

REVIEW



# Acute mig

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*Practical Neurology*, 2004, 4, 6–19

### INTRODUCTION

Primary headache disorders are the most frequent reason for referral to neurologists worldwide, and most of these patients have migraine (Menken 1996; Sempere *et al.* 2002; Rajput *et al.* 1988). Migraine is a common and frequently incapacitating headache disorder characterized by episodic attacks of moderate-to-severe headache, along with various combinations of neurological, gastrointestinal and autonomic symptoms (Goadsby *et al.* 2002). The one-year prevalence of migraine is 11% in the United States and Western Europe (6% for males and 15–18% for females) and one quarter of migraine patients experience one or more attacks per week (Goadsby *et al.* 2002; Hamelsky *et al.* 2001). A recent report by the World Health Organization ranks migraine as one of the most disabling chronic conditions and equates a day with severe migraine to the disability associated with a day with quadriplegia, psychosis or dementia (Menken *et al.* 2000).

The aggregate impact of migraine on quality of life reflects not only the pain severity and associated symptoms, but also its effect on psychological well-being, family relationships and occupational performance. Migraine headaches are invariably: intense, > 80% of patient describe the pain as severe or very severe; frequent, median attack frequency 1–2 migraines/month; long-lasting, about two-thirds of attacks in women, and one-half of attacks in men last longer than 24 h; and up to one-half of attacks

begin in the early morning between 4 am and 9 am (Hamelsky *et al.* 2001; Fox & Davis 1998).

The most unpleasant associated symptoms are nausea and vomiting. In 500 self-reported migraine sufferers, just over one-half experienced nausea in more than half their attacks, and nearly one-third experienced nausea and vomiting during every attack (Silberstein 1995). In the American Migraine Study II, almost all migraine sufferers reported some functional impairment associated with their headache (Lipton *et al.* 2001). As a result, it is not surprising that recent estimates in the USA indicate that migraine sufferers spend a total of 112 million days bedridden, and health-related quality of life is significantly lower than population norms (Hu *et al.* 1999; Dahlof & Solomon 1998).

### TREATMENT OPTIONS FOR THE ACUTE ATTACK

There is now the potential for most migraine patients to achieve significant and lasting relief of pain; physicians and patients have at their disposal numerous options:

- non-pharmacological therapy biofeedback and relaxation therapy;
- non-specific analgesia – acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, combination agents containing caffeine, isometheptene, barbiturates and/or opiates;
- migraine-specific therapy (dihydroergotamine and the triptans) (Silberstein 2000).

# migraine which triptan?

The acute treatment of migraine was revolutionized in 1991 by the introduction of sumatriptan (Humphrey 2001). This was quickly followed by the 'second-generation' triptans and now there is a wide array of triptan options in a variety of formulations (Table 1). The efficacy and safety of the triptans have been well established after 15 years of clinical trials and experience. Triptans have become the standard of care for moderate to severe migraine headache, and for those with mild attacks who have failed to respond to non-specific analgesia. Triptans represent a multibillion dollar industry worldwide and correspondingly there are extensive marketing campaigns emphasizing the differences between the various triptan options.

With so many options available, it is difficult to decide which treatment is best in general and, more importantly, which treatment is best for the specific patient sitting in the physician's office. This challenge is evident from US and European population surveys, which showed that only about one-third of patients are completely or very satisfied with their current acute migraine therapy (Lipton & Stewart 1999; MacGregor *et al.* 2003). The most common reasons for dissatisfaction were pain relief takes too long (87%), incomplete pain relief (84%), the medications were inconsistently effective (84%), and headache recurrence (71%). Only one-third complained about adverse effects (Lipton & Stewart 1999). One of the main reasons for these findings may be that – remarkably – only about 10% were prescribed a triptan (MacGregor *et al.* 2003).

## EVALUATING THE EFFICACY OF TRIPTANS

The clinical development programme of the triptans over the past 15 years has been extensive, and a large number of outcomes have been used in the clinical trials (International Headache Society Committee on Clinical Trials in Migraine 1991; Tfelt-Hansen *et al.* 2000). Headache response is defined as a decrease in headache intensity from moderate-to-severe to mild-to-none, evaluated at prespecified time points (i.e. 1, 2 or 4 h). A pain-free outcome (moderate-severe to none) has also been measured at prespecified time intervals (i.e. 2, 4 or 24 h). By convention, recurrence of headache means the re-emergence of a moderate-to-severe headache after an initial headache response. Consistency of response refers to reproducible pain relief from attack to attack. Other commonly used secondary outcomes are the ability to diminish nausea, vomiting, photophobia and phonophobia. Reduction in clinical disability refers to the medication's ability to reduce functional impairment due to headache pain and any associated symptoms. Overall, these outcomes may be measured within a single attack or across multiple attacks.

Most of these outcome measures are pre-specified as a mandatory component in clinical trials to satisfy licensing requirements. However, pain-free outcomes (2-h pain free and sustained pain free over 24 h) are the most desired by patients (Lipton & Stewart 1999), and are now considered by the International Headache Society to be the standard by which all new acute migraine medications should be evaluated (Tfelt-Hansen *et al.* 2000).

## THE TRIPTANS

### How triptans work

The triptans are thought to act predominantly as agonists at the 5-HT<sub>1B/D</sub> receptor, although binding at other subtypes may be relevant to their therapeutic effect. During an attack of migraine, triptans, through stimulation of the 5-HT<sub>1B</sub> receptors on cranial blood vessels, are thought to lead to vasoconstriction that is relatively selective for these vessels, because vasoconstriction in the peripheral circulation is mediated predominantly by 5-HT<sub>2</sub> receptors. In addition, triptans activate inhibitory presynaptic 5-HT<sub>1D</sub> receptors located on the terminal endings of trigeminal nociceptive afferents, effectively decreasing the release of neuropep-

**Table 1** Migraine specific medications and formulations available

	TABLET	ORALLY DISINTEGRATING	NASAL SPRAY	INJECTABLE
Almotriptan	✓			
Eletriptan	✓			
Frovatriptan	✓			
Naratriptan	✓			
Rizatriptan	✓	✓		
Sumatriptan	✓		✓	✓
Zolmitriptan	✓	✓	✓	
Dihydroergotamine			✓	✓
Ergotamine tartrate	✓			

tides that are responsible for vasodilatation of meningeal and cerebral blood vessels, and for activation of second order neurons in the trigeminal nucleus caudalis. Recently, 5-HT<sub>1D</sub> receptors have been demonstrated on postsynaptic second order neurons within the caudal trigeminal nucleus. Whether triptans bind to and modulate the activity of these neurons is as yet unclear.

### What patients want from a triptan

The physician treating patients with migraine is now able to choose from seven triptans (Table 1). These products differ, to a greater or lesser extent, on a range of attributes whose importance may vary from patient to patient. One agent may have a faster onset of action while another may have greater efficacy over 24 h. One may give rise to a lower recurrence rate, while another may be better tolerated. The difficulty the physician faces is choosing among the alternative triptans to optimize treatment for an individual patient, whose needs are uniquely personal. How can the physician best match product attributes with patient characteristics? How can the patient's perspective be incorporated into the choice of triptan?

Insight into patients' hierarchical ranking of treatment attributes they most value is critical in matching patient needs to the appropriate treatment options. Lipton and colleagues asked individuals with migraine to rank which treatment attributes were important or very important: 87% indicated complete pain relief, 86% no headache recurrence, 83% rapid onset of action, 79% no adverse effects, 76% relief of associated symptoms, and 56% the route of administration (Lipton & Stewart 1999). In the TRIPSTAR analysis, migraine sufferers indicated that 1-h pain-free response was more important than tolerability, which in turn was considered more important than consistency of effect. This was consistent with the prioritization of treatment attributes by primary care physicians and neurologists. Based on these findings, pain-free and tolerability outcomes are the most important to consider when selecting the best triptan for an individual patient.

### Routes of administration

For each individual patient, the most appropriate route of administration is one of the most important factors in triptan selection. Gastroin-

testinal symptoms play a crucial role in drug efficacy and preference: gastric emptying may be delayed and oral drug absorption impaired during a migraine attack (even without nausea), nausea can interfere with the ability to take oral medications, and vomiting may result in drug loss (Volans 1978). Correspondingly, non-oral (IV, IM, subcutaneous, intranasal, rectal) and oral formulations that don't require liquids or exacerbate nausea (oral disintegrating tablets) have been designed to bypass the influence of these gastrointestinal disturbances (Gladstone & Gawel 2003).

### Tablets

Migraine sufferers and their physicians have seven options from which to select. Oral formulations are preferred by patients and have the advantage of greater convenience, patient familiarity, tolerability and lower cost. Potential disadvantages are slower absorption and onset of action, especially in patients with prominent nausea or vomiting. Although oral triptans have the same mechanism of action and very similar selective binding affinity to 5HT<sub>1B/D/F</sub> receptors, there are differences between them in terms of pharmacokinetic parameters, efficacy, tolerability and drug interactions.

### Oral disintegrating tablets/wafers

Fast-dissolving tablets (also known as oral disintegrating tablets/wafers) have rapidly gained acceptance as an important new drug delivery system (Gladstone & Gawel in press). The disintegrating tablets were developed as an alternative to conventional tablets, with the objective of offering greater patient tolerability and convenience. This novel formulation consists of a solid dosage form that rapidly dissolves or disintegrates on the tongue (within seconds) without the need for liquids or chewing. It is swallowed with saliva and absorbed from the gastrointestinal tract. Therefore rapid dissolving formulations may be useful for those patients who find it difficult to swallow tablets, and they may allow earlier treatment because they do not require water (Gladstone & Gawel 2003): they can be taken anywhere (e.g. while driving or at a business meeting) at the onset of a migraine attack (i.e. before the headache increases in severity). There are two oral-disintegrating tablet formulations currently available: rizatriptan (Maxalt-MLT®) and zolmitriptan (Zolmitriptan-ZMT®).

The choice of medication and route of administration depends on the intensity and how quickly the pain peaks, the timing and intensity of gastrointestinal symptoms, and the patient's prior experience with non-specific analgesics

#### Parenteral

Parenteral formulations offer the fastest and most effective relief of headache. As early as 10 min after subcutaneous injection, sumatriptan provides superior headache relief compared with placebo and, by 2 hours, headache response rates and pain-free rates are approximately 80% and 60% (Dahlof 2001). Although parenteral formulations have the disadvantages of inconvenience, expense, patient discomfort and greater adverse effect rates compared with oral formulations, they should be considered for patients in whom significant nausea or vomiting precludes (or makes difficult) oral administration of medication, who have rapid onset and progression of pain, whose pain quickly reaches severe intensity, and in patients who fail to respond to any oral or intranasal triptans. Sumatriptan is the only triptan currently available with a parenteral formulation (Dahlof 2001).

#### Intranasal spray

Intranasal formulations provide another potentially fast and effective alternative for patients who find parenteral drugs too invasive and oral medications too difficult to tolerate because of nausea and vomiting (Gladstone & Gawel 2003). Advantages include convenience (relative to subcutaneous administration) and speed of onset of headache relief. The disadvantages include nasal irritation, bitter after-taste, less discreet administration, inconsistent absorp-

tion, and variable efficacy because of incorrect self-administration technique. Sumatriptan nasal spray has been available for several years, while zolmitriptan nasal spray has recently become available in several European countries and the United States.

#### Rectal suppositories

Absorption via the rectal mucosa is another alternative route of administration for migraineurs with significant nausea and/or vomiting. This has the advantage of partial avoidance of first pass metabolism of the liver, thereby leading to high and consistent drug levels. The major disadvantages are inconvenience, discomfort, lack of patient acceptability in some parts of the world, possible irritation of the rectal mucosa, interruption of absorption by defecation, and erratic absorption (Gladstone & Gawel 2003). Currently, rectal sumatriptan suppositories are available in several European countries but not in North America.

#### When to use the triptans

The objective of acute migraine therapy is to restore the patient's ability to function normally by rapidly and consistently relieving pain and the associated symptoms of nausea and vomiting, without recurrence of pain within 24 h, and with minimal or no adverse effects (Gladstone & Dodick 2003). The choice of medication and route of administration depends on the intensity and how quickly the pain peaks, the timing and intensity of gastrointestinal symptoms, and the patient's prior experience with non-specific analgesics (almost all patients have tried one or more before seeking medical advice).

Recent evidence-based guidelines from a multidisciplinary headache consortium in the USA recommend migraine specific agents (triptans, dihydroergotamine, ergotamine tartrate) in patients with moderate-to-severe migraine or whose mild-to-moderate headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen (paracetamol) plus caffeine (Silberstein 2000). It is recommended that a non-oral route of administration be used for patients with severe nausea or vomiting. It is also important to try to limit the use of any acute migraine medications to no more than 2 days per week to avoid medication overuse headache. And of course it is important to remember that treatment with triptans for acute migraine does not exclude concomitant treatment with certain other symptomatic

therapies. Co-administration of a triptan with a NSAID, or a rapidly dissolving aspirin preparation, is a reasonable and often effective approach. Additionally, for those with prominent nausea, an anti-emetic should be considered.

### How to use the triptans

Perhaps the most important aspect of acute migraine treatment is the timing of drug administration in relation to the pretreatment intensity and onset of the attack (Pascual 2002). It has clearly been demonstrated that triptans can prevent, but not reverse, central sensitization, a phenomenon that occurs in approximately three-quarters of patients 20–60 min into the attack (Burstein *et al.* 2001). Experimental, open-label and randomized controlled trials confirm what has been known intuitively for decades – acute therapy is more effective when given early in the attack or while pain intensity is mild. Treatment while pain is mild has been shown to increase the percentage of patients pain-free and back to normal function at 1, 2, and 24 h, and decreases attack progression and headache recurrence (Pascual 2002). Therefore, triptans should be administered as soon as possible after the onset of the attack, especially in those patients who have recognized that late treatment does not provide prompt and effective pain relief. However, patients who report at least one attack per week, or frequent non-migraine headache, must be educated that excessive use of triptans (> 2 days per week) can lead to medication-overuse headache.

### WHICH TRIPTAN TO CHOOSE

The six second-generation triptans that have followed sumatriptan are all structurally similar, they all act on the same 5HT<sub>1B/D</sub> receptor complexes with broadly comparable receptor-binding affinities, but each has been designed to differ somewhat from sumatriptan with respect to their pharmacokinetic profiles (Table 2). It was hoped that these differences would translate into clinically meaningful treatment differences.

The triptans have been evaluated in many double-blind, placebo-controlled trials, but in substantially fewer head-to-head trials, and together they have been evaluated in two meta-analyses (Ferrari *et al.* 2001; Oldman *et al.* 2002). Unfortunately in many studies, especially comparator trials, there are methodological flaws or shortcomings in statistical analysis, and meta-analysis is problematic due to differences in patient populations, study periods and study design. Consequently, there is a significant degree of scholarly debate world-wide surrounding the merits and weaknesses of many of the trials and the meta-analyses (Salonen 2002). Here we will try to provide a rational approach to triptan selection based on the evidence and personal experience.

When approaching the acute treatment of migraine it is important to realize that the differences between individual patients are greater than the differences between individual triptans (Saper 2001). There are significant differences between patients in attack profile and treat-

**Table 2** Pharmacokinetic parameters

DRUG	TIME TO PEAK LEVELS	ELIMINATION HALF-LIFE (HOURS)	BIOAVAILABILITY (%)	PRIMARY ELIMINATION
Almotriptan*	1.5–2 h	3.5	70	Renal 55%; CYP3A4 12%; MAOA 26%
Eletriptan	1.5–2 h	4	50	Hepatic, CYP3A4
Frovatriptan	2–4 h	26	22–40	Renal 38–49%; CYP1A2
Naratriptan	2–3 h	6	74 (f) 63 (m)	Hepatic, CP450/renal
Rizatriptan	1–1.5 h	2	40–45	Hepatic/renal
Sumatriptan oral	2–3 h	2	14	Hepatic, MAOA
Sumatriptan sc	12 min	1.9		Hepatic, MAOA
Zolmitriptan	1–1.5 h	2.5	40–46	Hepatic, MAOA

MAOA, monamine oxidase.  
\*Dahlof 2001.

ment preferences, and significant heterogeneity within patients in attack characteristics. Correspondingly, before selecting a triptan for an individual patient, it is crucial to have a complete understanding of their migraine attack profile including:

- typical time of migraine onset (during the night, upon morning awakening, or during the day);
- rapidity of onset of an attack (maximal severity reached abruptly, within 30 minutes or gradually);
- usual severity of attacks (mild, moderate or severe intensity);
- presence and timing of any gastrointestinal symptoms;
- typical level of disability (bed-bound, ability to function or work productivity decreased);
- frequency and pattern of attacks (sporadic or clustered such as menstrual migraine).

Furthermore, the clinician needs to know about previous experience with non-triptan acute medications, and triptans including efficacy, consistency, treatment strategy employed (early or delayed), headache recurrence, and frequency of adverse effects. Additionally, the clinician must inquire about the patient's acceptance of potential treatment modalities (Table 3). The following seven scenarios illustrate clinically relevant circumstances in which the clinician can use his or her knowledge of the individual triptans and their formulations to tailor treatment decisions to the particular patient (Fig. 1 and Table 4).

**Table 3** Information to gather before making treatment decisions

<b>Attack characteristics</b>
Typical time of migraine onset (upon awakening, during the day, during sleep)
Time to peak pain intensity
Usual severity and degree of impairment
Presence and timing of any gastrointestinal symptoms
Frequency and pattern of attacks (sporadic or clustered such as menstrual migraine)
<b>Previous treatment failure</b>
Determine reason for 'failure'
Efficacy
Consistency
Delayed strategy
Headache recurrence
Adverse effects
<b>Treatment preferences</b>
Route of administration
Treatment priority (rapid onset, pain-free, sustained response, tolerability)

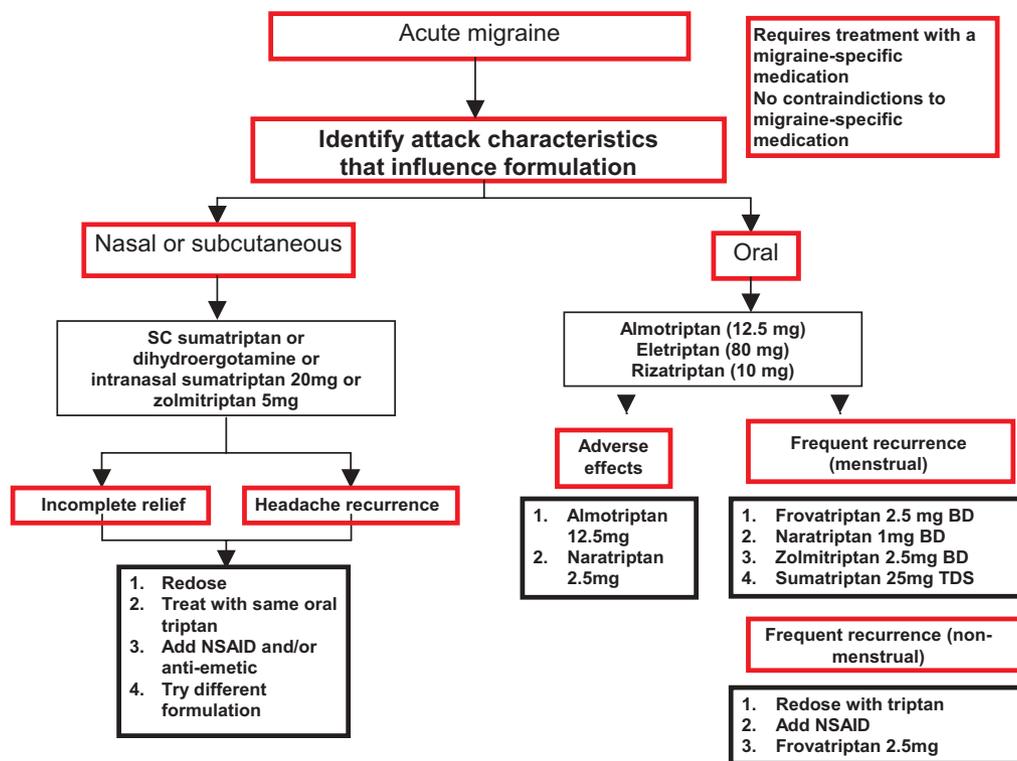


Figure 1 Treatment algorithm.

Table 4 Triptan selection in a variety of common clinical scenarios

Daytime migraine associated with moderate-to-severe intensity
Oral triptan – first-line agents almotriptan 12.5 mg, eletriptan 80 mg (if available), rizatriptan 10 mg
Pain, or gastrointestinal symptoms which evolve rapidly (including attacks which occur during sleep or upon awakening)
Subcutaneous sumatriptan
Intranasal sumatriptan, zolmitriptan or dihydroergotamine
Fast-acting oral triptan (almotriptan, eletriptan, rizatriptan, sumatriptan, zolmitriptan)
Previous adverse effects or tolerability a major concern
Almotriptan 12.5 mg
Naratriptan 2.5 mg
Headaches of long duration (> 24 h) and/or frequent headache recurrence
Non-menstrual
Early treatment with 1st-line oral triptan (consider combining triptan plus NSAID)
Almotriptan 12.5 mg
Eletriptan 40/80 mg
Rizatriptan 10 mg
Use triptan with long half-life
Frovatriptan 2.5 mg
Naratriptan 2.5 mg
Menstrual migraine
Short-term prevention with triptan (if frequent recurrence and NSAIDs or oestrogen not effective)
frovatriptan 2.5 mg bd
naratriptan 1 mg or 2.5 mg bd
zolmitriptan 2.5 mg bd
sumatriptan 25 mg tds
Always use the same brand (e.g. sumatriptan or zolmitriptan) if patients require more than one formulation.

### Daytime migraine of moderate-to-severe intensity

This presentation is typical of most migraine sufferers and most migraine attacks. Fortunately, at least three-quarters of these patients can be treated successfully with one of the triptans. The onset of action of most of the oral triptans (oral and oral disintegrating tablets) is 30–60 min, 15 min for sumatriptan intranasal sprays and 10 min with subcutaneous sumatriptan (and intranasal zolmitriptan) (Fig. 2). Currently, in this population of patients, oral sumatriptan is the most commonly prescribed triptan for a variety of reasons: physician and patient familiarity, the most extensively studied, the largest range of approved doses (three) and formulations (four), and the largest postmarketing cardiovascular and pregnancy safety experience. However, a recent meta-analysis (Ferrari *et al.* 2001) suggests that the 2-h pain-free and sustained pain free efficacy outcomes are greatest with eletriptan 80 mg, rizatriptan 10 mg and almotriptan 12.5 mg. Based on the two meta-analyses and the TRIPSTAR analysis (Ferrari *et al.* 2001; Oldman *et al.* 2002; Dodick *et al.* 2002b), any of these oral triptans would be reasonable first-line agents in triptan-naïve patients who do not have attack characteristics that would preclude the use of oral therapy for a significant proportion of their attacks.

### Prominent or early gastrointestinal symptoms

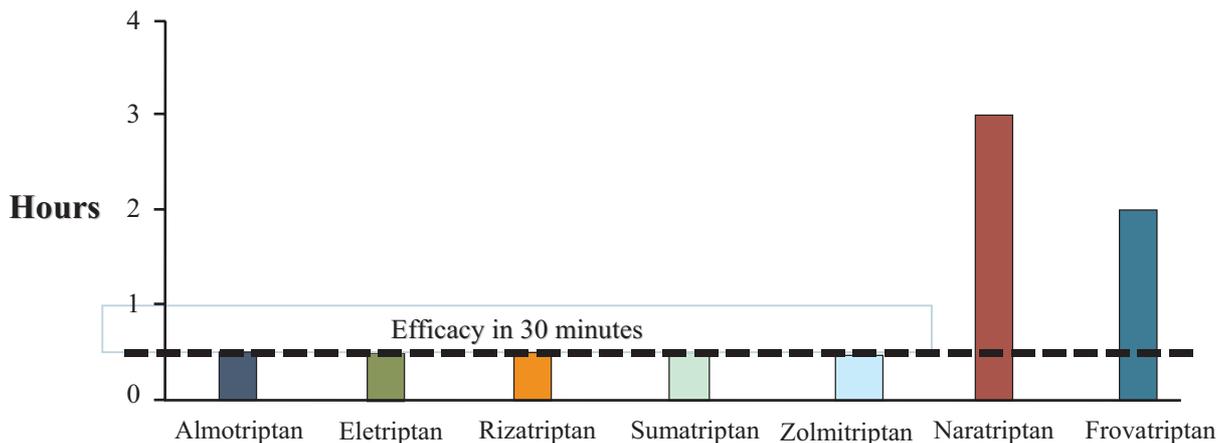
A substantial proportion of migraineurs suffer needlessly because their nausea and vomiting

are not reported to or recognized by physicians (Fox & Davis 1998; Becker 1999). They suffer not only directly as a result of the morbidity associated with these symptoms, but also indirectly as nausea may lead to a delay in treatment and impaired oral absorption. Severe nausea and vomiting will usually preclude the use and certainly impede the effectiveness of oral agents.

Patients with prominent gastrointestinal symptoms may be first tried on a combination of an oral tablet with an anti-emetic (either oral or as a rectal suppository). The oral triptan should be one with an early onset of action, or an orally disintegrating tablet. Failing this, patients should be quickly switched to non-oral formulations (subcutaneous, intranasal, rectal). Typically, an oral tablet that is the same compound as the alternative non-oral formulation is given for any headache recurrence, or for attacks without significant gastrointestinal upset (e.g. zolmitriptan tablets in patients administered zolmitriptan nasal spray).

### Migraine that awakens patients or appears upon awakening

Patients who awake from their sleep with a migraine, and those who awake in the morning with migraine, typically have attacks that are fully developed when they first become aware of them and so require acute therapies with a rapid onset of action. Subcutaneous sumatriptan is the fastest acting triptan due to its rapid absorption and high bioavailability. In randomized, placebo-controlled studies,



**Figure 2** Time to onset of efficacy of the oral triptans based on randomized controlled trials (with permission from Dahlof C, Dodick DW, Dawson AJ, *et al.* Almotriptan: extending therapeutic options in migraine. *Headache* 2002, **42**, 99–113).

sumatriptan provided superior headache relief compared to placebo as early as 10 min after subcutaneous injection (Dahlof 2001). Subcutaneous sumatriptan is the only triptan systematically studied in placebo-controlled trials of early morning migraine therapy (Bousser *et al.* 1993; Winner *et al.* 2003). In one, 2-h headache response was significantly more likely with subcutaneous sumatriptan than with placebo across two attacks (78% first attack, 70% second attack vs. 28% first attack, 20% second attack) (Bousser *et al.* 1993). In a similar study, significantly more subcutaneously treated patients were pain-free at 2 h (49% vs. 17%) and significantly more were able to function normally at 2 h (55% vs. 22%). Alternatively, initial therapy with an intranasal triptan (sumatriptan or zolmitriptan) may be considered as both provide headache relief as early as 15 min after drug administration (Dahlof 2001; Charlesworth *et al.* 2003). Importantly, in the subcutaneous sumatriptan study, 35% of subcutaneous sumatriptan-treated patients had headache recurrence. Therefore, it is important to provide education on redosing with a matched (i.e. the same drug) oral triptan.

### **Migraine that reaches peak intensity rapidly**

Treating headaches that start during the day and reach maximal intensity rapidly is like treating early morning headache. It is desirable to use a medication that is rapidly absorbed and reaches maximal concentration quickly. Therefore, subcutaneous or intranasal formulations are particularly useful when rapid relief is required due to work or other obligations. Intranasal zolmitriptan is unique amongst the nasal sprays used for migraine in that approximately 40% of the drug is absorbed through the nasal mucosa. This results in rapid appearance of the drug in serum within 2 minutes, appearance in the brain at 5 minutes, and 40% of the  $c_{max}$  is achieved within 15 minutes.

### **Headaches of long duration and/or frequent headache recurrence**

Many patients complain of migraines, treated or untreated, lasting 24, 48 or even 72 h or more. A commonly held belief is that headache recurrence is reduced by treatment with a medication with a prolonged half-life. In placebo-controlled and comparator studies,

recurrence rates have been purported to be lowest for naratriptan (half-life 6 h) and frovatriptan (half-life 26 h) (Geraud *et al.* 2003). However, frovatriptan, even with by far the longest half-life of the triptans, has recurrence rates approaching 25%. And in studies with repeated triptan dosing to maintain plasma concentrations for extended periods, recurrence rates are not affected (Sheftell & Tepper 2002).

Emerging evidence suggests that early treatment during the mild phase of an attack increases not only the percentage of patients who are pain-free at early time points, but also decreases attack progression and recurrence. Therefore, to prevent headache recurrence, a compelling argument can be made to use drugs with rapid onset of action and high pain-free rates early in the course of an attack. Alternatively, employing a long-acting NSAID in combination with an oral triptan appears to decrease recurrence rate (Krymchantowski & Barbosa 2002). It is noteworthy that a rapid onset triptan followed by a longer half-life triptan has not been demonstrated to be either safe or effective, and because the co-administration of different triptans is contraindicated within 24 h of each other, this is not a strategy that is recommended.

### **Menstrual migraine**

Some women have migraine only around the time of menstruation (pure menstrual migraine) and others have significant and predictable exacerbations around the time of menstruation (menstrually related migraine) (Mannix 2003). Each of the triptans is equally effective in treating menstrually associated migraine. However, headache recurrence is common and in some patients short-term prevention (from 2 days before the expected period through the duration of menstruation) is necessary to avoid or minimize the occurrence of menstrual migraine. The simplest and often most effective treatment is a long-acting NSAID or transdermal oestrogen (100 µg patch changed every 2 days for a period of 6 days). If this strategy is contraindicated or ineffective, several triptans, including sumatriptan 25 mg three times daily, naratriptan 1 mg twice daily, frovatriptan 2.5 mg twice daily, and zolmitriptan 2.5 mg twice daily, have been shown to be safe and effective in preventing or attenuating the severity of menstrual associated migraine when used on a daily basis just prior to and during menstruation.

### Migraine patients who have 'failed' a prior triptan trial

In clinical trials, approximately one-third of patients do not respond during a single attack to an individual triptan. However, the non-response rate is less in clinical practice. Unlike controlled clinical trials where patients are asked to wait until the pain intensifies to a moderate-severe level before taking the drug, in clinical practice patients are often instructed or intuitively will use the triptan early in the course of the attack and hence increase the likelihood of response. Furthermore, patients are usually instructed to try an individual triptan for at least two attacks at an adequate dosage before abandoning the drug. If a patient reports non-response to a triptan, it is important to explore the possible reasons:

- unrealistic expectations of immediate and complete relief of headache;
- pain relief accompanied by nuisance or frightening adverse effects;
- early vomiting resulting in loss of the medication;
- headache recurrence after initial response;
- inappropriate dose treating late into the course of the headache – often patients initially treat with their usual over-the-counter or prescription agents, re-dose, and only after their headache has proven to be sufficiently intense and refractory will they then try the triptan.

Patients who have truly 'failed' an adequate trial with an individual triptan should be given another triptan – a significant proportion of 'triptan failures' respond to a different triptan (Stark *et al.* 2000; Farkkila *et al.* 2003; Mathew *et al.* 2000). Patient response to a particular triptan is highly variable and altogether unpredictable – why one patient responds to one triptan exclusively or preferentially is unknown. There are few data to assist clinicians in differentiating which patient and/or attack characteristics predict a favourable response to triptans as a class or to a specific triptan. **Patients, educated in appropriate treatment strategies, should be tried on each of the oral triptans (each tried twice) until the desired treatment goal is achieved (sustained pain-free with minimal or no adverse events). Alternatively, failure to respond to three oral triptans may prompt a trial with a non-oral formulation.**

### PROMINENT TRIPTAN ADVERSE EFFECTS OR FEAR OF ADVERSE EFFECTS

Concerns about the cardiovascular safety of

the triptans are often cited as a major barrier to prescription by physicians (Tepper & Millson 2003). Similarly, concerns about adverse effects are a major factor in a patient's decision to delay or avoid migraine-specific treatment (Gallagher & Kunkel 2003). In a recent survey by the National Headache Foundation in the USA, about one-third of 2444 migraine patients reported often or always experiencing adverse effects with their prescription-based acute antimigraine medication, and about two-thirds reported that they delayed or avoided their prescription medications due to concerns about adverse effects (Gallagher & Kunkel 2003).

It is important to remember the difference between safety and tolerability. From a tolerability perspective, there are significant differences within the triptan class. Conversely, from a safety perspective, all seven triptans share the same theoretical cardiac risks and contraindications – there is no 'safest' triptan.

### Triptan safety

Prescribers' concerns about the cardiovascular safety of triptans is prompted in part by the observation that some patients report burning, tingling or tightness in the face, limbs or chest. These symptoms, which are characteristic of the triptan class, have been designated triptan sensations. In placebo-controlled trials, chest tightness, heaviness, pain or pressure were reported in approximately 1–7% of patients taking therapeutic doses of triptan tablets. Triptan-associated chest symptoms are almost always mild and transient and, when investigated, are not associated with electrocardiographic or enzymatic evidence of myocardial ischaemia.

However, because 5HT<sub>1B</sub> receptors are located on coronary arteries, albeit at significantly lower concentrations than on cerebral arteries, triptans can contract isolated human coronary arteries. In early *in vitro* studies, the magnitude of this human coronary-artery contraction produced by sumatriptan was one-fifth that produced by serotonin. The triptans do not appear to differ from one another in this regard, consistent with their similar pharmacological profiles. For each triptan, the clinically effective maximum plasma concentration is less than 40% of that required to evoke half of the maximal coronary artery contraction elicited by the drugs. This suggests that, at plasma concentrations achieved in ordinary clinical use, these 5-HT<sub>1B/1D</sub> agonists are associated with minimal or no contraction of nondiseased coronary arteries.

In 2002, the Triptan Cardiovascular Safety Expert Panel was convened by the American Headache Society – a multidisciplinary group of experts in neurology, primary care, cardiology, pharmacology, women's health and epidemiology – to evaluate the evidence for triptan-associated cardiovascular risk and to formulate consensus recommendations for informed prescribing (Dodick *et al.* in). The panel concluded that while serious cardiovascular adverse events have occurred after the use of triptans, the frequency in both clinical trials and clinical practice appeared to be extremely low (less than 1 per 1 million exposed). Overall, the risk-benefit profile of triptans favours their use if there are no contraindications (familial hemiplegic migraine, basilar type migraine, ischaemic stroke, ischaemic heart disease, Prinzmetal's angina, and uncontrolled hypertension) and in patients at low risk of coronary artery disease. Triptans can be confidently prescribed in these patients (the vast majority of all migraine sufferers) without the need for prior cardiac evaluation. Overall, all triptans are equally safe when prescribed appropriately.

### Tolerability

Tolerability is an important factor when choosing between the triptans (Nappi *et al.* 2003). Unfortunately, differentiating tolerability differences amongst the seven triptans is difficult due to a paucity of head-to-head trials and the variations in adverse events reporting from study to study.

Triptan tolerability is not infrequently limited by the so-called triptan sensations – paraesthesias, sensations of warmth, heaviness, pressure or tightness in different parts of the body including the throat, neck and chest. Most chest symptoms occur in young to middle-aged women who generally have a low frequency of cardiovascular risk factors. The chest symptoms in clinical trials were transient, mild and never attributable to ischaemia. Several non-ischaemic mechanisms for triptan-associated chest symptoms have been proposed (abnormal oesophageal motility, effect on the pulmonary vasculature, alterations in skeletal muscle energy metabolism, central sensitization of pain pathways, generalized vasospastic disorder, and lowered pain threshold among migraineurs).

In clinical trials, at therapeutic doses, the frequency of chest-related symptoms ranged from 1 to 6%, whereas in postmarketing surveillance studies, in those specifically asked about chest

Triptan-associated chest symptoms are almost always mild and transient and, when investigated, are not associated with electrocardiographic or enzymatic evidence of myocardial ischaemia.

symptoms up to 24% of patients using oral sumatriptan and 41% using subcutaneous sumatriptan report them. Often these symptoms alarm patients, especially when not specifically warned, prompting them to abandon treatment. Amongst the triptans, almotriptan 12.5 mg (0.1–0.2%) and naratriptan 2.5 mg (< 1.0%) have the lowest frequency of chest symptoms, similar to placebo (Dodick in press).

The frequency of CNS adverse effects with some triptans (fatigue, somnolence, dizziness, difficulty concentrating, etc.) is as high as 15% and may be associated with considerable functional impairment and decreased productivity (Dodick *et al.* in press). Therefore, some patients may choose to avoid or delay treatment to avoid somnolence or dizziness that may interfere with work, child-care or driving. In the triptan meta-analysis, the lowest frequency of CNS adverse effects was found with almotriptan 12.5 mg (1.5%), naratriptan 2.5 mg (1.9%), and sumatriptan 50 mg (3.7%) compared with zolmitriptan 2.5 mg (11.5%), rizatriptan 10 mg (9.4%), and eletriptan 40 mg (7.5%) or 80 mg (14.6%).

### Concern about drug-drug interactions

As a class, the triptans have relatively few important drug–drug interactions (Rapoport 2003). None of the triptans should be coadministered within 24 h of ergots or a different triptan brand. Patients on monoamine oxidase inhibi-

tors should avoid sumatriptan, zolmitriptan and rizatriptan because their metabolism can be delayed and their peak blood levels increased. Propranolol increases the plasma concentration of rizatriptan, so the lower 5 mg dose should be used. Cimetidine increases the plasma concentration of zolmitriptan and patients require the lower 2.5 mg dose when used concurrently. Eletriptan is metabolized mostly by the hepatic cytochrome P450 isoenzyme CYP3A4 and transported out of the brain by the p-glycoprotein pump. Therefore, eletriptan should be avoided in patients who are being treated with drugs that are potent inhibitors of the CYP3A4 isoenzyme (Mathew *et al.* 2003). None of the triptans demonstrate significant interactions with selective serotonin reuptake inhibitors and their coadministration is not contraindicated. Indeed, the serotonin syndrome is exceedingly rare in patients receiving both classes of drug.

## CONCLUSIONS

An extensive body of evidence and clinical experience has established the safety and efficacy of triptans. They are considered the standard of care for acute migraine of moderate to severe intensity, and for headaches that are generally not responsive to non-specific analgesics. Currently, patients and their physicians can choose between seven triptans and five different formulations. There is no single triptan of first choice. Instead, selection of the most appropriate triptan depends on the unique attack characteristics, patient preferences for formulations, and the other attributes (e.g. speed, adverse effect profile) most important to patients. It is important to recall that while the difference in response rates in populations of patients appears to be small, the response to these drugs can vary considerably between individuals. Two patients with similar attack profiles can respond differently to the same drug. The response also varies between the triptans. The same individual may respond quite differently to different triptans. Therefore, the optimal triptan for an individual patient is the one that achieves the therapeutic objective – a pain-free response which is rapid (1–2 h), sustained (no recurrence), and associated with minimal or no adverse events.

Finding the most effective acute treatment strategy is a rewarding experience for the patient and physician. The process truly combines the best of the art and science of medicine – while some patients can be successfully matched to the

optimal triptan and formulation at their initial consultation, other patients require empiricism and trial and error. However, at the end of the day, the vast majority of patients can be effectively managed.

## ACKNOWLEDGEMENTS

The paper was reviewed by Professor Peter Goadsby, London.

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