Triptans for the Management of Migraine

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Abstract

Migraine is a chronic, recurrent, disabling condition that affects millions of people in the US and worldwide. Proper acute care treatment for migrainers is essential for a full return of function and productivity. Triptans are serotonin (5-HT₁B/D) receptor agonists that are generally effective, well tolerated and safe. Seven triptans are available worldwide, although not all are available in every country, with multiple routes of administration, giving doctors and patients a wide choice. Despite the similarities of the available triptans, pharmacological heterogeneity offers slightly different efficacy profiles. All triptans are superior to placebo in clinical trials, and some, such as rizatriptan 10 mg, eletriptan 40 mg, almotriptan 12.5 mg, and zolmitriptan 2.5 and 5 mg are very similar to each other and to the prototype triptan, sumatriptan 100 mg. These five are known as the fast-acting triptans. Increased dosing can offer increased efficacy but may confer a higher risk of adverse events, which are usually mild to moderate and transient in nature. This paper critically reviews efficacy, safety and tolerability for the different formulations of sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan and frovatriptan.
1. Migraine

1.1 Epidemiology

Migraine is ranked 19th by the WHO for disabling diseases on its Classification of Functioning, Disability and Health.[1] The cumulative lifetime incidence of migraine in The American Migraine Prevalence and Prevention Study was reported to be 43% of women and 18% of men.[2] The loss of productive work time due to headache pain in 2002 in the US alone was $US19.6 billion.[3] Despite the prevalence and debilitating nature of this disorder, migraine is still underdiagnosed and undertreated. In 2004, only about 50% of those suffering from migraine received a diagnosis of such, and in 2006, only 23.8% of those with episodic migraine were using triptans.[4] Instead, 21.1% used barbiturates or opioids even though neither of these medications are specifically approved for migraine, and both tend to make headaches worse and harder to treat. This underscores the importance of understanding migraine and triptan mechanisms. Making the correct diagnosis and initiating acute care therapy early in the attack is essential to effective and lasting treatment with minimal adverse effects.

1.2 Mechanisms

Since the 1860s, during the advent of ergots, migraines were thought to be due to vasodilation as a primary mechanism.[5] In the 1930s and 1940s, Graham and Woolf showed evidence that ergotamine tartrate reduced the pulsations of the external carotid artery system and it was thought that this was the mechanism of migraine and the resulting pain control. Ergots were the mainstay of treatment until 1991, when sumatriptan was introduced around the world (except in the US, where it was launched in 1993). Sumatriptan was discovered by Patrick Humphrey of the UK, who was looking for a vasoconstrictor that stimulated appropriate serotonin receptors and had some of the properties of ergots without the same systemic adverse effect profile and long-term vasoconstriction.[4,5]

While the extremely complex physiological events leading to a migraine attack are still not completely understood, current literature suggests that migraine may be an inherited physiological dysfunction in normal brain anatomical pathways and that the earliest event in migraine with aura, and maybe even migraine without aura, is cortical spreading depression. Additionally, all migraineurs seem to develop activation of the trigeminal pain pathways peripherally and subsequently centrally if the attack progresses without effective therapy. In this case, there will be involvement of various brainstem structures, such as the trigeminal nucleus caudalis, leading to autonomic activation, central sensitization, allodynia and increased pain, with potential dysfunction of thalamic and cortical structures.[5,6]

The trigeminal pain pathway involves input from nociceptors in close approximation to arteries and veins found in the skin, muscles of the face and neck, periosteum, and intracranial dura and dural sinuses. These perivascular nociceptors transmit pain signals to the trigeminal ganglion along the first branch of the trigeminal nerve and on into the pons. These nerves synapse with the second-order neuron in the trigeminal nucleus caudalis in the pons and medulla where central sensitization occurs in some patients. These signals may then be projected to the third-order neuron in the thalamus and on to the cortex where perception of pain occurs.[7] Various chemicals are released antidromically from the distal end of the first branch of the fifth cranial nerve in close approximation to blood vessels, and may also be released centrally in the brainstem. Substances released include calcitonin gene-related peptide (CGRP), neurokinin-A and substance P, which trigger release of inflammatory cytokines from local mast cells. These inflammatory substances in turn stimulate the nociceptors, sending pain signals back into the brainstem. CGRP has been found to be elevated in jugular venous outflow during migraine and cluster attacks.[7-9]

2. Triptans

2.1 Mechanism of Action

Triptans are agonists of serotonin (5-HT)_{1B} and 5-HT_{1D} receptors (which are found on blood
vessels and presynaptically on sensory nerves, respectively). Triptans are thought to work in three main ways: peripheral inhibition of release of CGRP and substance P from trigeminal nociceptive afferents; modulation of second-order neurons centrally in the trigeminocervical pathway, including trigeminal nucleus caudalis, periaqueductal grey and the thalamus; and, finally, vasoconstriction.[7,8,10,11] Cranial vasoconstriction is debated as a key mechanism for several reasons; the most important is that modification of vascular tone is not essential for effective migraine treatment.[12] Nonetheless, vasoconstriction continues to be a widely published triptan mechanism. Moreover, alterations in serotonin metabolism have also been reported to be a trigger of noiception and neurogenic inflammation; thus, triptans are thought to increase serotonin receptor stimulation and thereby abort this cascade.[7,12,13]

Migraine is vastly undertreated; however, triptans are generally very effective, with few adverse events when used appropriately. Characteristics of individual attacks as well as efficacy, safety and tolerability determine which triptan will be best suited for a particular patient. Despite pharmacological similarities of triptans, the pharmacokinetics and routes of administration differ, resulting in diverse efficacy, safety and tolerability profiles.

The aim of this paper is to provide a critical review of the efficacy, safety and tolerability profiles of the seven triptans to further delineate appropriate acute treatment of migraine. The literature obtained in this review includes articles from randomized controlled trials, reviews, meta-analyses and original articles from the PubMed database. Search terms included 'triptans', 'migraine', 'efficacy', 'safety', 'tolerability', 'review', 'sumatriptan', 'naratriptan', 'almotriptan', 'zolmitriptan', 'rizatriptan', 'frovatriptan', 'eletriptan' and 'meta analysis'. Date limits were from 1 January 2000 to 1 July 2010. Exclusion criteria included full texts not written in English.

2.2 Efficacy

All triptans are both more effective than placebo and well tolerated.[11] However, differences in efficacy between the triptans are clinically relevant and likely to be due in part to genetic differences and pharmacological heterogeneity in formulation and route of administration.[14] No randomized, placebo-controlled trials compare all triptans with each other within one study. Available trials are usually head-to-head versus sumatriptan or placebo, or occasionally to one other triptan. Meta-analyses and comprehensive review articles, such as from the Cochrane Database, must be used to compare efficacy endpoints between triptans to broaden studied populations in the absence of one large head-to-head trial, although few methodically sound reviews have been done. Most are 6–9 years old, yet still remain very relevant given their high quality. In this report, we attempt to review the current methodologically sound literature for assessing efficacy, safety and tolerability.

The most widely reported efficacy endpoints used in these reviews and randomized controlled trials include pain-free response at 2 hours (defined as improvement from moderate or severe pain to pain free at 2 hours post-dose), headache relief at 2 hours (defined as improvement from moderate or severe to mild or no pain 2 hours post-dose), 24-hour recurrence rate (headache relief at 2 or 4 hours with recurrence of moderate to severe pain within the next 22 or 20 hours), and adverse events compared with placebo or another triptan. For the purpose of this review, single smaller trials using other endpoints are not discussed.

2.2.1 Route of Administration

Several different routes of triptan administration are currently available in the US. These include subcutaneous injections, oral tablets, orally disintegrating tablets (ODTs) and nasal sprays. Other types of triptan administration are being considered, such as buccal patch and a unique device for nasal administration of a triptan powder. An iontophoretically driven transdermal patch recently finished a phase III trial which reported good efficacy and excellent tolerability.[15] Benefits and drawbacks of each route must be considered in making the optimal choice of triptan for each patient.

Subcutaneous sumatriptan injection was the first triptan formulation available worldwide. It
offers the fastest relief with the most rapid onset and best 1- and 2-hour headache relief data, making it still the most effective route for patients who can tolerate an injection. The initial injection apparatus was a little large, its administration somewhat cumbersome and it produced many adverse events, thus many patients were happy to see the launch of the tablet. However, those who did well on the injection, generally did not want to switch to the tablet, whereas those who were naive to the drug usually selected the tablet when both forms were available.

Oral tablets are the preferred mode of administration by patients and the most commonly prescribed formulations. They are easy to administer and generally have good bioavailability and efficacy. The oral formulation now represents over 90% of the sumatriptan market in the US. Oral tablets are less efficacious and tolerable if nausea, vomiting or decreased functioning of the gastrointestinal (GI) tract is a significant component of the attack, as time to maximum plasma and brain drug concentration can increase in these situations. This decreased concentration and efficacy is due in part to GI stasis, decreased transit time in the stomach and poor absorption of drug from the small bowel.

Nasal sprays are absorbed through the olfactory epithelium and pass more quickly into the bloodstream, making GI absorption much less important and also bypassing first-pass metabolism. This results in quicker entry into the brain and more rapid relief. Drawbacks of the nasal sprays include altered or bad taste, which is more tolerable to patients if the time to relief is fast and the efficacy is good.

The ODTs are preferred by some patients as they are easy to use and do not have to be taken with water; however, they do have a slightly longer time to peak plasma concentration. This can be seen in both rizatriptan and zolmitriptan ODT versus their comparable tablets. This is partly because the ODT dissolves in saliva, is swallowed for GI absorption and does not get to the stomach quite as fast as a tablet. Patients often do not notice or complain about slower onset of action of the ODT. Some think that they work faster than tablets. In fact, the 2-hour pain-free rates of the zolmitriptan ODT are the highest of all zolmitriptan formulations.

### 2.2.2 Sumatriptan

Sumatriptan is currently available in subcutaneous injection, nasal spray and oral tablet formulations in the US and is also available as a rectal suppository in Europe. Since its launch 19 years ago, six other triptans have been manufactured and launched in several different forms, but sumatriptan remains the most commonly prescribed and studied triptan. Sumatriptan is available without prescription in New Zealand and the UK. It is an effective, safe and well tolerated acute treatment for a migraine attack. The 6 mg subcutaneous formulation is the most effective migraine treatment in terms of headache response at 2 hours, pain-free response at 2 hours, sustained pain-free rates at 24 hours and consistency between attacks. The subcutaneous injection has a time to maximum plasma concentration of 10 minutes and is 97% bioavailable (see table I).

In a Cochrane review from 2003, 25 randomized trials of oral sumatriptan 100 mg were reviewed, 14 of which were placebo-controlled. Eight homogeneous trials (n = 2221) reported the pain-free response to be significantly better than placebo with a number needed to treat of 5.1 (NNT is defined as the number of patients that must be treated to achieve a pain-free response at 2 hours in one patient). In 11 of these trials, headache relief at 2 hours was also superior to placebo at this dose. However, recurrence rates at 24 hours were not significantly better versus placebo, although the concept of headache recurrence from a placebo is difficult to understand. Eight of 11 studies reviewing sumatriptan 100 mg versus placebo showed increased adverse events over placebo, but the other three showed no difference. The most frequent adverse events were nausea, vomiting, fatigue, dizziness, vertigo, paraesthesias, tingling and somnolence. This dose of sumatriptan did not result in higher withdrawals versus placebo in clinical trials due to adverse events.

In the same review, three homogeneous studies (n = 420) comparing sumatriptan 50 mg tablets versus placebo found significant superiority over
Table I. Pharmacokinetics and common trial outcome measures per triptan. A summary of ranges of trial outcome measures reported.[11,13,16,19-22] Time to peak plasma concentration (t_{max}), bioavailability, half-lives (t_{1/2}), 24-h recurrence rate means from several studies combined, and therapeutic gain for 2-h headache response (improvement from moderate or severe to mild or pain free at 2 h, placebo subtracted) are all shown.

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Route and dose (mg)</th>
<th>t_{max} (h)</th>
<th>Bioavailability (%)</th>
<th>t_{1/2} (h)</th>
<th>Mean 24-h recurrence (%)</th>
<th>Therapeutic gain for headache response at 2 h (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>SC 6</td>
<td>0.2</td>
<td>97</td>
<td>2</td>
<td>34-38</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>PO 50</td>
<td>2.5</td>
<td>14</td>
<td>2</td>
<td>32</td>
<td>29-36</td>
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<tr>
<td></td>
<td>PO 100</td>
<td>2.5</td>
<td>14</td>
<td>2</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>NS 20</td>
<td>1</td>
<td>17</td>
<td>2</td>
<td>32-34</td>
<td>28-55</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>PO 2.5</td>
<td>1.5</td>
<td>40-48</td>
<td>3</td>
<td>22-37</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>PO 5</td>
<td>1.5</td>
<td>40-48</td>
<td>2.71</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>ODT 2.5</td>
<td>3.3</td>
<td>40-48</td>
<td>2.5-3</td>
<td>NA</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>NS 5</td>
<td>2</td>
<td>42</td>
<td>2.82</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>PO 10</td>
<td>1.2</td>
<td>45</td>
<td>2</td>
<td>30-47</td>
<td>27-40</td>
</tr>
<tr>
<td></td>
<td>ODT 10</td>
<td>1.6-2.5</td>
<td>45</td>
<td>2</td>
<td>NA</td>
<td>19-46</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>PO 2.5</td>
<td>2-3</td>
<td>63-74</td>
<td>5-6.3</td>
<td>17-28</td>
<td>16-22</td>
</tr>
<tr>
<td>Alamotriptan</td>
<td>PO 12.5</td>
<td>1.4-3.8</td>
<td>70-80</td>
<td>3.2-3.7</td>
<td>18-29</td>
<td>26-32</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>PO 40</td>
<td>1-2</td>
<td>50</td>
<td>3.6-5.5</td>
<td>19-30</td>
<td>22-41</td>
</tr>
<tr>
<td></td>
<td>PO 80</td>
<td>1-2</td>
<td>50</td>
<td>3.6-5.5</td>
<td>&lt;33</td>
<td>30-53</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>PO 2.5</td>
<td>2.0-4.0</td>
<td>22-30</td>
<td>26</td>
<td>7-25</td>
<td>16-19</td>
</tr>
</tbody>
</table>

NA = data not available; NS = nasal spray; ODT = orally disintegrating tablet; PO = oral tablet; SC = subcutaneous injection.

placebo for headache relief at 2 hours. Headache recurrence at 24 hours in three studies showed either a 5% lower recurrence rate in the sumatriptan 50 mg patients or no superiority over placebo.[14] Adverse events in four studies (n = 1100) were similar between sumatriptan 50 mg and placebo.[23]

Sumatriptan 25 mg is also better than placebo with an NNT of 7.5 for pain-free response at 2 hours. Headache relief at 2 hours in two trials (n = 226) showed statistically significant benefit over placebo with an NNT of 3.4. Recurrence rates have been reported to be similar to placebo. Adverse events reported were no different between sumatriptan 25 mg and placebo in three homogeneous trials (n = 628).[23]

There was no significant difference found in pain freedom or headache response rate at 2 hours when comparing sumatriptan 100 mg versus 50 mg in a review of four trials.[23] Recurrence at 24 hours was similar between the two doses.[11,23] More recently, oral sumatriptan was made into a rapid-release formulation, which is reported to disintegrate in and transit through the stomach more rapidly than the older tablet. It is effective in acute migraine treatment, with some data showing that it works slightly faster than the standard form. Patients also report higher satisfaction with the rapid-release formulation if they were previously unsatisfied with other formulations or lower doses of sumatriptan.[24] Sumatriptan 50 mg is not significantly superior to the 25 mg dose with respect to pain freedom or headache relief at 2 hours; however, 100 mg is superior to 25 mg in these outcomes.[11] Adverse events are dose dependent with a higher frequency at higher doses.

The nasal spray form of sumatriptan is superior to placebo and quicker in onset than oral tablets. It is also better tolerated if patients have nausea or vomiting, although it has a bad taste, but has a similar half-life, pain freedom results and headache response at 2 hours to the oral tablet.[16,17]

In summary, all sumatriptan doses have higher efficacy than placebo, with sumatriptan 100 mg being equal to the 50 mg dose and superior to the 25 mg dose, and the 50 mg dose similar to the 25 mg dose. Although efficacy appears to be superior with the 100 mg dose versus the 25 mg dose, adverse event risk is higher as well. The nasal spray formulation is effective and better tolerated in patients with nausea or vomiting, in spite of its
bad taste. More recent studies of the rapid-release formulation of sumatriptan 100 mg and 50 mg tablets, given early when the headache was mild, showed superior efficacy for the 100 mg tablet for the first time.[24]

2.2.3 Zolmitriptan

Zolmitriptan was the second triptan available in the US and many other countries, and is available in oral tablet, nasal spray and ODT formulations. In tablet form, it is different from sumatriptan in that it is more lipophilic and rapidly absorbed, and has an active metabolite with a 50% longer half-life. It is also more potent at serotonin receptors.[13,19] It has a bioavailability of 40–48% with a half-life of 3 hours. Zolmitriptan has a high therapeutic gain (percentage difference between the response to drug vs that for placebo) for headache response, for all doses and formulations, of between 34% and 40%, making it highly effective (see table I).[11,16]

Zolmitriptan 2.5 and 5 mg tablets are both superior to placebo when considering headache relief, pain freedom and sustained pain-free responses. The 2.5 mg dose was similar to the 5 mg dose in terms of adverse events, but was less effective in achieving pain freedom at 1 or 2 hours.[25]

Results were similar for 2-hour pain-free response and 2-hour headache relief when comparing sumatriptan 100 mg with zolmitriptan 5 mg, as were recurrence rates at 24 hours and the rate of adverse events.[11,23,25] Similarly, it was reported that zolmitriptan 2.5 and 5 mg are not superior to sumatriptan 50 mg with regards to headache response at 2 hours.[11,26]

Zolmitriptan was compared with almotriptan in a randomized, double-blind, multicentre, parallel study of 1062 patients by Goadsby et al.[27] in 2007. No significant difference in pain freedom at 2 hours was found between almotriptan 12.5 mg and zolmitriptan 2.5 mg. However, zolmitriptan 5 mg (more effective vs placebo than the 2.5 mg dose for pain freedom) was not compared with almotriptan 12.5 mg. Almotriptan had fewer adverse events than zolmitriptan, making it better tolerated at these doses. However, the treatment satisfaction between the two groups was similar.[27]

In a recent meta-analysis of 24 randomized controlled trials of more than 15 000 patients, zolmitriptan 2.5 mg was reported to be as effective for 2-hour pain freedom and headache relief as almotriptan 12.5 mg, eletriptan 40 mg and rizatriptan 10 mg.[25] It was also found to be less effective than eletriptan 80 mg (not available in the US and many countries), but more effective than naratriptan 2.5 mg. For sustained pain-free rates, it was inferior to rizatriptan 10 mg. Adverse events were similar when comparing zolmitriptan 2.5 mg with almotriptan 12.5 mg, eletriptan 40 mg and sumatriptan 50 mg, but were higher than naratriptan 2.5 mg and rizatriptan 10 mg and fewer than eletriptan 80 mg. Of note, this analysis reports some heterogeneity of placebo responses in the included studies, which may result in variability in the findings versus placebo.

The ODT has similar efficacy to the tablets versus placebo as shown in three randomized, placebo-controlled trials, although larger trials have not been conducted.[18] Zolmitriptan 5 mg nasal spray has also been shown to be safe in long-term trials and quite well tolerated.[28] The 5 mg nasal spray is superior to the 2.5 mg spray and the 2.5 mg tablet in headache relief, and is the only size nasal spray available in the US. The 5 mg nasal spray has been approved for the treatment of cluster headache in the EU, even though in the meta-analysis of the European and US studies, the 10 mg dose worked on more patients than the 5 mg dose.[29] The 2.5 mg tablet is similar in efficacy and adverse events to the 2.5 mg nasal spray dose, although the nasal spray has a quicker onset of action.[25]

In summary, zolmitriptan in all doses and formulations is superior to placebo. Zolmitriptan 5 mg is similar to sumatriptan 100 mg, and zolmitriptan 2.5 mg is similar to sumatriptan 50 mg, almotriptan 12.5 mg, eletriptan 40 mg and rizatriptan 10 mg in efficacy. Zolmitriptan 5 mg has a better 2-hour pain-free rate than the 2.5 mg dose. Adverse events for these comparisons were also similar, except that zolmitriptan 2.5 mg had more adverse events and a higher efficacy than naratriptan 2.5 mg. Eletriptan 80 mg was more effective and had a higher risk of adverse events than zolmitriptan 2.5 mg, and is not available in most
countries. The eletriptan 80 mg dose was not studied against zolmitriptan 5 mg, which would have been the more appropriate comparative dose. The nasal spray has a quicker onset of action than the tablets and is well tolerated, with only a few patients complaining of taste alteration.

### 2.2.4 Rizatriptan

Rizatriptan was designed to be faster acting than its predecessors.\(^{[13]}\) It is available in tablet and ODT formulations. It has a rapid onset, similar bioavailability to other oral triptans and a 2-hour half-life (see table I). A recent review of the past 10 years of rizatriptan use reports that the 10 mg dose is statistically superior to placebo in all clinical endpoints including pain-free response at 2 hours and sustained pain freedom at 24 hours.\(^{[11,30]}\) This review also reported significant superiority of rizatriptan 10 mg over naratriptan 2.5 mg and sumatriptan 50 mg in time to onset of pain relief.

A similar review stated that rizatriptan 10 mg tablets were as effective at 2-hour pain freedom and headache relief as almotriptan 12.5 mg, eletriptan 40 mg and zolmitriptan 2.5 mg.\(^{[25]}\)

When assessed through a meta-analysis of placebo-controlled trials, rizatriptan 10 mg is reported to be 38% better for pain freedom at 2 hours, 17% better for headache relief and 25% better for sustained pain freedom at 24 hours versus sumatriptan 100 mg.\(^{[11,30]}\) The authors point out that while these differences were small, they were clinically relevant for patients. Additionally, rizatriptan 10 mg was reported to have high consistency of efficacy, stating 67% for headache relief and 58% pain freedom for three of three attacks. Tolerability of rizatriptan 10 mg and sumatriptan 100 mg was also similar. However, these data were somewhat limited given the different study designs.\(^{[11]}\) Patients were also reported to prefer rizatriptan 10 mg ODT over sumatriptan 50 mg and eletriptan 40 mg tablets for faster pain relief.\(^{[30]}\)

A review of 38 double-blind, randomized, controlled trials on all oral triptans concluded that patients receiving rizatriptan 10 mg had more headache recurrence at 24 hours versus placebo, which was statistically significant.\(^{[14]}\) This review homogenized the results of the 38 trials by reporting only the data on the first attack and first treatment of each patient’s migraine. The authors do not explain the possible reasons for increased 24-hour recurrences versus placebo, although they report similar findings in four other studies.

In a recent single-blind, parallel-group study, 197 subjects with migraine were randomized to receive either 9 or 27 rizatriptan 10 mg ODTs for 1 month for the acute treatment of migraine. The mean number of migraine days was reported before and after treatment. None of the patients reported a progression to chronic migraine when using more than ten tablets per month.\(^{[31]}\)

Overall, the rizatriptan 10 mg tablet has higher efficacy and consistency than placebo, and produces more rapid pain relief than sumatriptan 50 mg and naratriptan 2.5 mg. It is similar in efficacy to almotriptan 12.5 mg, eletriptan 40 mg and zolmitriptan 2.5 mg, and is well tolerated, even when taking more than ten tablets per month. The ODT form is preferred by patients for faster pain relief (even though the time to peak concentration is no shorter) and convenience. Reported recurrence rates are mixed.

### 2.2.5 Naratriptan

Naratriptan was the third triptan available in the US for acute migraine treatment. It is different from sumatriptan in that it has a longer half-life, with higher bioavailability and lipophilicity, making it more readily absorbed and less readily metabolized (see table I).\(^{[13,32]}\) Naratriptan 2.5 mg has been shown to be less effective and has a slower onset of action, but is better tolerated than sumatriptan 100 mg.\(^{[11,13,33]}\) More specifically, it has lower pain-free and headache response rates at 2 hours and lower sustained pain-free rates at 24 hours.\(^{[11]}\) It is one of the two slower-acting triptans.

Naratriptan 2.5 mg has also been reported to have less therapeutic gain versus other triptans at 2 hours,\(^{[13]}\) which was also reported in a review of 48 publications that showed it to have the highest NNT of the triptans.\(^{[34]}\) However, because naratriptan has a slower onset, its therapeutic gain at 4 hours is higher than at 2 hours, ranging from 26–34%, and this should be taken into consideration when comparing its efficacy with other triptans.
Consistency over multiple attacks is also lower with naratriptan than with sumatriptan 100 mg.\textsuperscript{[11]} When compared with sumatriptan 100 mg, naratriptan 2.5 mg has a lower recurrence rate.\textsuperscript{[13,33]} (Note that if efficacy is lower at 2 hours, recurrence will also be lower as you have to have headache relief at 2 hours to have a recurrence.) Recurrence rates could not be directly compared in the meta-analysis by Ferrari et al.\textsuperscript{[11]} because of different definitions, although in more recent reviews of head-to-head trials, recurrence of headache after 4-hour headache response is lower with naratriptan than with rizatriptan 10 mg and oral sumatriptan doses.\textsuperscript{[16]} In 2003, Rapoport et al.\textsuperscript{[16]} also concluded that naratriptan had a 17–28% recurrence rate after 4-hour headache response, making the likelihood of needing to take a rescue dose of naratriptan low, similar to that of dihydroergotamine (DHE). Despite its lower efficacy, the risk of adverse events has been reported as similar to placebo, making naratriptan better tolerated than other triptans.\textsuperscript{[11,16]} It is likely that when Glaxo marketed naratriptan, they picked the lowest effective dose, 2.5 mg, which had a low adverse event rate compared with placebo, to distinguish it from their currently available triptan at that time, sumatriptan.\textsuperscript{[11,16]}

### 2.2.6 Almotriptan

Almotriptan is a somewhat newer 5-HT\textsubscript{1B/1D/1F} agonist that is rapidly absorbed, and has a higher bioavailability and a slightly longer half-life than most other oral triptans (see Table 1).\textsuperscript{[35]} Almotriptan has a low probability of drug-drug interactions as it is metabolized by three pathways: monoamine-mediated oxidative deamination, cytochrome P450 (CYP) 3A4-mediated oxidation and flavin mono-oxygenase.

In a recent meta-analysis of almotriptan in 2007, Chen and Ashcroft\textsuperscript{[36]} reviewed nearly 5000 patients in eight randomized controlled trials. They found almotriptan 12.5 mg to be superior to placebo in all efficacy endpoints, and the 25 mg dose to be superior to the 12.5 mg dose at 1 hour, although it had a higher risk of adverse events. There was no significant difference between almotriptan 12.5 mg, sumatriptan 100 mg and zolmitriptan 2.5 mg in all primary efficacy endpoints. This was re-established in a double-blind, parallel-group study from 2002, in which almotriptan 12.5 mg and 25 mg were compared with sumatriptan 100 mg and all were found to provide similar headache relief at 2 hours.\textsuperscript{[37]}

An earlier meta-analysis reported that almotriptan 12.5 mg was 24% better for pain freedom at 2 hours, 30% better for recurrence at 24 hours and 57% better for adverse events versus sumatriptan 100 mg.\textsuperscript{[11]} Almotriptan was also reported to have significantly fewer adverse events, making it better tolerated than zolmitriptan 2.5 mg and sumatriptan 100 mg.\textsuperscript{[36]}

Almotriptan has been repeatedly found to have fewer adverse events, with lower rates reported with almotriptan 12.5 mg than with sumatriptan 100 mg;\textsuperscript{[36]} however, almotriptan 25 mg (not approved in the US or elsewhere) and sumatriptan 100 mg had similar adverse event reports.\textsuperscript{[38]} The low lipophilicity of almotriptan is thought to be the reason it has such low reports of adverse events.\textsuperscript{[39]}

Almotriptan was also shown to have favourable efficacy in triptan-naive patients for sustained freedom from pain and adverse events as well as recurrence at 24 hours versus triptan-experienced patients, making it a good first triptan after failure of NSAIDs in migraine treatment.\textsuperscript{[35]} It has also been reported to be more cost effective than sumatriptan for the endpoints of efficacy and tolerability.\textsuperscript{[40]}

In summary, almotriptan 12.5 mg is more effective than placebo, and is similar in efficacy to sumatriptan 100 mg, zolmitriptan 2.5 mg, rizatriptan 10 mg and eletriptan 40 mg. However, almotriptan has a much lower risk of adverse events than the other four, making it better tolerated and a good, cost-effective choice for triptan-naive patients. Clinicians often switch patients to almotriptan if two or more triptans have resulted in too many adverse events.\textsuperscript{[41]}

### 2.2.7 Eletriptan

Eletriptan is an effective acute care migraine medication with a rapid onset, similar bioavailability to other oral triptans and a slightly longer half-life than most other triptans, with the exception...
of frovatriptan and naratriptan (see table 1). Eletriptan 80 mg has been shown to be superior to sumatriptan 100 mg for 2-hour pain freedom (NNT = 7.0) and headache relief at 2 hours (NNT = 5.1). Eletriptan 80 mg also had a 10% better headache response and 25% lower recurrence at 24 hours versus sumatriptan 100 mg. Eletriptan 20 and 40 mg doses are not significantly different from each other in 2-hour pain freedom or in 2-hour headache relief.11

In a randomized, placebo-controlled European trial by Sandrini et al.42 in 2002, eletriptan 40 and 80 mg (only the 20 and 40 mg doses are approved in the US) were significantly superior to encapsulated sumatriptan 50 or 100 mg at 2 hours, with more patients on eletriptan 80 mg yielding a consistent response in pain relief.

In a review of eletriptan,43 the 20 mg dose was similar in efficacy to sumatriptan 100 mg, with eletriptan 40 and 80 mg superior in efficacy to sumatriptan 50 or 100 mg. In another article in 2003, Mathew et al.44 also reported superiority of eletriptan 40 mg over encapsulated sumatriptan 100 mg, and stated that the eletriptan 40 mg dose achieved significantly greater efficacy in functional response and had fewer adverse events. Thus, given its superiority to sumatriptan in the Mathew et al.44 and Sandrini et al.42 trials, the US FDA allows eletriptan 40 mg to be marketed as superior to sumatriptan 100 mg in head-to-head trials for 2-hour headache relief rates and all other endpoints studied. Some clinicians feel that the 80 mg dose would have been the most effective of all the triptans had it been approved by the FDA.

2.2.8 Frovatriptan

Frovatriptan has a much longer half-life than all other triptans at 26 hours and has few drug-drug interactions because of its dual route of metabolism due to its excretion by the kidney and metabolism in the liver via CYP1A2. It is 22–30% bioavailable and reaches peak plasma concentration at 2–4 hours.21

In a review of three randomized, double-blind, placebo-controlled, parallel group trials of over 2600 lifelong migraineurs, frovatriptan 2.5 mg was found to be superior to placebo for headache response at 2 hours (37–46% vs 21–27% for placebo, with therapeutic gain at 2 hours of 16–19%). It has a better therapeutic gain at 4 hours than naratriptan (frovatriptan ranging from 25% to 37% and naratriptan ranging from 26% to 34%).49 The 4-hour headache response rate is 66%. Pain-free response was significantly superior to placebo at 2 and 4 hours.49

Despite its efficacy versus placebo, frovatriptan is inferior to all other triptans for these efficacy endpoints at 2 hours but catches up in some of them at 4 hours. In that regard it is similar to naratriptan, which is slower in onset than the other triptans. Therefore, it is reasonable to look at both of these drugs at 4 hours rather than 2 hours to compare efficacy. Frovatriptan has been shown to be beneficial in menstrually-related migraine, with ‘mini-prophylaxis’ started about 2 days prior
to the menstrually-related headache. In two randomized, double-blind, placebo-controlled clinical trials, frovatriptan was found to be safe and effective for miniprophylaxis in menstrually-related migraine. The drug was given twice per day for 3 days, starting with a double dose. The FDA denied Endo Pharmaceuticals this indication for frovatriptan despite these two positive, well done, multicentre trials which were without serious adverse events.\[150\]

Despite its longer half-life, there is no significant difference in the headache recurrence rate for frovatriptan at 24 hours versus sumatriptan 100 mg, although it is lower than placebo.\[21\] Thus, a long half-life does not necessarily translate to a lower recurrence rate.\[49\] Adverse events are slightly higher than with placebo (47% vs 34%) but lower than sumatriptan 100 mg (43% vs 36%) and similar in quality to those from placebo, making frovatriptan an overall well tolerated medication.\[21\,49\]

In summary, although frovatriptan is one of the two slower-acting triptans, it is quite effective at 4 hours and has a good adverse event profile. Clinically, although considered slower acting, frovatriptan seems to work rapidly in about one-third of patients who take it early in the course of their migraine attack.

2.2.9 Summary

All triptans have been shown to be more effective than placebo and all have been compared with the oral tablet of sumatriptan 100 mg. The most effective triptans are similar to sumatriptan 100 mg and include rizatriptan 10 mg, eletriptan 40 mg, almotriptan 12.5 mg and zolmitriptan 2.5 mg.\[11\,25\,45\] Eletriptan 40 and 80 mg have been shown to be more effective than sumatriptan 100 and 50 mg in two large trials. The least effective triptans versus sumatriptan 100 mg are sumatriptan 25 mg, naratriptan 2.5 mg, eletriptan 20 mg and frovatriptan 2.5 mg.\[11\,14\,50\]

2.3 Safety

Safety is defined as a lack of clinically significant serious adverse events such as liver toxicity, myocardial infarction or stroke. This could manifest as a clinical state or significant laboratory finding. All triptans are considered safe with a very low potential risk of clinically significant serious adverse events. Contraindications to triptan use include uncontrolled hypertension, ischaemic heart disease, coronary vasospasm, cerebrovascular disease, peripheral vascular disease, and basilar or hemiplegic migraine.

The potential for coronary vasoconstriction is the most serious consideration for safety assessment. In a review article by Dodick et al.\[52\] in 2004, the post-marketing cardiovascular safety data of triptans was assessed. The authors describe the possible mechanism of chest sensations during triptan use as being the modest pressor response of muscular arteries (temporal and brachial) more than elastic arteries (carotid) when compared with placebo, as shown by applanation tonometry or ultrasound. Angiogram studies in patients after administration of triptans show mixed data of increased coronary diameter, unchanged diameter and slightly decreased diameter. The studies had small sample sizes and the significance of diameter changes cannot therefore be assessed. Even placebos cause a slight degree of arterial constriction. Positron emission tomography studies have also been performed on a few patients in some trials and have not found a significant decrease in myocardial perfusion despite patients having chest tightness after triptan administration while being scanned. ECG results in a study of 62 patients with 92 injections of sumatriptan showed no ischaemic changes despite 15% of patients having chest symptoms.\[53\] In their 2004 article, Dodick and colleagues\[52\] conclude that these chest symptoms are infrequent, not the result of myocardial ischaemia, are not serious, and other causes such as oesophageal or pulmonary changes require additional research to show causality.\[52\]

An FDA-issued alert in 2006 warned about serotonin syndrome as a possible risk for patients taking selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) with triptans. Despite several case reports, large controlled trials of more than 50 000 patients have not shown any reported cases of serotonin syndrome and only rare cases are seen by headache specialists in patients taking
these combinations of medications.\textsuperscript{[30]} Given their main mechanism of metabolism, hepatic failure is a contraindication to triptans. Renal impairment is a relative contraindication, with caution advised.

Drug-drug interactions include those most notably with monoamine oxidase (MAO) inhibitors, SSRIs, oral contraceptive pills containing oestrogen (OCPs), cigarettes and CYP3A4 inhibitors. Additionally, triptan-specific interactions can occur. Eletriptan (as well as DHE and ergotamine tartrate) is metabolized by the CYP3A4 hepatic enzyme system; thus, similarly metabolized medications could increase serum eletriptan concentrations causing increased adverse events. These drugs include antifungals such as ketoconazole, macrolide antibiotics such as clarithromycin, and some antivirals such as ritonavir. Eletriptan is contraindicated if the patient is on any one of seven specific CYP3A4 inhibitors.\textsuperscript{[43]} Zolmitriptan is unlikely to interact with other drugs given its low level of binding to plasma proteins, with the possible exceptions of MAO inhibitors and cimetidine. This includes relative safety with coadministration of MAO-B inhibitors, metoclopramide, propranolol and fluoxetine.\textsuperscript{[16]} The metabolism of rizatriptan is decreased by propranolol, causing increased plasma rizatriptan concentrations. If a patient is receiving propranolol, only 5 mg of rizatriptan should be given instead of the usual 10 mg. Other \(\beta\)-adrenoceptor antagonists (\(\beta\)-blockers) have not displayed these pharmacokinetic interactions. Almotriptan has fewer drug-drug interactions due to its multiple pathways of metabolism and, therefore, it is safe with MAO inhibitors or CYP inducers. Frovatriptan is not influenced by MAO inhibitors or other drugs. Naratriptan is the 'gentle triptan', with no known drug interactions.\textsuperscript{[54]} Patients who are smokers or on OCPs should avoid naratriptan. The three triptans contraindicated with MOA inhibitors are sumatriptan, rizatriptan and zolmitriptan.

### 2.4 Tolerability

Efficacy and tolerability are positively correlated; thus, higher sustained pain-free outcomes at 24 hours seem to be correlated with increased adverse events. However, patients are more willing to tolerate adverse events if there is better efficacy.\textsuperscript{[55]} Different triptans, by various routes of administration, differ in terms of efficacy and tolerability, with the best combination for a given patient obviously having high efficacy, good tolerability and ease of administration.

The subcutaneous route offers the fastest relief with the most rapid onset, but has low tolerability given that the injection can be painful and irritating to the skin with a higher risk of triptan-related adverse events. Oral tablets are easy to administer and generally have good tolerability if nausea and vomiting are not a big component of a patient's migraine attack.\textsuperscript{[13,16]} Nasal sprays offer a quicker onset of action than their comparable tablets and, thereby, more rapid relief, if the patient finds the taste tolerable.\textsuperscript{[17]} The nasal sprays are also a good way to bypass the GI tract in patients with poor absorption and nausea and vomiting. The ODT form obviates the need for water when nausea is a factor and is well tolerated and convenient, but does not work any faster than a tablet according to the literature.\textsuperscript{[18]} Nonetheless, some patients claim that it works faster for them. Adverse events do not cause safety issues but may decrease tolerability. They are considered irritating but not clinically significant or dangerous. Most adverse events do not stop patients from continuing to take that particular triptan. For example, dizziness, paraesthesias and a warm sensation may be tolerated if a drug has good efficacy. However, adverse events must be interpreted with caution. Most clinical trials report patients to have adverse events regardless of the number or type, and some are not drug related.\textsuperscript{[11]} When the frequency of adverse events is not reported, or when specific adverse events are not detailed, it leads to publication bias and limits interpretation of the data.\textsuperscript{[14]} Reviews of randomized controlled trials with significant heterogeneity are hard to interpret; adverse events and clinical endpoints should not be compared from one study to another, but only in a well done, head-to-head trial.

That being said, most triptans have adverse event risks above placebo except for naratriptan 2.5 mg, which has a similar adverse event profile...
The highest rates of adverse events reported were with use of eletriptan 80 mg, which is not available in the US. A review of triptan CNS adverse effects shows sleepiness, tiredness and difficulty thinking were most common and can lead to a delay in medication taking, which usually decreases triptan efficacy. In turn, this leads to decreased performance at work, school or home. Increased lipophilicity of a triptan, which results in better penetration into the CNS through the blood-brain barrier, is thought to produce increased CNS adverse effects. Thus, triptans with lower lipophilicity should be considered in patients who tend to experience more CNS adverse events.

Tolerability is best when adverse events rates are similar to those with placebo. High tolerability combined with good efficacy leads to optimal therapy for migraine and offers the highest patient satisfaction. Almotriptan 12.5 mg has been shown to be the best tolerated versus sumatriptan 100 mg, with fewer (30%) adverse events than expected given that higher efficacy is often correlated with lower tolerability. Lower doses of sumatriptan (25 mg), naratriptan 2.5 mg and eletriptan 20 mg were also better tolerated versus sumatriptan 100 mg, but all are less effective than sumatriptan. Conversely, eletriptan was reported in an article by Dodick et al. to have higher (20%) than expected adverse events given its efficacy. The authors concluded that the high adverse event rate was due to the lipophilicity of the compound penetrating the CNS more easily.

3. Conclusions

All triptans are generally effective, safe and well tolerated. Pharmacokinetic heterogeneity plays a role in triptan efficacy and tolerability, which can result in patients switching to alternative triptans or different doses or routes of administration. Most patients can find a triptan that gives them optimal results in migraine treatment. The current literature is limited to a few meta-analyses that compare all triptans. However, many randomized controlled trials are heterogeneous, making reviews and meta-analyses difficult to interpret. No one triptan is most effective in all clinical endpoints or outcomes, and they are certainly more alike than different. Some triptans can be more effective at higher doses, especially in patients who are less susceptible to adverse events. Regardless of triptan formulation or dose, there are very few patients who cannot tolerate triptans. It would be helpful to have alternatives for triptan nonresponders and patients in whom triptans are contraindicated. Thus, research on newer migraine acute care medications and delivery systems such as oral CGRP antagonists (telcagepant), orally inhaled DHE (Levadex™), oral fast-acting NSAIDs in solution (Cambia™), sumatriptan by skin patch (Zelrix™) and oral 5-HT7 receptor agonists is necessary and potentially promising.

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References


47. Sheffell FD, Ryan R, Pitman V. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a

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multicenter, double blind placebo controlled study conducted in the United States. Headache 2003; 43: 202-13


56. Dodick DW, Martin V.Triptans and CNS side-effects: pharmacokinetic and metabolic mechanisms. Cephalalgia 2004; 24: 417-24

57. Dodick DW, Sandrini G, Williams P. Use of the sustained pain-free plus no adverse events endpoint in clinical trials of triptans in acute migraine. CNS Drugs 2007; 21 (1): 73-82

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