Acute Migraine Treatment: Recent Advance in Combination Therapy

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Migraine: A common problem

Nurse practitioners (NP) working with clients in primary or emergency care are likely to encounter migraines as a frequent illness that must be treated; it is estimated that 2.7 million Canadians suffer from migraines.[1] Migraines have significant impact on day-to-day functioning, with those suffering migraines reporting missing work, school and social events (Table 1).[2] Worldwide, migraine is the 6th highest cause of years lost to disability.[3] Not only are there concerns for the impact on overall quality of life for migraineurs, but there is an associated cost to this disabling condition. CIHI data has found that the direct and indirect costs of headaches on the health system are on par with those associated with other neurologic conditions such as epilepsy and multiple sclerosis.[4]

Table 1. How does migraine impact patients and families?

School, Work, and Social Impact in Previous 3 Months	
Missed ≥ 1 day of work/school	25%
Work/school productivity reduced by ≥ 50%	28%
Did no household work	48%
Household productivity reduced by ≥ 50%	34%
Missed family or social activity	29%

Lipton RB et al., Neurology. 2007;68:343-349

Unfortunately, the most recent Health Canada survey on the topic, found that the average time to diagnosis from onset of symptoms was 3.6 years and only 42% of migraineurs had ever tried a prescription medication.[1] That migraines are often under-recognized and under-treated is a concern given the significant impact they have on both patients, often in their most productive years of life, and the health care system.

Migraines: How to recognize them

The Lipton 3 item ID migraine screener is a tool NPs can use to help them diagnose migraines.

Continued on page 5

Acute Migraine Treatment: Recent Advance in Combination Therapy

Continued from page 3

With a positive response to 2 of the 3 items there is a 93% predictive value, making it a quick, simple and effective tool (Table 2).[5] Although effective, it is critical to always keep in mind during clinical assessments for headache, the SNOOP4 red flags (Table 3).[6] Migraine headache is frequently misdiagnosed as sinus headache. In a study of patients who had a history of HCP- or self-diagnosed sinus headache, 80% of patients met the International Headache Society criteria for migraine.[7] Migraine symptoms that closely resemble sinus headache symptoms include facial pain and pressure over frontal sinuses and nasal congestion.[8]

Migraines: How and when to treat

It is important that clinicians understand not only how a migraine presents but also how and when to treat to most effectively manage the migraine. To do so, a review of the physiologic changes that occur with migraine and the associated symptoms is useful.

Migraines are a complex neurologic condition involving the trigeminal vascular system, neurogenic inflammation, and CNS hyperexcitability. They occur in 4 phases: prodrome, aura, headache, and postdrome.

Table 2. 3-Item ID migraine screener

During the last three months, did you have any of the following with your headaches?	Yes / No
You felt nauseated or sick to your stomach when you had a headache?	Yes ☐ No ☐
Light bothered you (a lot more than when you don't have headaches?)	Yes ☐ No ☐
Your headaches limited your ability to work, study or do what you need to do for at least one day?	Yes ☐ No ☐

Table 3. Red flags in headache: SNOOP4

S	**S**ystemic signs or symptoms	Fever, myalgias, weight loss, malignancy, HIV
N	**N**eurologic signs or symptoms	Hemiparesis, hemi-sensory loss, diplopia, dysarthria
O	**O**nset sudden	Thunderclap – Sudden onset is split-second & out of the blue
O	**O**lder	Onset after age 50
P	**P**attern change	**P**rogressive headache – loss of headache-free periods **P**recipitated by Valsalva maneuver **P**ostural aggravation – worse standing or lying **P**apilledema

Dodick D. Pearls: Headache. Semin Neurol. 2010;30:74-81.

Continued on page 6

Acute Migraine Treatment: Recent Advance in Combination Therapy

Continued from page 5

Patient Assessment Questions to Guide Therapy

- Where does the headache begin?
- What is the frequency and duration of the headache?
- Where is the pain? Can you describe it?
    - Like an icepick? Stabbing? Throbbing? Pulsing? Pressure?
- Does the headache come with associated symptoms?
    - Sensitivity to light, noise, smell? Nausea or vomiting?
- Describe the level of disability?
    - Does it interfere with work? Home?
    - Is patient bedridden or able to function?
- Are there any red flags?
- How is headache treated now? What has patient already tried? For acute treatment, prevention or rescue?
- What is the monthly frequency of attacks and use of medications?

– Dr. Rose Giammarco

The headache phase can be considered in two parts, early, when pain is mild, and late when pain is moderate to severe. Regardless which medication is chosen, the most ideal time to treat a migraine is when the headache first begins and is mild.[9,10]

It has also been shown that if treatment is delayed and central sensitization has occurred (as evidenced for example by allodynia) then treatment efficacy with triptans is reduced.[10]

Working with patients to help them understand the phases of their migraines and the ideal window in which to treat can help them achieve more effective control. Early treatment of migraine and associated symptoms may prevent allodynia and reduces the risk of recurrence and need for rescue medication.

What is central sensitization?[11,12]

- When the brain's neurons become hyper-excitable and once it has begun, it maintains itself without any input
- The main symptom is allodynia

What is allodynia and how do I teach my patient to recognize it?

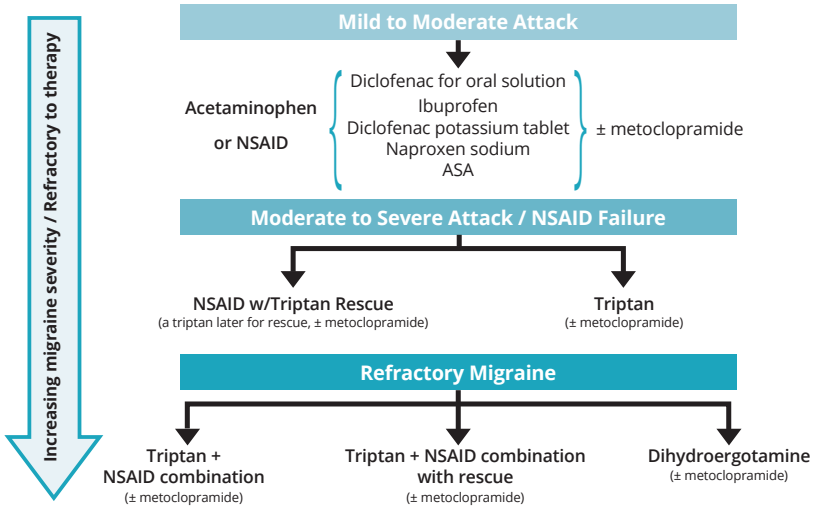
- Patient feels pain from something that normally should not cause pain
- The most common places to see cutaneous allodynia in migraineurs are the scalp, face and neck
- Examples of allodynia symptoms include feeling pain from wearing glasses, brushing hair, water on face from shower

Migraines: How to treat

The Canadian Headache Society (CHS) offers guidelines on the treatment of acute migraines.[10] The CHS recommends acetaminophen or NSAIDs for mild to moderate migraine attacks. An NSAID with tripan rescue or a triptan is recommended for moderate to severe migraines or when NSAIDs alone have failed (Figure 1).

Medication recommendations for patients should be individualized, attending to both severity of episodes and previously trialed medications and responses.

Figure 1. CHS acute migraine treatment strategies



Adapted from Worthington et al., Can J Neurol Sci 2013;40:S1-S84

Continued on page 9

Acute Migraine Treatment: Recent Advance in Combination Therapy

Continued from page 7

When working with patients to determine the most effective medications for their migraine attacks the CHS suggests a "step care across attacks" approach, beginning with an NSAID, then moving to a triptan and then moving to a combination of the two.

Role of combination therapy

Due to the multiple mechanisms at play in the pathophysiology of migraines, there is a role for combination therapy using both an NSAID and a triptan. The CHS recommends a triptan and NSAID combination with or without rescue or dihydroergotamine for refractory migraine.[10]

Sumatriptan/naproxen fixed dose combination tablet (85/500 mg)

A fixed-dose, single tablet combination medication which contains the NSAID naproxen sodium and the triptan sumatriptan (Suvexx) is available in Canada as of September 2020. Despite being new to the Canadian market, Suvexx has been available and in use in the United States for over a decade under the brand name Treximet.

Brandes et al. conducted two parallel group randomized control trials comparing sumatriptan/naproxen single tablet (Suvexx) to naproxen alone, sumatriptan alone and placebo.[13] The fixed-dose single tablet sumatriptan/naproxen was more effective for headache relief at 2 hours (more than half of patients had pain relief at 2 hours) and for sustained 2-24 hours headache pain relief than either naproxen or sumatriptan alone.[13] The fixed-dose single tablet-treated patients also required significantly fewer rescue medications to treat their migraine attack and showed a higher percentage of patients who were pain-free post-treatment.[13]

> "The use of sumatriptan and naproxen sodium in a combination tablet "to treat migraine attacks is based on several randomized controlled trials which have shown that the combination is more effective than either drug used alone." – CHS Guidelines

As has been demonstrated in multiple studies, triptans are more effective when taken early in the migraine. Silberstein et al. conducted two double-blind, placebo controlled randomized control trials and found that the fixed-dose, single tablet sumatriptan/naproxen when taken within one hour of headache onset and while pain was still mild, was significantly more effective at providing 2-hour pain-free response

Continued on page 10

Acute Migraine Treatment: Recent Advance in Combination Therapy

Continued from page 9

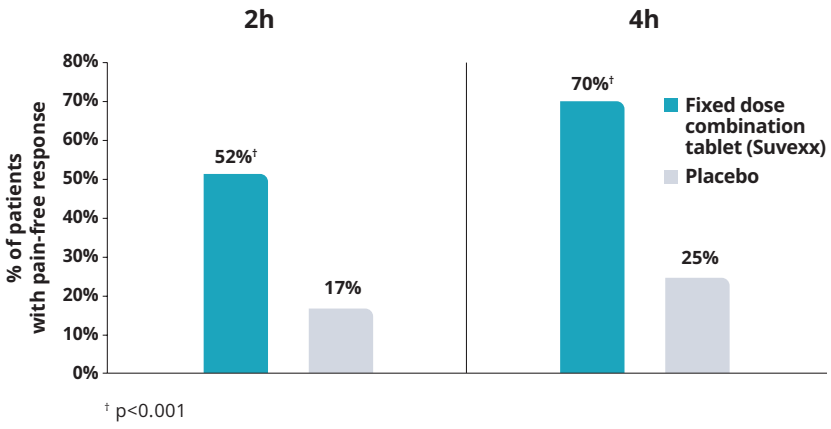
vs placebo (Figure 2). Furthermore, 86% of patients who were pain-free at 2 hours remained pain-free at 24 hours.[14]

In examining the pharmacokinetics, the fixed dose single tablet combination reveals differences. The maximal plasma concentration (T_{max}) of sumatriptan is reached earlier than when given alone, and the T_{max} of naproxen is delayed by 5 hours than when components are taken individually (Figure 3).[15,16]

Two subsets of migraineurs may uniquely benefit from combination therapy: those who have had multiple triptan failures and those with menstrual migraines.

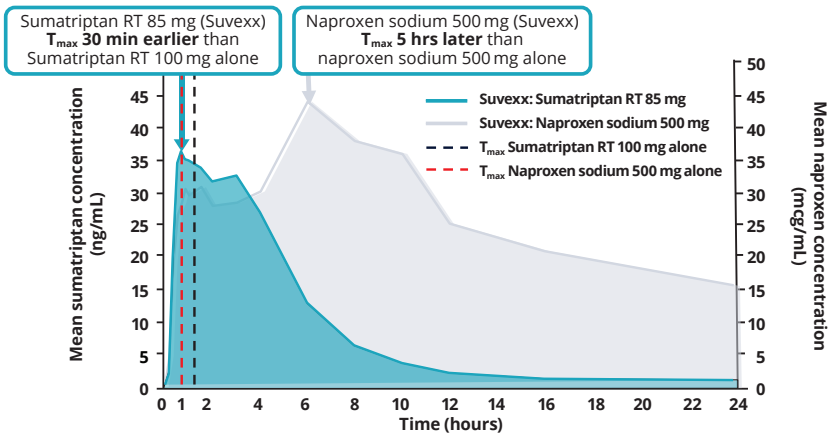
Mathew et al, undertook a multi-site double-blind placebo controlled RCT with patients who had trialed an average of 3.3 triptans and had discontinued them due to either ineffectiveness or intolerability.[17] Participants were again instructed to take the medication within 1 hour of headache onset when still mild. The authors found that compared to placebo, participants had improved pain-free response at both the 2hr and sustained pain-free response from 2-24 hours

Figure 2. Early intervention with fixed-dose combination tablet: pain-free outcomes



Silberstein S et al. Neurology 2008;71:114-121

Figure 3. Earlier sumatriptan T_{max} and delayed naproxen T_{max} in combination tablet vs. the components taken alone



Adapted from Haberer L et al. Headache 2010;Mar:357-373

(Figure 4).[17] This was very similar to outcomes seen in a less refractory population.

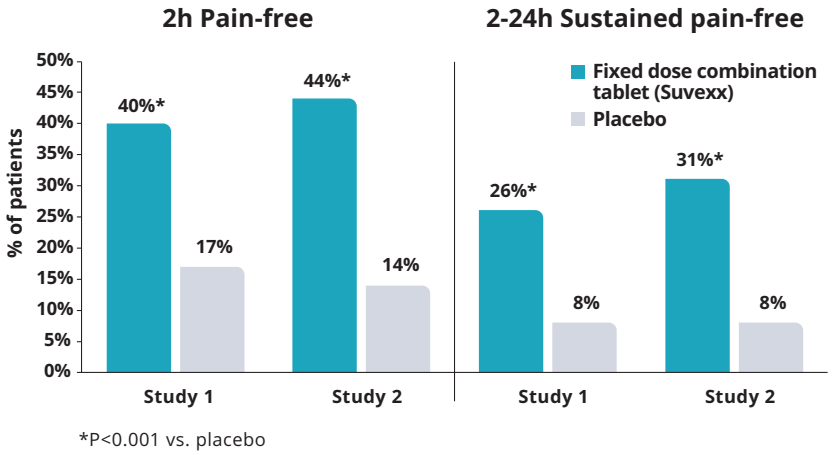
Menstrual migraines are defined as a migraine which occurs either 2 days prior to or 3 days following the onset of menses. Migraines associated with menses are typically harder to treat and longer lasting.[10] Mannix et al, undertook 2 replicate double-blind placebo controlled RCTs to evaluate sumatriptan/naproxen single tablet combination therapy in women who suffer menstrual-related migraines.[18] Patients were more likely to be pain-free at 2 hours and most patients treated with the fixed dose combination tablets continued to be pain-free through 24 hours compared to placebo (Figure 5). The fixed dose combination tablet also significantly decreased non-painful menstrual symptoms of bloating, tiredness and irritability versus placebo.

Side effects/compliance

The safety profile of the single table sumatriptan/naproxen is similar to both drugs alone and the side effect profile is similar as when used in monotherapy. Adverse events seen with the fixed dose combination tablet treatment did not differ meaningfully from those seen with sumatriptan or naproxen monotherapy in controlled trials.[16]

Compliance is likely to be enhanced by a single tablet combination therapy over combination therapy using each component individually.

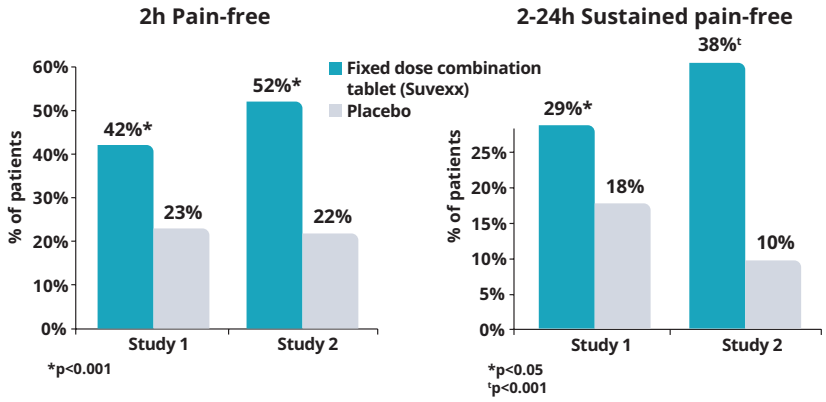
Figure 4. Efficacy of fixed dose combination tablet in triptan poor responders



*P<0.001 vs. placebo

Adapted from Mathew et al. 2009.

Figure 5. Menstrual migraine and dysmenorrhea 2h and sustained pain-free response



*p<0.001

*p<0.05
†p<0.001

Rescue medication after 2h was permitted

Mannix LK, et al Obstet Gynecol 2009; 114:106-13.

Patients prescribed both an NSAID and triptan to use in combination were found to vary their medication use with only 10% using their NSAID and triptan in their next attack at the same time.[19]

Being able to prescribe combination therapy in a single tablet offers an opportunity to mediate these obstacles and increase compliance in the effort to help patients achieve better migraine control and more pain-free days.

Continued on page 12

Acute Migraine Treatment: Recent Advance in Combination Therapy

Continued from page 11

Summary

Migraine is a commonly encountered clinical problem that greatly impacts patients' quality of life. Accurate diagnosis of migraine is essential for directing therapeutic choices and educating patients on how best to manage their migraines. The Canadian Headache Society guidelines provide evidence-based direction on therapeutic choice. A fixed-dose, single tablet NSAID/triptan combination medication of naproxen sodium and sumatriptan (Suvexx) is now available in Canada. Patients who could benefit from this treatment combination include those with moderate to severe migraines, menstrual migraine, triptan poor responders, those patients who experience a recurrence of migraine within the first 24 hours.

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