**Therapeutics**

**Triptans for symptomatic treatment of migraine headache**

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A 30 year old woman has debilitating, pulsating right sided headaches up to twice a month for several years. Her pain builds up rapidly and usually lasts 24 hours. She has to lie down during episodes, which are associated with sensitivity to light, severe nausea, and occasional vomiting. Over the counter analgesics such as ibuprofen or paracetamol were initially helpful in relieving pain, but not recently. She asks if any treatments may help with her headaches and allow her to return to her usual activities sooner.

**What are triptans?**

Migraine is a common clinical problem, with a global prevalence of 14.7%, and is the eighth most common cause globally of years lived with disability. The triptans are selective 5-hydroxytryptamine (5HT) receptor agonists, with high affinity for the 5HT1B and 5HT1D receptors. 5HT1D receptors are on smooth muscle cells of blood vessels and cause vasoconstriction when stimulated. 5HT1B receptors lie on perivascular trigeminal nerve terminals and in the dorsal horn, and their stimulation blocks the release of vasoactive peptides from trigeminal neurons and the release of neurotransmitters in the dorsal horn that convey nociceptive information to the thalamus. Seven triptans are commercially available—sumatriptan, naratriptan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, and almotriptan—with minor pharmacokinetic and pharmacodynamic differences between them. Sumatriptan was the first commercially available triptan and has been used in clinical practice since the early 1990s. Several different vehicle delivery systems are available for these drugs, including a subcutaneous injection, nasal spray, rapid melt tablet, and oral tablet (see table for formulations available, dosages, onset of action, number needed to treat, and drug interactions).

**How well do triptans work?**

Three systematic reviews of sumatriptan for the acute treatment of migraine were published in the Cochrane Library in 2012. They evaluated the oral tablet, nasal spray, and subcutaneous injection versus placebo or other treatments. These reviews found that the number needed to treat (NNT) for a pain-free response at two hours was 6.1 (95% confidence interval 5.5 to 6.9) for sumatriptan 50 mg tablet, 4.7 (4.3 to 5.1) for sumatriptan 100 mg tablet, 2.3 (2.1 to 2.4) for sumatriptan 6 mg subcutaneous injection, and 4.7 (4.0 to 5.9) for sumatriptan 20 mg nasal spray.

A recent systematic review and meta-analysis of 74 randomised controlled trials of oral triptans versus placebo or other triptans for acute treatment of migraine has shown that all seven triptans are superior to placebo, with a significantly greater odds of being pain free at two hours compared with placebo. Odds ratios and 95% credible intervals ranged from 1.68 (1.04 to 2.72) for naratriptan 2.5 mg, to 4.95 (3.75 to 6.59) for eletriptan 40 mg. Although this meta-analysis of multiple treatments found differences in efficacy between the various tablet formulations of the triptans, in clinical practice differences between patients seem more important than the differences between drugs. The response of individuals with migraine to a specific acute drug is unpredictable. If a patient does not respond well to one triptan, other triptans should be tried in subsequent attacks.

The Canadian Headache Society guideline strongly recommends the use of triptans for acute treatment of migraine attacks that are likely to become moderate or severe; this recommendation is based on high quality evidence. If patients experience initial substantial headache relief from a triptan, but this is followed by a recurrence (return of a more severe headache within 24 hours), a second triptan dose is usually effective. These guidelines also make a strong recommendation based

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**Triptans: pharmacokinetics; drug interactions; and NNT for 2 hour pain-free response**

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Formulations available</th>
<th>NNT for 2 hour pain free response vs placebo</th>
<th>Onset of action</th>
<th>Important drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Subcutaneous 6 mg; nasal spray 20 mg; tablet 50 mg, 100 mg</td>
<td>Subcutaneous 2.3 (95% CI 2.1 to 2.4)⁴; nasal spray 4.7 (4.0 to 5.9)³; 50 mg tablet 6.1 (5.5 to 6.9); 100 mg tablet 4.7 (3.3 to 5.3)³</td>
<td>Subcutaneous 15 min; nasal 15 min; oral 30 min</td>
<td>MAOIs (avoid use within 14 days); ergotamine, DHE, other triptans (within 24 hours)</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Tablet 12.5 mg</td>
<td>5.2 (4.0 to 7.2)²</td>
<td>0.5-2 h</td>
<td>Ergotamine, DHE, other triptans (within 24 h)</td>
</tr>
<tr>
<td>Ertiriptan</td>
<td>Tablet 20 mg, 40 mg</td>
<td>40 mg tablet 4.5 (3.9 to 5.1)¹</td>
<td>0.5-1 h</td>
<td>Contraindicated within 72 h of potent CYP3A4 inhibitors (such as ketoconazole, itraconazole); ergotamine, DHE, other triptans (within 24 h)</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Tablet 2.5 mg</td>
<td>12 (10 to 15)⁶</td>
<td>Precise data not available; slow onset for most patients</td>
<td>Ergotamine, DHE, other triptans (within 24 hours)</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Tablet 2.5 mg</td>
<td>8.2 (5.1 to 21)⁷</td>
<td>1-3 hours</td>
<td>Ergotamine, DHE, other triptans (within 24 hours)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Tablet 10 mg; orally disintegrating tablet 10 mg</td>
<td>3.1 (2.9, 3.5)⁷</td>
<td>0.5-1 h</td>
<td>MAOIs (avoid use within 14 days); propranolol (increased bioavailability of rizatriptan; maximum single dose 5 mg of rizatriptan, and 10 mg/24 h); ergotamine, DHE, other triptans (within 24 h)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Tablet 2.5 mg; orally disintegrating tablet 2.5 mg; nasal spray 5 mg</td>
<td>Table 5.9 (4.5 to 8.7)⁷</td>
<td>Oral 45 minutes; nasal 10-15 minutes</td>
<td>MAOIs (avoid use within 14 days); CYP1A2 inhibitors (such as cimetidine, fluvoxamine, ciproflaxacin); ergotamine, DHE, other triptans (within 24 h)</td>
</tr>
</tbody>
</table>

*NNTs presented are not derived from head to head comparative studies.
1CYP3A4; LA2=cyclooxgenase PGi50 34A/1A2, DHE=dihydroergotamine; MAOI=monoamine oxidase inhibitor; NNT=number needed to treat.
on moderate quality evidence that if a patient does not respond well to one triptan or tolerates it poorly, other triptans should be tried over time in subsequent attacks. It is recommended that patients wait 24 hours before trying another triptan.

UK National Institute for Health and Care Excellence (NICE) guidelines recommend that clinicians offer combination therapy with an oral triptan and a non-steroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, for the acute treatment of migraine.11 For people who prefer to take only one drug, the NICE guidelines recommend considering monotherapy with an oral triptan, NSAID, aspirin, or paracetamol. NICE recommends, when prescribing a triptan, to start with the triptan with the lowest acquisition cost, and if this is consistently ineffective, try one or more alternative triptans.

**How safe are triptans and what are the precautions?**

Overall, triptans are well tolerated, with most adverse events reported in randomised controlled trials being of mild or moderate severity and self limiting. According to the Cochrane systematic review of oral sumatriptan, the number needed to harm for any adverse event (regardless of severity) 24 hours after taking a dose is 13 for sumatriptan 50 mg versus placebo, and 5.2 for sumatriptan 100 mg versus placebo.2

**Cardiovascular safety**

Concerns about the cardiovascular safety of the triptans arise from the fact that 5HT1B receptors are present on coronary arteries. Triptans are therefore contraindicated in people with coronary artery disease, cerebrovascular disease, peripheral vascular disease, and uncontrolled hypertension. The triptan cardiovascular safety expert panel of the American Headache Society has concluded that although serious cardiovascular adverse events have occurred with triptans, the frequency of these events in clinical trials and in practice is fewer than one per million exposed.12 Around 1-7% of participants in clinical trials (without cardiovascular disease) experience “triptan sensations”—a burning, tingling, or tightness in the face, neck, limbs, or chest—which is not associated with electrocardiographic or enzymatic evidence of myocardial ischaemia.

**Drug interactions (also see table)**

In 2006, on the basis of 29 case reports, the United States Food and Drug Administration issued a warning about the potential for serotonin syndrome in patients taking triptans concomitantly with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline (norepinephrine) reuptake inhibitors (SNRIs). The American Headache Society critically examined these 29 cases and found that only 10 cases met Stembach criteria for diagnosing serotonin syndrome. The society concluded that the evidence from these case reports does not support limiting the use of triptans with SSRIs or SNRIs.13 Concomitant use of ergotamine within 24 hours of triptan use is contraindicated.

Concomitant use of monoamine oxidase inhibitors within two weeks is contraindicated with some triptans (table).

**Pregnancy**

Triptans are not recommended for use in pregnancy (rated FDA category C).14

**Breast feeding**

Data on the compatibility of triptans with breast feeding are scarce. Drugs with a relative infant dose of less than 10% of the maternal dose are generally considered compatible with breast feeding, and a dose of less than 10% has been confirmed in single studies of breast milk in women using sumatriptan and eletriptan only. As a class, it is thought that the triptans are probably compatible with breast feeding.15

**Medication overuse headache**

Triptans should be used on no more than nine days a month. Caution patients about the possibility of medication overuse headache—a near daily headache that can develop from regular overuse of triptans for three or more months. Headaches typically revert to their previous pattern within two months of discontinuing overuse.

**How cost effective are triptans?**

The NICE guidelines included a cost-utility analysis for the acute oral treatment of migraine, considering costs and quality adjusted life years (QALYs) from a UK NHS and personal social services perspective, with the sustained pain-free response at 24 hours as the intermediate outcome incorporated into the model.13 The cost of only one drug administration per acute migraine was included in the model. Interventions were ranked according to their mean net benefit, which depends on cost, QALYs, and willingness to pay (set at £20 000 (€24 200; $33 200)/QALY). Overall, triptan plus NSAID combination therapy was ranked the most cost effective treatment, followed by triptan plus paracetamol, and triptan monotherapy.

**How are triptans taken and monitored?**

Triptans can be taken orally (tablet or rapid melt formulation), intranasally, or subcutaneously. Consider patient preference and the characteristics of migraine attacks when recommending a particular drug formulation, because certain formulations have advantages over others in specific situations. For migraine attacks that reach maximal intensity rapidly or that are associated with early vomiting, subcutaneous sumatriptan may be more effective. People with severe nausea and vomiting later on in the attack may find nasal spray formulations more helpful than tablets. Patients whose nausea is exacerbated by taking fluids may find the orally dissolving tablet (rapid melt formulation) helpful.16

Advise people with migraine attacks that are usually of moderate to severe intensity if untreated to take triptans as early as possible after the onset of headache, while pain is still mild. Randomised controlled trials have found improved efficacy with early treatment.19 Provide education on medication overuse and how to differentiate migraine from tension-type headaches. The number of times a triptan can be used within a 24 hour period varies by drug, initial administered dosage, and jurisdiction.

In patients whose migraine attacks respond incompletely or inconsistently to triptans, or often recur within
TIPS FOR PATIENTS

Discuss with your doctor which triptan formulation is most appropriate for you, given the characteristics of your migraine attacks.

Learn how to tell the difference between migraine attacks and tension-type headaches on the basis of the features of your headache. Tension headaches are usually a mild, pressing, or tightening type of pain on both sides of the head and are not associated with nausea or vomiting. In contrast, migraine attacks are often associated with nausea or vomiting, pain is moderate to severe with a pulsating quality, and pain often occurs on one side of the head only.

If you are having a migraine, take your drug(s) as soon as possible, while the pain is still mild. Drugs are more likely to be effective if taken early.

Do not take triptans on more than nine days a month, because this may increase headache frequency (medication induced headache).

Triptans are not appropriate if you have a history of vascular disease, such as a heart attack, stroke, or very high blood pressure that is uncontrolled.

24 hours, multiple randomised controlled trials provide evidence that taking sumatriptan with a NSAID (naproxen) can improve headache response and some evidence that it can reduce headache recurrence.11

For patients who have migraine with typical aura, there is evidence that it is safe to take the triptan during the aura, although the triptan may be more effective if taken at the onset of pain rather than earlier in the aura. Randomised controlled trials in which triptans were taken during the aura phase rather than during the headache failed to show a significant difference from placebo in headache response.18-20 One of the concerns regarding triptan use during the aura phase relates to potential difficulties in differentiating early stroke symptoms from migraine aura. Although this is not a concern in most patients with an established history of migraine with visual aura, caution is warranted in those with more complex aura presentations.

The patient in our case scenario has severe headaches that increased rapidly in intensity and were associated with marked nausea and occasionally with vomiting. Although a rapidly acting oral triptan (such as rizatriptan, eletriptan, sumatriptan, zolmitriptan, or almotriptan) may be satisfactory for many of her attacks if she can treat early, she may find a nasal spray with good evidence for transnasal absorption (for example, zolmitriptan 5 mg) more efficacious. Self injected sumatriptan 6 mg may be the most efficacious treatment for her. If she does not wish to use an injection for every attack, she might still find it useful for selected attacks that she cannot treat early, or those with more pronounced nausea.

How do triptans compare with other drugs?

Relatively few randomised controlled trials have compared triptans with other classes of drugs for acute migraine, and most have compared sumatriptan with drugs such as ergotamine, dihydroergotamine, and various NSAID or paracetamol combinations with or without antiemetics. Most trials found non-significant differences between treatments, with the exception of trials that compared sumatriptan with ergotamine and dihydroergotamine, which found significantly higher rates of headache relief with sumatriptan.10 A recent Cochrane review of naproxen for acute migraine found an NNT of 11 (8.7 to 17) for a pain-free response at two hours with naproxen 500-825 mg compared with placebo,10 which is higher than the NNT for all triptans for this outcome. The lack of superiority of triptans to NSAIDs in randomised controlled trials contrasts with experience in clinical practice, where triptans are often superior to non-specific acute drugs. This discrepancy may be partly due to patient selection, as some comparative trials excluded patients with severe symptoms, or because most patients seen in headache specialty clinics have already tried and not responded to non-specific treatments.

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References are in the version on bmj.com.

Proceduralist’s neck

Musculoskeletal maladies are unique in that they are often named after the occupation where they are most common, such as “housemaid’s knee,” “tennis elbow,” and “writer’s cramp.” I would like to add a further condition to this lexicon, one that pertains to the medical profession, and those performing procedures in particular.

This condition, I suspect, may be a consequence of adopting a less than ideal posture while standing, or indeed seated, in the operating theatre, catheter laboratory, or endoscopy suite. When leaning over patients, one typically develops a reduced lumbar lordosis, increased thoracic kyphosis, and a marked cervical hyperextension, leading to a characteristic “question-mark” stoop, from which the proceduralist’s neck gets its name.

This may lead to acute and chronic spine problems, particularly if one maintains this posture for long periods, such as after long or multiple procedures with no or few breaks. As the variety and severity of conditions that can be intervened upon increases—by resection, revascularisation, or resynchronisation—perhaps we need to look at protecting our backs from preventable harm, although this is easier said than done.

It would be interesting to know just how common spine problems are in the medical profession (being well known among nursing staff) and whether they are any more common in those with a procedural leaning (pun intended).

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