects responded to sumatriptan given early in the headache, but not after 20–30 minutes and one-third responded anytime. Ketorolac in their experiment helped prevent sensitization at the trigeminal nucleus neurons.\textsuperscript{37} This helped to provide a background rationale for the use of a combination triptan–NSAID.

**Overview of pharmacology of sumatriptan–naproxen**

Sumatriptan–naproxen has a similar side effect profile to sumatriptan.\textsuperscript{38} Administration recommendation is similar to sumatriptan tablets, and despite the fact that it contains naproxen there is no recommendation to take it with food.\textsuperscript{12} Naproxen should be taken with food, milk or antacids as it may cause GI irritation (dysepsia, bleeding, ulceration, perforation).\textsuperscript{39} Food does not appreciably affect oral bioavailability of sumatriptan (but prolongs time to peak concentration).\textsuperscript{34,40–43}

Sumatriptan–naproxen contraindications, precautions, monitoring, pregnancy risk factor and breastfeeding recommendation are otherwise the same as that of its individual components.\textsuperscript{12}

Naproxen is contraindicated in: a) Patients with renal insufficiency, when the creatinine clearance is <30 mL/minute;\textsuperscript{13} b) Treatment of the perioperative pain of coronary artery bypass graft (CABG) surgery;\textsuperscript{44} c) Aspirin-sensitive asthma;\textsuperscript{13} with note that polymorphism in the leukotriene C(4) synthase promoter region (A444C) may contribute to the asthma reaction seen with NSAIDs use;\textsuperscript{45,46} d) Patients with known hypersensitivity to aspirin or NSAIDs, or any component of the formulation.\textsuperscript{13}

Naproxen should also be used with caution in patients with the following problems: a) Known cardiovascular disease or cardiovascular risk factors;\textsuperscript{13} b) Heart failure, as it may increase the risk of fluid accumulation and edema;\textsuperscript{13,47} c) Hypertension;\textsuperscript{13,47} d) On low-dose aspirin for antiplatelet therapy, as coadministration of naproxen and aspirin interferes with aspirin’s antiplatelet effect; therefore naproxen should be administered 2–8 hours or more before aspirin or 30–120 minutes after aspirin;\textsuperscript{13,48,51} e) History of
gastrointestinal (GI) disease, especially peptic ulcer disease or GI bleeding;\textsuperscript{13,52} f) Renal insufficiency, with creatinine clearance still \(>30\) mL/minute;\textsuperscript{13,53} g) Undergoing major surgery, as they interfere with platelet aggregation and increase the risk of bleeding; therefore, naproxen should be withheld for \(3–5\) half-lives prior to surgery;\textsuperscript{13,14} h) Asthma other than aspirin-sensitive asthma, as they may also have aspirin-sensitive asthma;\textsuperscript{13} i) Hepatic impairment;\textsuperscript{13,14} j) On medication with risk of agranulocytosis, such as clozapine and carbamazepine, as naproxen may rarely cause agranulocytosis;\textsuperscript{5,46} k) On lithium therapy, as naproxen may increase serum lithium levels, with a potential for lithium toxicity.\textsuperscript{13,14}

Sumatriptan is contraindicated in patients with:\textsuperscript{40,54,55} a) Known hypersensitivity to sumatriptan or any component of the formulation; b) Ischemic heart disease or signs or symptoms of ischemic heart disease; c) Cerebrovascular disease; d) Peripheral vascular syndromes; e) Uncontrolled hypertension; f) Prior use of ergotamine, ergotamine derivatives or another 5-HT\(_2\) agonist within the preceding 24-hour period; g) Prior (within \(2\) weeks) or current usage of MAO inhibitor; h) Hemiplegic or basilar migraine; i) Severe hepatic impairment.

Therefore, patients on sumatriptan–naproxen, because of the naproxen component, should be monitored for occult blood loss and for their urine output. In addition, periodic monitoring of liver function tests, complete blood counts (CBC), blood urea nitrogen (BUN) and serum creatinine should also be performed.\textsuperscript{13,14,56}

Due to a theoretical concern for increased incidence of serotonin syndrome,\textsuperscript{41,57–59} caution should be exercised when using sumatriptan–naproxen, sumatriptan alone, or any other triptan in patients with seizure disorders or with a lowered seizure threshold, as well as in patients who are on a selective serotonin reuptake inhibitor (SSRI) or SNRI. This theoretical risk seems however to be unwarranted, since the pathophysiology of the serotonin syndrome involves activation of 5-HT\(_{1A}\) and 5-HT\(_{2A}\) receptors, not the receptors to which triptans are agonist.\textsuperscript{60} Several reports also point to fact that this does not happen in clinical practice. Even when combining a triptan with a SSRI or SNRI, the FDA warning is not necessarily warranted.\textsuperscript{61–63}

In terms of hypersensitivity to sumatriptan–naproxen, patients should not take this medication if they are allergic to either one of its components. For NSAIDs, agents of the same class tend to show higher cross-sensitivity. For naproxen, other propionic acid based NSAIDs include: fenoprofen (Nalfon\textsuperscript{®}), flurbiprofen (Ocufen\textsuperscript{®}), ibuprofen (Addaprin; Advil\textsuperscript{®}; Caldolor\textsuperscript{TM}; Genpriel\textsuperscript{®}; I-Prin; Ibu-200; Ibu\textsuperscript{®}; Midol\textsuperscript{®}; Motrin\textsuperscript{®}; NeoProfen\textsuperscript{®}; Proprinal; Ultraprin), ketoprofen (Apo-Keto\textsuperscript{®}; Novo-Keto; Nu-Ketoprofen; Oruvail\textsuperscript{®}; Rhodis\textsuperscript{TM} and oxaprozin (Daypro\textsuperscript{®}).\textsuperscript{54} Therefore, patients with known sensitivity to any of these medications should be cautious in their use of sumatriptan–naproxen. On the other hand, true allergic reaction to triptans is extremely rare, and cross-reactivity among triptans is unknown. Some triptans, including sumatriptan, contain a sulfonamide structure. However cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides does not occur, or at most has an extremely low potential.\textsuperscript{65–67}

The most common side effects of triptans, including sumatriptan–naproxen, are chest and neck pressure, tingling, paresthesia, flushing, dizziness and sedation.\textsuperscript{40,54,55} As with any of the analgesics, one should always be aware of the risk for medication overuse headache with frequent use of triptans.\textsuperscript{68}

A major concern when using triptans in general, including sumatriptan and hence sumatriptan–naproxen, is the cardiovascular safety.\textsuperscript{69} A review of clinical data about the cardiovascular tolerability and safety of triptans indicates that most chest symptoms are nonspecific and nonsignificant. Serious cardiovascular events do occur rarely however, but it is in patients with multiple cardiovascular risk factors or known cardiovascular disease. Therefore, triptan should be considered safe in patients with no or low cardiovascular risk.\textsuperscript{70} As for the naproxen component, it does not seem to alter cardiovascular risk, despite the general recommendation that NSAIDs and selective COX-2 inhibitors may increase cardiovascular complications.\textsuperscript{71–74}

As for pregnancy risk, both naproxen and sumatriptan are classified as category C, that is “animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”.\textsuperscript{13,40,54,55} However, there has not been an association between naproxen and fetal defects.\textsuperscript{13} With sumatriptan, there is lack of adequate studies to assess the fetal risk, with some animal studies demonstrating a lethal effect on the embryo, while others demonstrating no such risk.\textsuperscript{50,54,55} There is an established pregnancy registry for sumatriptan (800-336-2176), and many experts in embryo-toxicity propagate it to be relatively safe to use sumatriptan in pregnant migraine patients, due to the high number of observed pregnancies without any severe malformations or other teratogenic effect.\textsuperscript{75,76}
Both naproxen and sumatriptan are excreted in breast milk, but the American Academy of Pediatrics considers them to be breastfeeding “compatible.”

Overview of pharmacokinetics of sumatriptan–naproxen

Though sumatriptan–naproxen shares a similar pharmacologic profile with its individual components, its pharmacokinetics are different.

Maximal concentration ($C_{\text{max}}$) for sumatriptan following administration of sumatriptan–naproxen occurs at approximately 1 hour (median, range 0.3 to 4.0 hours). $C_{\text{max}}$ for naproxen following administration of sumatriptan–naproxen occurs at approximately 5 hours (median, range 0.3 to 12 hours). The mean $C_{\text{max}}$ for sumatriptan when given as sumatriptan–naproxen is similar to that of sumatriptan when given as a 100 mg tablet alone. By contrast, naproxen administered alone reaches peak serum concentration in 1 to 4 hours. This is approximately 36% lower than with the combination tablet; thus, the combination tablet seems to delay the time to maximum concentration of the naproxen.

In the combination tablet, the sumatriptan half-life is approximately 2 hours (15% to 43% CV) and the naproxen half-life is approximately 19 hours (13% to 15% CV). The median sumatriptan time to maximum concentration ($T_{\text{max}}$) is only slightly different (1 hour for sumatriptan–naproxen and 1.5 hours for sumatriptan 100 mg tablets), and the $T_{\text{max}}$ occurs approximately 4 hours later from sumatriptan–naproxen than from the 550 mg naproxen sodium tablets. The areas under the curve however for sumatriptan and for naproxen are similar for sumatriptan–naproxen compared to the individual tablets of its component.

Naproxen is almost completely albumin bound in the serum with a volume of distribution of 0.16 L/kg. For the acute treatment of pain, it has a one hour onset of action. However, the onset of action of its anti-inflammatory effect is around 2 weeks, with a peak of action at 2–4 weeks. Its analgesic onset of action of its anti-inflammatory effect is around 12 hours. With a peak of action at 2–4 weeks. Its analgesic

It is recommended that sumatriptan, sumatriptan–naproxen and all other triptans be administered at the onset of headache, or as soon as possible in the migraine attack, but not during the aura symptoms that occur at the beginning of an attack. If the headache persists, then a second dose may be administered at 2 hours, with a maximum of 2 doses within a 24-hour period. This is true for all formulations and all dosages. It is not recommended to combine different triptans.

There are no specific dose adjustments required in the elderly. However, the free plasma level of naproxen is higher in geriatrics than in younger adults, and the elderly are at increased risk for adverse effects even at low doses. Therefore one might therefore need to start with lower dosages.

Sumatriptan–naproxen efficacy studies

Both concomitant administration of sumatriptan and naproxen and sumatriptan–naproxen fixed combination tablet (Treximet®) have been shown to have superior efficacy to either one of the two medicines used alone, with a synergistic effect being noted. Summary of the two seminal studies that led to the approval of sumatriptan–naproxen by the FDA is shown (Table 1).

Similar to sumatriptan, sumatriptan–naproxen addresses both the headache and the nonheadache symptoms of migraine, namely photophobia, phonophobia and nausea.

Sumatriptan–naproxen shows consistency of response in other study designs too. In two cross over studies, sumatriptan–naproxen combination shows greater response than placebo in terms of pain freedom 2-hour postdose (52% versus 25% in study 1 and 50% versus 20% in study 2), in sustained pain freedom at 24 hours (37% versus 17% in study 1 and 34% versus 12% in study 2), and in migraine freedom at 2 hours and 4 hours postdose (no pain, nausea, vomiting, photophobia, phonophobia, and no use of rescue medications). Adverse events were 9% (versus 7% in the placebo group) in study 1 and 13% (versus 9% in the placebo group) in study 2. More importantly, even in migraineurs who do not respond to sumatriptan monotherapy, sumatriptan–naproxen demonstrates greater efficacy than placebo in aborting migraine attacks, both in terms of pain as well as photophobia and phonophobia. In two studies by Mathew and colleagues a 2 hour pain free rate with sumatriptan–naproxen was 40% and 44% versus 17% and 14% for placebo, and sustained pain freedom rates at 2 to 24 hours with sumatriptan–naproxen were 26% and 37% versus with 8% and 8% for placebo.
Sumatriptan–naproxen is not only effective against the traditional symptoms of migraine (pain, nausea, vomiting, photophobia, phonophobia), but also the nontraditional migraine symptoms (neck pain/discomfort, sinus pain/pressure). In 2 identical, randomized, double-blind, placebo-controlled trials that enrolled 576 and 535 migraineurs respectively, with similar incidence of different migraine symptoms between the treated and the placebo group, after early treatment the nontraditional symptoms occurrence 2 hours and 4 hours post-treatment were significantly lower as compared to placebo (Table 2).\(^{115}\)

Sumatriptan–naproxen also showed superior efficacy and tolerability vs placebo in the treatment of menstrual migraine and dysmenorrhea in 2 replicate studies. This effect was seen for 2-hour pain response, 2 hour to 24 hours sustained pain response, use of rescue medications and in nonmigraine menstrual symptoms (bloating, tiredness, irritability, overall nonmigraine pain intensity), except for menstrual pain.\(^{116}\)

Despite the advantage of sumatriptan–naproxen, there is a relative lack of data comparing it directly to its components. The improved efficacy in clinical trials over sumatriptan is in the range of only 5% to 10%. In addition, the efficacy of sumatriptan in the sumatriptan–naproxen studies is lower than was previously reported.\(^{117}\) One must therefore weigh this advantage against the significantly higher price of sumatriptan–naproxen compared to its components, where sumatriptan–naproxen costs around $22.00 per dose versus $6.60 per dose for generic sumatriptan 100 mg and generic naproxen 500 mg.\(^{118}\)

### Table 1 Percentage of patients with 2-hour pain relief and sustained pain relief following treatment\(^{118}\)

<table>
<thead>
<tr>
<th></th>
<th>Sumatriptan–naproxen</th>
<th>Sumatriptan 85 mg</th>
<th>Naproxen sodium 500 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-hour pain relief</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1 (all patients)</td>
<td>65%(^{1})</td>
<td>55%</td>
<td>44%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>n = 364</td>
<td>n = 361</td>
<td>n = 356</td>
<td>n = 360</td>
</tr>
<tr>
<td>Study 2 (all patients)</td>
<td>57%(^{1})</td>
<td>50%</td>
<td>43%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>n = 362</td>
<td>n = 362</td>
<td>n = 364</td>
<td>n = 382</td>
</tr>
<tr>
<td>Sustained pain relief (2 to 24 hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>25%(^{1})</td>
<td>16%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>n = 364</td>
<td>n = 361</td>
<td>n = 356</td>
<td>n = 360</td>
</tr>
<tr>
<td>Study 2</td>
<td>23%(^{1})</td>
<td>14%</td>
<td>10%</td>
<td>7%</td>
</tr>
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<td></td>
<td>n = 362</td>
<td>n = 362</td>
<td>n = 364</td>
<td>n = 382</td>
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</tbody>
</table>

\(^{1}\) P values provided only for prespecified comparisons.
\(^{1}\) P < 0.05 versus placebo and sumatriptan.
\(^{1}\) P < 0.01 versus placebo, sumatriptan, and naproxen sodium.

### Table 2 Occurrence of nontraditional migraine symptoms 2-hour and 4-hour following treatment\(^{115}\)

<table>
<thead>
<tr>
<th></th>
<th>Study 1 Sumatriptan–naproxen</th>
<th>Placebo</th>
<th>Study 2 Sumatriptan–naproxen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck pain/discomfort 2-hour postdose</td>
<td>35%</td>
<td>44%</td>
<td>28%</td>
<td>54%</td>
</tr>
<tr>
<td>Neck pain/discomfort 4-hour postdose</td>
<td>19%</td>
<td>46%</td>
<td>19%</td>
<td>46%</td>
</tr>
<tr>
<td>Sinus pressure/pain 2-hour postdose</td>
<td>19%</td>
<td>35%</td>
<td>23%</td>
<td>38%</td>
</tr>
<tr>
<td>Sinus pressure/pain 4-hour postdose</td>
<td>10%</td>
<td>30%</td>
<td>15%</td>
<td>32%</td>
</tr>
</tbody>
</table>

All results significant at 0.001 or less.

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**Patient focused perspectives such as quality of life, patient satisfaction/acceptability, adherence and uptake**

A recent study identified 5 factors that predict patient adherence to triptan therapy.\(^{119}\) In decreasing order of importance, these include: a) Confidence in the triptan’s ability to abort the migraine attack; b) The perceived importance of the triptan in the treatment of the migraine attack; c) Satisfaction with the triptan; d) Speed of onset of triptan analgesic effect; e) Time to disability resolution and patient’s return to normal activities. A negative predictive factor was the occurrence of side effects. Migraine severity was not a predictive factor of adherence to therapy.

Sumatriptan–naproxen, with its consistent efficacy response and favorable side effect profile\(^{113}\) increases the likelihood of adherence by patients. Over a 12-month period, it demonstrated consistent efficacy with low recurrence rates,
and tolerability with low side effect rates and improved quality of life scores, again resulting in improved patient satisfaction and hence improved patient compliance.\textsuperscript{120}

Conclusions and place in therapy

Sumatriptan–naproxen sodium fixed combination tablet (Treximet<sup>®</sup>) theoretically will abort migraine in its initial stages at the trigeminal ganglion and will prevent the slow central sensitization.

The combination is modestly superior to sumatriptan or naproxen alone, as shown in the 2 seminal studies,\textsuperscript{38} however the 50% to 55% 2-hour pain relief and 14% to 16% 2 hour pain freedom for sumatriptan are lower than the efficacy reported for sumatriptan in the triptan meta-analysis by Ferrari and colleagues.\textsuperscript{117}

Sumatriptan–naproxen may restore responsiveness in subjects that have become tachyphylactic to triptans, and has a favorable side-effect profile, making it an effective and well-tolerated migraine abortive treatment, but it is far from being the gold standard treatment. Research to develop additional medication is still needed.

Disclosures

The authors report no conflicts of interest in this work.

References