Review

Optimizing triptan therapy in clinical practice

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Practice Points

- The prevalence of migraine is 12–16% of the general population and is two- to three-times higher in women than men.
- WHO identified migraine among the world's top leading causes of disability. Even so, migraine is still an under-diagnosed and under-treated disorder.
- The pharmacological therapy of migraine includes two kinds of treatment: symptomatic treatment to treat acute attacks and prophylactic treatment to prevent frequent attacks.
- The triptans and the ergot derivatives are specific medications for migraine. The triptans are selectively specific for the 5-HT_{1B} and 5-HT_{1D} serotonin receptor subtypes. Seven different triptan formulations, each with distinctive pharmacokinetic properties, are available.
- The triptans are available in several formulations; tablets, orally disintegrating tablets, nasal sprays, subcutaneous injections and suppositories.
- The early intake of triptans, when the pain is mild, is associated with a significantly better outcome.

SUMMARY Migraine is a chronic neurological disorder characterized by episodic attacks of headache and associated symptoms. The pathophysiology of migraine is not completely understood. The goals of treatment include reducing the intensity and duration of acute attacks, minimizing the frequency of attacks and headache-related disability, and maximizing health-related quality of life. Acute medications are needed by all migraine sufferers for symptomatic treatment and, for the majority of patients who have infrequent attacks, are the only therapy required. Triptans, serotonin 5-$HT_{1B/1D}$ receptor agonists, as well as revolutionizing the treatment of migraine, also stimulated groundbreaking research that provided insights into

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the anatomy, physiology and molecular pharmacology of migraine. The selection of a triptan for a patient depends upon the stratification of the patient's migraine attack by peak intensity, time to peak intensity, level of associated symptoms, time to associated symptoms and concomitant treatments that might cause drug interactions.

Migraine is one of the most common disorders in the general population, known to us through writings since 3000 BC. Migraine is a neurovascular disorder characterized by attacks of severe headache and autonomic and neurological symptoms [1].

Over the past 30 years, the field of migraine research has witnessed an explosion of information on the understanding of the pathophysiology and mechanisms involved in the disorder. Advances in molecular biology, genomic science and imaging techniques have helped to better define pathways involved in the migraine process [2].

The attacks are acute, intermittent and tend to be disruptive, with sufferers experiencing a significant loss in quality of life and an inability to perform their normal daily activities. In addition to lost wages and productivity due to absenteeism, many patients with migraine also experience reduced productivity while at work and disruption of their family, social and leisure activities [3]. Migraine is a common disorder, mostly affecting young and middle-aged people, and is two- to three-times more common in women than in men [4].

Studies conducted around the world have consistently shown that migraine affects approximately 10–12% of the general adult population [5]. In up to a third of patients with migraine, the headaches are accompanied by focal neurologic symptoms (often visual) known as aura.

The attacks usually start in childhood or adolescence; it is rare for new cases to occur at over 35–40 years of age. However, the peak prevalence occurs between the ages of 25 and 55 years for both genders [6]. Migraine is a heterogeneous disorder characterized by attacks that vary in frequency, duration, severity and associated symptoms. This variability exists both between different sufferers and within the individual sufferer over their separate attacks.

In some women there is a clinical impression that migraines are more common and severe around the time of menses, even if in other women attacks have no menstrual relationship [7]. In some studies, focused on women with menstrually associated migraines, it was shown that attacks of menstrual migraine are more severe, of longer duration and more resistant to treatment than migraine attacks at other times of the month [8,9].

Migraine sufferers experience disability and reduced quality of life during their attacks and even between attacks [10], which, over a lifetime's illness, can lead to profound consequences on their lifestyles. In 2001 WHO published the annual World Health Report, using the methodology of the Global Burden of Disease study. In this report WHO identified migraine among the world's top 20 leading causes of years lived with disability in all ages, ranking 19th for both sexes and 12th for females [11]. Disability refers to the impact of illness on work and function in various settings and roles. Information on disability in migraine complements the diagnosis by helping the physician to assess the need for treatment. Reduction in headache-related disability is one of the main goals of the US Headache Consortium guidelines, which recommend a stratified care approach based on the level of disability [12].

The results of the American Migraine Study II showed that more than half (53%) of migraineurs reported severe impairment in activity or the requirement for bed rest with severe headaches. Work or school productivity was reduced by at least 50% among half of migraine sufferers. Moreover, migraine influences health status and behavior between as well as during attacks. Of people with migraine, 85% reported substantial reductions in their ability to do household work and chores, 45% missed family social and leisure activities and 32% avoided making plans for fear of cancellation due to headaches. Partners of people with migraine reported decreased work performance and dissatisfaction with their work demands, responsibilities and duties [13]. Anxiety, depression and fear are common among migraine sufferers, either as a direct result of the condition or due to coexisting psychiatric disorders.

Migraine is now recognized as a disabling condition with clinical characteristics that distinguish it from other headache types. This allows migraineurs to be specifically diagnosed

and treated as having a true medical condition that burdens the patients and their families. In the long run migraine has a favorable prognosis in most patients [14].

The first step in the effective management of headache is to make the correct diagnosis when the patient first consults. It is important that the patients are made to appreciate that they have a recognized disorder that is not trivial and that the physician appreciates is distressing [15]. The International Headache Society (IHS) published the first edition of the International Classification of Headache Disorders in 1988 and the second edition in 2004 [16]. These classifications have transformed research into migraine and the management of the condition by providing a standardized means of identifying migraine patients for physicians. These criteria are a benchmark, making it possible to standardize terms used in different settings and by different investigators. According to these criteria, migraine is a diagnosis of both inclusion and exclusion: inclusion because certain features must be fulfilled, and exclusion because secondary headaches must be ruled out as a prelude to diagnosis. The IHS criteria include migraine without aura and six subtypes of migraine with aura; the criteria for migraine with aura and for the subform 'typical aura with migraine headache' are illustrated in **Box 1**.

Many headache sufferers with features of migraine fail to fully meet the IHS criteria for migraine with aura or without aura. Most of these subjects meet criteria for 'probable migraine' (PM), a migraine subtype fulfilling all criteria but one for migraine with or without aura. The 1-year period prevalence of PM was found to be 4.5% in the AMPP study [17]. PM seems to be a frequent, under-treated, sometimes disabling disorder. Most PM sufferers have never used a

Box 1. Diagnostic criteria for two types of migraine.

Migraine without aura

A At least five attacks fulfilling criteria B–D

B Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)

C Headache has at least two of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

D During headache at least one of the following:

- Nausea and/or vomiting
- Photophobia and phonophobia

E Not attributed to another disorder

Migraine with aura

Typical aura with migraine headache

A At least two attacks fulfilling criteria B–D

B Aura consisting of at least one of the following, but no motor weakness:

- Fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (e.g., loss of vision)
- Fully reversible sensory symptoms including positive features (e.g., pins and needles) and/or negative features (e.g., numbness)
- Fully reversible dysphasic speech disturbance

C At least two of the following:

- Homonymous visual symptoms and/or unilateral sensory symptoms
- At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms
- Occur in succession over ≥5 min
- Each symptom lasts between 5 and 60 min

D Headache fulfilling criteria B–D for 'Migraine without aura' begins during the aura or follows aura within 60 min

E Not attributed to another disease

Adapted with permission from [16].

migraine-preventive treatment, whereas the vast majority need to take acute treatments, although 71% usually treat with over-the-counter (OTC) medication.

Since most headache patients have normal neurologic and physical examinations, the most important tool for making a correct diagnosis is a detailed and relevant history. To establish a diagnosis of migraine under the IHS classification, certain clinical features must be present and organic disease (especially in case of first or worst headache) must be excluded. To diagnose migraine without aura, five attacks are needed, each lasting 4–72 h. As far as migraine with aura is concerned, at least two attacks are required to make such a diagnosis.

Although many effective treatments are now available for migraine, the sufferer who consults a physician and receives an accurate diagnosis still may not receive appropriate therapy. Most migraine sufferers in Europe and North America rely on OTC medications, with relatively few taking prescription drugs [18]. Furthermore, many migraine sufferers do not report effective relief with their antimigraine drugs. In the USA, only 29% of migraine sufferers stated that they were satisfied with their usual acute treatments. Features that led to dissatisfaction included a lack of overall relief, delay in the onset of relief and too many side effects [19]. Recent studies demonstrated that, despite a slow increase in diagnosis and treatment rates in the past 15 years, migraine remains an under-treated illness [20].

The extraordinary medical advances coupled with education initiatives seen in the headache field in the past decade have not translated into a proportionate increase in the use of prescription medications for migraine management [21].

Migraine sufferers differ in their management needs, largely due to the variation in severity of symptoms and their impact on the sufferer. Medications for the treatment of migraine can be given in two ways: acutely for the symptomatic treatment of individual attacks and prophylactically to prevent the development of future attacks. Prior to specialist referral, the migraine treatment is often suboptimal according to current guidelines, with under-utilization of triptans and prophylactic medications [22]. The goals of treatment include reducing the intensity and duration of acute attacks, minimizing the frequency of attacks, minimizing headache-related disability, maximizing health-related quality of life and avoiding headache escalation and medication misuse [23]. Effective migraine treatment depends on making an accurate diagnosis, teaching the patient to identify and avoid headache triggers, and developing a treatment plan that reduces the impact of migraine on the individual patient, targeting the most disturbing symptoms.

Acute medications are needed by all migraine sufferers for symptomatic treatment and, for the majority of patients who have infrequent attacks, are the only therapy required. Acute treatment can be specific (ergots and triptans) or nonspecific (analgesics, antiemetics and NSAIDs). The ergot alkaloids include: ergotamine, available in tablets and suppositories, usually in combination with caffeine; and dihydroergotamine, available in injections and nasal spray. These drugs were not considered in this review, which specifically focuses on the triptans.

There are two possible strategies that one can employ to arrive at the best patient–therapy combination. The traditional approach is the step care paradigm, but there is also an alternative strategy, which is stratified care. Step care essentially uses a trial-and-error approach, starting with migraine-nonspecific medications, progressing through a series of alternatives and combinations and culminating in migraine-specific treatments, if the previous therapies have not been effective. By contrast, stratified care bases therapy selection on the initial assessment of illness severity and treatment needs. According to the magnitude of needs, an individualized treatment program can be developed [24]. Studies have demonstrated that, for more disabled headache patients, the stratified care approach results in more robust headache response with less disability and greater cost–effectiveness than step care [25].

The triptans: an overview

Triptans are extremely effective in the range of mild, moderate and severe migraine attacks. The medications that have become known as the triptans have revolutionized the acute treatment of migraine headache during the past 20 years. The introduction of the triptans was a major breakthrough in the treatment of migraine, changing millions of lives for the better. Triptans were the main advance in migraine treatment during the latter part of the 20th century. Many migraine sufferers were liberated in a way that they had not previously known, clinical trial guidelines

were refined and revised and clinical studies were well organized and uniform. Triptans ushered in a new era in acute migraine therapy, with their ability to provide rapid relief of headache and associated symptoms. With the introduction of triptans, migraine therapy has made a quantum leap forward. Triptans are the first-choice drugs for moderate-to-severe migraine attacks in all the management guidelines published in several countries, including the USA [26], UK, Italy, Canada, Germany and France. Triptans have several advantages when compared with ergot derivatives and nonspecific drugs, especially regarding their selective pharmacology, simple and consistent pharmacokinetics, evidence-based dose recommendations, and established efficacy based on large, well-designed, controlled trials [27,28]. Seven oral triptan formulations are now available for the treatment of migraine, each with its own characteristic strengths over a range of treatment attributes. Triptans are selective 5-HT_{1B} and 5-HT_{1D} receptor agonists. These drugs are believed to have four potential mechanisms of action to relieve the symptoms perceived during the acute attacks of migraine [29]:

- Stimulation of the 5-HT_{1B} receptor on cranial vascular smooth muscle is hypothesized to increase the tonus of the vessel wall, which counteracts the pulse synchronic activation of stretch receptors that may be responsible for throbbing headache;
- Stimulation of the 5-HT_{1D} receptors on trigeminal nerve terminals innervating the meningeal blood vessels to block the release of neuropeptides that are theorized to induce pain/inflammation [30];
- Stimulation of central 5-$HT_{1B/1D/1F}$ receptors in the trigeminal nucleus caudalis to impair the transmission of afferent signaling from the first-order to the second-order trigeminal sensory neurons, and prevent wind-up (temporal summation) in the second-order trigeminal sensory neurons and long-lasting central sensitization (pain hypersensitivity);
- Stimulation of the 5-$HT_{1B/1D}$ receptors in the ventroposteromedial thalamus to inhibit the process of nociceptive input from the second-order to the third-order trigeminal sensory neurons in the ventroposteromedial thalamus [31].

All triptans act peripherally, but are lipophilic to different extents. Some can penetrate the blood–brain barrier and hence also act significantly also on central 5-HT_{1D} receptors.

Although the pharmacological mechanism of the triptans is similar, their pharmacokinetic properties are distinct [32]. Such diverse properties will influence the effectiveness of the compounds and favor the prescription of one over another in different patient populations. The different pharmacokinetic profiles of these compounds help to explain the variable response that patients show to these drugs. Given that the triptans have very distinctive pharmacokinetic profiles, a broad array of them may be necessary to successfully treat this very heterogeneous patient population. The main pharmacokinetic properties of the different triptans are reported in **Table 1** [33].

Evidence-based guidelines to select the triptans with the highest likelihood of success for individual patients are strongly recommended. A meta-analysis of triptan clinical trial data found small but clinically relevant differences in efficacy (pain-free status and recurrence of headache), tolerability and consistency of effect between the different commercially available triptans [34]. The main weakness of the meta-analytic approach is that there is no randomization. In addition, the population may not be totally comparable; there is a possible bias in time with recruiting over many years. Moreover, instructions to patients may vary and severity of headache (moderate/severe) may differ in different trial programs. Moreover, the aforementioned meta-analysis ignored parenteral drugs as gold standards, and used an end point that was unlike any in the underlying clinical trials. Ultimately, many of its findings relied upon the manipulation of efficacy data into therapeutic gains; when therapeutic ratios are derived from the same data, then the outcome of the meta-analysis appears to be quite different.

Triptans relieve head pain and also the associated symptoms of nausea, vomiting, photophobia and phonophobia. They are most effective when administered while the pain is mild. Quite frequently migraine patients report premonitory, prodrome symptoms, such as fatigue, yawning, stiff neck, concentration problems, irritability, depression and craving [35]. Early intervention in the migraine process at the level of mild pain may significantly increase the success rates, with

Table 1. Pharmacokinetic properties of triptans.

Triptan	Route	Dose (mg)	T_{max} (h)	Bioavailability (%)	$T_{1/2}$ (h)	Mean 24-h recurrence (%)
Sumatriptan	sc.	6	0.2	97	2.0	34–38
	p.o.	50	2.5	14	2.0	32
	p.o.	100	2.5	14	2.0	32
	NS	20	1.0	17	2.0	32–34
Zolmitriptan	p.o.	2.5	1.5	40–48	3.0	22–37
	p.o.	5	1.5	40–48	2.7	32
	ODT	2.5	3.3	40–48	2.5–3.0	NA
	NS	5	2.0	42	2.8	26
Naratriptan	p.o.	2.5	2.0–3.0	63–74	5.0–6.3	17–28
Rizatriptan	p.o.	10	1.2	45	2.0	30–47
	ODT	10	1.6–2.5	45	2.0	NA
Almotriptan	p.o.	12.5	1.4–3.8	70–80	3.2–3.7	18–29
Eletriptan	p.o.	40	1.0–2.0	50	3.6–5.5	19–30
	p.o.	80	1.0–2.0	50	3.6–5.5	<33
Frovatriptan	p.o.	2.5	2.0–4.0	22–30	26.0	7–25

NA: Data not available; NS: Nasal spray; ODT: Orally disintegrating tablet; p.o.: *Per os*; sc.: Subcutaneous; $T_{1/2}$: Half-life; T_{max}: Time to peak plasma concentration.
Data taken from [33].

headache recurrence consequently dropping to lower percentages.

A variety of studies, conducted with different triptans, demonstrated that, with early intervention, pain was less likely to intensify, fewer attacks required redosing, more attacks remained pain free 24-h postdose and normal function returned more quickly [36,37]. Furthermore, rapid headache response is associated with faster return to functioning.

As for migraine with aura, it was shown that the administration of triptans during the migraine aura phase is not significantly effective in preventing progression of a migraine headache. Therefore, there seems to be no benefit in treatment with triptan therapy prior to the development of a mild or moderate headache [38].

Triptans improve patients' quality of life and their use is cost effective. Cost savings are frequently reported for triptans compared with other treatments [39]. Several studies have demonstrated that, despite the increased cost surrounding the triptans, they could make substantial impacts on healthcare costs by reducing office and emergency visits and improving productivity in the workplace [40]. Triptans are generally well tolerated, with adverse events being characteristic of the class of drugs, including in particular an unpleasant but short-lived feeling of discomfort, heaviness or tightness, mainly in the chest [41]. Other side effects may be nausea, paresthesia and CNS symptoms such as somnolence, dizziness and drowsiness. The CNS symptoms seem to be correlated with the drug lipophilicity and the grade of penetration through the blood–brain barrier [42].

The only real contraindication for the use of triptans is the presence of risk factors for cardiovascular disease. Patients aged over 65 years should not take triptans but it is, however, generally thought that they may use these medications if, and as long as, they have no cardiovascular contraindications. A large study of triptan use in general practice, also in elderly patients with various risk factors, has shown that there is no increased risk of stroke, myocardial infarction, cardiovascular death, ischemic heart disease or mortality [43]. When triptans are used in elderly patients, periodic cardiac screening (e.g., an ECG every 3 months) is advised [44,45]. The risk of cardiovascular adverse events in adult patients is extremely low [46]. For example, sumatriptan has been shown to be well tolerated in the treatment of over 300,000 migraine attacks in clinical trials and over 200 million attacks in clinical practice [47]. Significant cardiovascular and cerebrovascular events were very rarely reported [48]. The Triptan Cardiovascular Safety Expert Panel, in particular, reported that the incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low and consequently the cardiovascular risk:benefit profile of triptans favors

their use in the absence of contraindications [49]. The chest symptoms occurring during use of triptans are generally nonserious and are not explained by ischemia. Conversely, overuse of ergotamine may increase the risk of cardiovascular events, especially in those patients simultaneously using cardiovascular drugs [50]. Other contraindications for the use of triptans are untreated arterial hypertension, Raynaud's disease, lactation and severe liver or renal failure. Information on the safety of triptan therapy during pregnancy is available mainly for sumatriptan in the GlaxoSmithKline sumatriptan pregnancy registry [51]. Triptan therapy during pregnancy has not been associated with an overall increased risk of congenital malformations so far. In a prospective study perinatal and pregnancy outcome did not differ between patients who had and patients who had not used sumatriptan after conception [51].

In 2006, a US FDA alert warned about the potential life-threatening risk of serotonin syndrome when triptans are used in combination with selective serotonin reuptake inhibitors or selective serotonin/norepinephrine reuptake inhibitors. In 2010, the American Headache Society published a position paper declaring that the evidence available in the literature on this issue is inadequate to determine the risk of serotonin syndrome with the addition of a triptan to selective serotonin reuptake inhibitors or selective serotonin/norepinephrine reuptake inhibitors, and that the currently available evidence does not support limiting the use of triptans with these antidepressants. However, given the seriousness of serotonin syndrome, caution is certainly warranted and clinicians should be vigilant to serotonin toxicity symptoms and signs to ensure prompt treatment [52].

Moreover, antimigraine compounds in the triptan class (sumatriptan and zolmitriptan) are metabolized to varying extents by monoamine oxidase type A. In fact, coadministration of oral sumatriptan or zolmitriptan with monoamine oxidase inhibitors is contraindicated in current product labeling [33]. Other triptans, such as eletriptan, also are substrates for the ATP-dependent efflux transporter P-glycoprotein pump. As a consequence cotreatment with P-glycoprotein pump inhibitors, such as omeprazole, amiodarone, clarithromycin, verapamil, ketoconazole and ritonavir, should be avoided [53].

With a much better and more diverse armamentarium than ever before, physicians can now select migraine therapy to satisfy the preferences of migraine sufferers, provided physicians understand what migraineurs want from therapy [54]. To better understand patients' expectations, a survey in a representative sample of migraine sufferers in the USA was conducted. The efficacy measures used by researchers in clinical trials for acute treatment were weighed up by the patients, who were asked to rate the importance of various drug attributes [55]. According to the migraine sufferers the three most important attributes of a migraine medication were complete relief of headache (87%), lack of recurrence (86%) and rapid onset of pain relief (83%). Other important outcome measures were no side effects (79%), relief of associated symptoms (76%) and route of administration (56%). The majority of migraine sufferers preferred an oral tablet or capsule as a first-choice route of administration (73%) and an oral, rapidly dissolving tablet as a second-choice route (51%).

The efficacy of acute therapies for migraine can be measured in many ways. Traditional end points, such as pain free at 2 h, headache response, recurrence and consistency, are used for regulatory purposes, but do not reflect all components of the migraine syndrome, nor, necessarily, what is most valued by patients and clinicians. Fast, complete pain relief is one important factor in determining short-term patient satisfaction with treatment. Pain free at 2 h was considered the primary measure of efficacy in most clinical trials and meta-analyses [56]. This measure is sound, statistically powerful and very useful to demonstrate efficacy versus placebo; this parameter should usually be the primary measure of efficacy, but the IHS also pointed out that it is not the only one. A migraine attack typically lasts 18–24 h; therefore, efficacy measures should address the impact of a drug throughout the course of a migraine attack, and not only in the first 2 h. Patients judge the value of their medication based on multiple attributes. Furthermore, recurrence is an important outcome measure of acute migraine therapy and it can be perceived by the patient as a treatment failure. The recurrence is common to all acute treatments (occurring in up to a third of attacks) and should be considered as an important efficacy index [57].

Good management of migraine requires that the patient actively participate in decisions regarding therapeutic intervention. Headache severity, frequency and duration, as well as associated symptoms, such as nausea, vomiting or previous treatment responses, can guide selection of medication for acute treatment. Since patients are treated on an individual basis, the more important question is not which triptan is best relative to another, but whether the triptan given to the patient provides the outcome desired by the patient and healthcare provider.

Patients balance a variety of treatment attributes, such as efficacy (in particular pain free at 2 h), consistency, tolerability, recurrence, formulation and convenience, when assessing the overall acceptability of a drug. The relative importance of each characteristic may differ among patients or even for an individual patient, depending on the specific situation [58]. Sustained pain free is a composite measure that encompasses pain free at 2 h and no recurrence or use of additional medications from 2 to 24 h. This outcome measure can be identified as the ideal response to a drug for treatment of a migraine attack but, as a matter of fact, with current drugs it can be obtained in up to 25–30% of attacks treated. Thus, at the present time, it should be used as a secondary efficacy measure [59]. Migraine therapy that provides rapid, complete and sustained pain relief, with restoration of functional ability, has the most beneficial impact on short-term health-related quality of life for migraineurs.

Composite end points, such as sustained pain free and patient preference, which combine the attributes of treatment that patients desire, have been introduced in order to capture clinically relevant aspects of therapy. Evaluating patient preferences could provide additional information to supplement the traditional tests of efficacy in randomized controlled trials [60].

In conclusion, although the triptans have simple and consistent pharmacokinetic features, there are specific differences among individual agents that may account for their different clinical attributes. For example, frovatriptan has the longest half-life, almotriptan has the greatest bioavailability, eletriptan has the highest lipophilicity and rizatriptan has the shortest T_{max}. By understanding the particular attributes of the individual triptans, physicians can match their patients with the treatment that promises the highest likelihood of success. Continued clinical use and familiarity with results of clinical trials should make it possible for the interested and knowledgeable physician to match individual patient needs with the specific characteristics of the triptans to optimize therapeutic benefit [61].

The triptans in clinical practice

The triptans are available in several different formulations, such as conventional oral tablets, orally disintegrating tablets (ODTs) or wafers, subcutaneous injections, nasal sprays and suppositories, which provide an excellent opportunity to tailor therapy to the individual patient's needs [62]. In selecting acute medications to treat migraine, the individual pharmacokinetic properties are also important in achieving an optimal outcome. The selection of a triptan for a patient depends upon the stratification of the patient's migraine attack by peak intensity, time to peak intensity, level of associated symptoms, time to associated symptoms and concomitant treatments that might cause drug–drug interactions [63]. Specific differences among the triptans exist, as evidenced by different pharmacological profiles including half-life, time to peak plasma concentrations, peak plasma concentrations, area under the concentration–time curve, metabolism and drug–drug interaction profiles. How or whether these differences translate to clinical efficacy and tolerability advantages for one agent over another is not well differentiated. However, delivery systems may play an important role in the onset of action. Subcutaneous sumatriptan injection offers the fastest relief with the most rapid onset. Rather complex pharmacokinetic mechanisms underlie this clinical evidence. As a matter of fact, no simple plasma concentration–response relationship exists that is sufficiently robust to apply to both subcutaneous and oral sumatriptan [64]. Oral tablets are less efficacious if nausea, vomiting or decreased functioning of the GI tract form a significant component of the attack, as time to maximum plasma and brain drug concentration can increase in these situations. Gastric stasis has been associated with migraine and this disturbance contributes to poor absorption of oral medications. This association has been based on evidence of impaired gastric emptying, that is, differences in pharmacokinetics

inside and outside of a migraine attack and use of prokinetics to enhance absorption. In a study that investigated this phenomenon, it was shown that migraineurs suffer from gastric stasis both during and outside an acute migraine attack [65]. Nasal sprays are absorbed through the olfactory epithelium and pass more quickly into the bloodstream, making gastrointestinal absorption much less important and also bypassing first-pass metabolism. This results in quicker entry into the brain and more rapid relief.

Due to the pharmacokinetic differences among triptans, some authors have proposed a subdivision of the class, taking into account T_{max} and half-life in particular. However, it has never been adequately determined which pharmacokinetic characteristics produce the most beneficial clinical effects. A short T_{max} might produce a quicker start to efficacy or a long half-life might increase the length of effect of a triptan, but these facts have not been proven. However, triptans have been distinguished into rapid onset and long half-life compounds, as reported in **Box 2** [66].

Some studies showed that a nonresponder to one triptan may well benefit from another triptan, or even the same compound via a different route of administration. If the first triptan tried is not ideal in all clinical respects, a second or third should be tried. The patient should be questioned carefully to determine if the triptan taken is ideal in terms of rapid onset of action, complete response to attain a pain-free state, consistency, a lack of recurrence and tolerability [67].

Several guidelines for the acute treatment of migraine have been developed in different countries, each with its own strengths of evidence. Sumatriptan and naratriptan were approved as OTC drugs in pharmacies in the UK and Germany, respectively. Recently, a multinational society, the European Federation of Neurological Societies (EFNS) published guidelines (first edition in 2006 and revised version in 2009) aimed at giving evidence-based recommendations for the drug treatment of migraine headaches [68]. The evidence of classification includes four classes, where class I points out the strongest and most powerful evidence, while class IV is associated with the poorest reliability. Accordingly, there are three levels of recommendations, where level A indicates the highest rate of evidence-based recommendation, as shown in **Box 3**.

The EFNS guidelines for acute migraine treatment with triptans are reported in **Table 2**. The different triptans are shown in order according to the time of marketing. Sumatriptan was the first triptan to be developed, followed by zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan.

Sumatriptan

Sumatriptan has the largest portfolio of clinical data of all the triptans. It is fairly rapidly absorbed, but has low bioavailability and CNS penetration. Sumatriptan is available in a self-injectable preparation (6 and in some countries 4 mg subcutaneously), a nasal spray (20 mg for adults and 10 mg for adolescents), tablets (25 mg only in USA, 50 mg and 100 mg) and, in a few countries, in a suppository formulation (25 mg). Sumatriptan should not be used within 2 weeks after the discontinuation of a monoamine oxidase inhibitor.

The clinical profile has been elucidated for all four formulations. Randomized controlled clinical trials have shown that all oral doses of sumatriptan were significantly superior to placebo for the acute treatment of migraine. The 50- and 100-mg doses were equivalent in efficacy for moderate-to-severe headache, and significantly superior to the 25-mg dose. As for the other triptans, early intervention with oral sumatriptan, when the pain intensity is mild, provides a better efficacy [69]. As for oral formulation, sumatriptan tablets have been developed in a fast-disintegrating, rapid-release formulation designed to facilitate tablet disintegration and drug dispersion [70]. The patients who respond to the nasal spray report a faster onset of action than with the oral formulations. In clinical

Box 2. Subdivision of the triptans based on their pharmacokinetic profiles.

Rapid-onset triptans
- Rizatriptan
- Eletriptan
- Sumatriptan
- Zolmitriptan
- Almotriptan

Long half-life triptans
- Frovatriptan
- Naratriptan

Data taken from [66].

Box 3. European Federation of Neurological Societies rating of recommendations.

Level A

- Requires at least one convincing class I study or at least two consistent, convincing class II studies

Level B

- Requires at least one convincing class II study or overwhelming class III evidence

Level C

- Requires at least two convincing class III studies

Data taken from [68].

practice, however, the overall efficacy and the consistency of response of nasal spray seem to be lower in comparison with the tablets. An important exception is constituted by the adolescent sufferers, whose response to triptans seems to be rather poor and not significantly superior to placebo. Nasal spray sumatriptan was shown to be an effective treatment for migraine attacks in adolescents, aged 12–17 years, and this formulation was approved by the FDA for this particular group of migraineurs [71]. The most frequently reported adverse event following sumatriptan nasal spray was a taste disturbance caused by the bitterness of the formulation. Subcutaneous sumatriptan has a very rapid onset of action, reaching peak plasma concentrations within 10 min of treatment. Sumatriptan injection is unanimously considered as the most effective of all the triptan formulations. The injection was found to be superior to oral formulation in a within-patient comparison. Patients with extremely severe attacks and those with vomiting can greatly benefit from the injection. However, more adverse events were reported with subcutaneous sumatriptan than with oral triptans, especially injection site reactions, flushing, dizziness/vertigo and paresthesia/tingling.

Recently, a subcutaneous needle-free delivery system was developed, which was demonstrated to be bioequivalent to the needle autoinjector. It uses a blast of air to create a small hole in the skin through which medication passes into the subcutaneous tissues [72]. Moreover, sumatriptan administration using a novel iontophoretic transdermal technology was found to deliver drug plasma levels within the range for nasal spray, tablet and injectable formulation [73].

Indications for the use of sumatriptan are:

- Rapid-onset, moderate-to-severe attacks: tablets
- Rapid-onset attacks, with early nausea and vomiting: injections, nasal sprays or suppositories
- Extremely severe attacks: injections

Zolmitriptan

Zolmitriptan is absorbed rapidly and has a high bioavailability. It is more lipophilic than sumatriptan and penetrates the CNS to a significant extent. Zolmitriptan should not be taken within 2 weeks of monoamine oxidase inhibitor drugs. It is available as 2.5- and 5-mg tablets, as 2.5- and 5-mg ODTs, and as a 2.5- and 5-mg nasal spray. Patients take a single 2.5-mg tablet to treat their attacks, but can increase the dose to 5 mg for subsequent attacks if this dose is not effective [74]. For the tablets, the efficacy of the two doses was similar in clinical trials; however, more adverse events were reported following the 5-mg dose [75]. The ODT formulation is a nonfriable orange-flavored tablet and it was shown to have a

Table 2. Triptans recommended for acute migraine treatment.

Triptan	Route	Dose (mg)	Level	Comment
Sumatriptan	Oral including rapid release	25, 50 and 100	A	100 mg sumatriptan is the dose of reference to be compared with the other triptans
	Suppository	25	A	
	Nasal spray	10 and 20	A	
	Subcutaneous	6	A	
Zolmitriptan	Oral including disintegrating form	2.5 and 5	A	
	Nasal spray	2.5 and 5	A	
Naratriptan	Oral	2.5	A	Less but longer efficacy than sumatriptan
Rizatriptan	Oral including wafer form	10	A	5 mg when taking propranolol
Almotriptan	Oral	12.5	A	Probably fewer side effects than sumatriptan
Eletriptan	Oral	20 and 40	A	80 mg eletriptan allowed if 40 mg is not effective
Frovatriptan	Oral	2.5	A	Less but longer efficacy than sumatriptan

Data taken from [68].

similar clinical profile to the conventional tablet. It is a convenient alternative for those patients who prefer not to take conventional tablets or who are nauseated and cannot swallow water with their pill [76].

Zolmitriptan nasal spray, 5 mg, provides rapid onset of relief of migraine, with the first signs of efficacy apparent within 15 min [77]. It combines a rapid onset of action and consistently high response rates with a good tolerability profile. In addition, intranasal administration offers a viable alternative to subcutaneous injection when oral administration is undesirable or precluded [78].

Indications for the use of zolmitriptan are:

- Rapid-onset, moderate-to-severe attacks: tablets
- Rapid-onset, moderate-to-severe attacks with early nausea: ODTs
- Rapid-onset attacks with early nausea and vomiting: nasal spray

Naratriptan

Naratriptan is available as 1- (in the USA) and 2.5-mg tablets, and as OTC in some European countries. The recommended dose is 2.5 mg. At first glance, naratriptan appears to be one of the least effective of the triptan class, with a rather low rate of headache relief 2 h after treatment. However, its full efficacy is reported to occur 4 h after the intake. The efficacy of naratriptan was maintained over a 24-h period following treatment and it has one of the lowest reported recurrence rates of any triptan [79,80].

The side-effect profile of naratriptan is generally equal to that of placebo in controlled trials, so this drug has been referred to as the 'gentle triptan' [81]. Owing to its prolonged action, naratriptan has been studied as a preventative drug for different migraine subtypes [82]. Studies have shown that it was effective for the prevention of migraine during the prodrome phase of the attack [83].

Indications for the use of naratriptan are:

- Gradually developing, long-lasting attacks
- Moderate-to-severe attacks with high rates of recurrence

Rizatriptan

Rizatriptan is available in two oral dose strengths of 10 and 5 mg. It is also available as orally disintegrating wafers that can be taken without liquids in the same dosages as the conventional tablet [84,85]. The recommended starting dose is 10 mg, except in patients who are taking propranolol for prevention, for whom the recommended dose is 5 mg. In the triptan class rizatriptan has the quickest absorption, the shortest T_{max} (which is inversely associated with the speed of action) and was shown to be the fastest-acting oral triptan [86,87].

Taking rizatriptan at the onset of headache was associated with more rapid relief of headache and reversal of functional disability. The early intake of the drug when the pain is mild rather than moderate or severe was significantly more likely than placebo to produce a pain-free response within 2 h [88].

Indications for the use of rizatriptan are:

- Rapid-onset, moderate-to-severe attacks: tablets
- Rapid-onset, moderate-to-severe attacks with early nausea: orally disintegrating wafers

Almotriptan

Almotriptan is available as a 12.5-mg tablet; it is also available as a 6.25-mg tablet in the USA and as OTC in Germany. The recommended initial dose is 12.5 mg, which can be repeated after 2 h if the headache recurs. Its tolerability profile is comparable to that of placebo, with few chest symptoms being reported [89]. A variety of clinical trials showed that almotriptan should be taken in the early phase of migraine attacks to improve the clinical outcome [90]. When used for mild-intensity head pain, almotriptan 12.5 mg produced a higher incidence of pain-free status at 1 and 2 h, and a lower incidence of recurrence and need for rescue medication.

In particular, early initiation of treatment with almotriptan within the first hour after acute migraine onset, when pain is mild, resulted in a significantly higher sustained pain-free response compared with delayed intake, when pain is moderate or severe [91,92]. The 12.5-mg oral formulation was efficacious for relieving migraine headache pain in adolescents and was well tolerated in patients aged 12–17 years [93]. The use in adolescents was approved by the FDA in 2009, but in Europe this indication has not yet been approved.

Indications for the use of almotriptan are:

- Rapid-onset, moderate-to-severe attacks
- Triptan-naive patients, adolescents
- Adverse events when using other triptans

Eletriptan

Eletriptan is an oral triptan with high potency and oral bioavailability that is selective for intracranial blood vessels over extracranial vessels. It is available as 20-, 40- and in some countries 80-mg tablets. It is metabolized by the CYP3A4 hepatic enzymatic system. Eletriptan should not be used within 3 days after the intake of potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir or nelfinavir. This triptan is the most lipophilic in the class and therefore appears to cross the blood–brain barrier and enter the brain more extensively as compared with the other triptans [94]. This is most likely the reason why CNS adverse events appear to be more common with eletriptan. This triptan was demonstrated to be extremely efficacious, displaying high consistency of response over multiple attacks [95].

Eletriptan has also shown efficacy in difficult-to-treat patients who were dissatisfied with their previous treatment with NSAIDs, ergotamine and other triptans [96,97]. In a recent study, treatment with eletriptan was associated with significant improvement on three scales aimed to evaluate the multidimensional impact of acute migraine on work productivity [98].

Indications for the use of eletriptan are:

- Rapid-onset, moderate-to-severe attacks: 40-mg tablets
- Rapid-onset, extremely severe attacks: 80-mg tablets

Frovatriptan

Frovatriptan is available as a 2.5-mg tablet. The mean half-life is 26 h, the longest in the triptan class. The molecule was selected for development based upon its distinctive pharmacologic characteristics, which suggested that it would have the clinical potential for a long duration of action and a low likelihood of side effects and drug interactions [99]. Frovatriptan demonstrated functional selectivity for the cerebral arteries compared with the coronary arteries *in vitro* [100]. This selectivity may confer a benefit in reducing the risk of unwanted coronary and peripheral vascular effects. In an exploratory study of migraineurs, some of whom were aged over 65 years, with, or at high risk of, coronary artery disease, frovatriptan was well tolerated and not associated with an increase in cardiovascular monitoring abnormalities [100].

Moreover, due to its long action, frovatriptan has been investigated as a preventative or prophylactic drug for different predictable headache subtypes, in particular menstrually associated migraines [101] and headaches that occur mostly on weekends.

Frovatriptan was also proven to be effective for the prevention of migraine when taken during the prodrome phase of the attack. In three randomized, double-blind, crossover patient preference trials comparing frovatriptan versus other triptans (i.e., zolmitriptan, rizatriptan and almotriptan), pain free at 2 h rates were similar between the two groups. The recurrence rate was, however, lower for frovatriptan when compared with almotriptan [102] and rizatriptan [103].

Indications for the use of frovatriptan are:

- Gradually developing, long-lasting attacks
- Moderate-to-severe attacks with high rates of recurrence
- Adverse events when using other triptans
- Predictable attacks

Conclusion & future perspective

Because of advances in the understanding of migraine pathophysiology, new acute treatments will challenge the supremacy of triptans in the next few years.

Initial studies with CGRP antagonists (telcagepant and other related compounds) suggested they were effective, with a good cardiovascular safety profile [104]. They were supposed to become available in 2011 but in July 2011 it was reported that Merck & Co. were discontinuing the clinical development program for telcagepant [201]. The decision was based on an assessment of data across the clinical program, including findings from a recently completed 6-month Phase III study, showing that the intake of the medication was associated in some patients with significant elevations in serum transaminases.

Other potential future therapies may include 5-HT_{1F} agonists (lasmitidan), adenosine

receptor agonists, glutamate receptor antagonists, nitric oxide synthase inhibitors or even nonpharmaceutical alternatives such as repetitive transcranial magnetic stimulation [105].

In the meantime, in some countries but not in Europe, a combination of sumatriptan 85 mg and naproxen sodium 500 mg in a single-tablet, fixed-dose agent has been developed. The lack of pharmacokinetic interaction between sumatriptan and naproxen was previously reported in a randomized Latin-square design study. The literature contains several studies that suggest that the efficacy of triptans is improved when NSAIDs are given concomitantly. This combination of therapies seems to be more effective than placebo or either agent given as monotherapy in achieving headache relief at 2 h [106]. It also appears to offer improvement in 24-h outcome measures, such as higher 24-h headache response rates and lower recurrence rates. The rapid absorption of sumatriptan with the delayed-release properties of naproxen sodium might contribute to its therapeutic advantage over monotherapy with either component. In clinical practice, migraine patients may elect to treat severe attacks with more than one medication. Treatment with drugs of different classes produces a synergistic effect. NSAIDs are effective in treating migraine. They may work by suppressing inflammation and preventing and treating central sensitization by blocking glial production of prostaglandins. They may also help to treat nontraditional migraine symptoms, such as neck pain, fatigue and sinus pressure, which are commonly associated with acute migraine attacks. A possible concern is that combination analgesics seem to be more frequently associated with the development of medication overuse headache. Regardless, it appears that triptans, in combination and monotherapy, will remain a mainstay and will continue to have a key role in the treatment of acute migraine.

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