

# Acute migraine: Current treatment and emerging therapies

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**Abstract:** Migraine is a common disabling primary headache disorder. Despite the need for a perfect treatment of this debilitating condition, the ideal “cure” eludes us. In 1992, the first triptan was released in the US for use in acute migraine. Triptans are more specific for the serotonin receptor 5-hydroxy triptamine (5-HT) 1 than previously prescribed drugs, such as ergotamines, with fewer side effects. This was an important first step in specific acute migraine therapy. Today however, triptans continue to be underutilized. There remains a concern, among practitioners and patients, about possible cardiovascular safety issues, despite the lack of strong evidence of serious adverse events. In fact, triptans now have a safe track record over more than a decade of use. Other perceived downfalls to use, include cost and variable efficacy. The more we learn about the clinical features and pathophysiology of migraine, the closer we are to finding a satisfactory monotherapy. Until then, recognizing that mixed mechanisms underlie migraine symptoms, rational polytherapy can be useful. Research on the roles of serotonin, calcitonin gene related peptide, glutamine and N-methyl-D-aspartate in the trigeminovascular system holds promise for those searching for the perfect migraine headache cure.

**Keywords:** migraine, pathophysiology, acute, treatment

## Introduction

Migraine is a debilitating recurring primary headache disorder. Twenty eight million people in the US suffer from migraine with a prevalence of 18.2% among females and 6.5% among males (Lipton et al 2001a). Limited information about the pathophysiology of migraine may lead to diagnostic and therapeutic challenges, as well as delayed and/or partial relief, with risk of progression from a relapsing/remitting state to a chronic, more severe condition. Chronic daily headache is present in up to 4% of the US population (Lipton et al 2001b).

Although the onset is usually over the age of 12, migraine in young children is well recognized. In the pediatric population worldwide, the prevalence has been reported to be between 3–24.5% (Lipton and Bigal 2005). The mean age at onset for boys is 7.2 years and for girls is 10.9 years. Until puberty, boys have a slightly higher prevalence than girls do. In adults, migraine prevalence peaks between the ages of 25–55: the most productive years. Migraine costs 15.5 billion dollars a year in lost revenue from loss of work hours and use of medical facilities (Stewart et al 1996). Three-fourths of adult migraineurs are women. It occurs in all races, with the highest prevalence in the US among Caucasians. The migraineur, suffers not only from pain but also lives with a diminished to poor quality of life.

## Clinical presentation

Migraine is a chronic neurological disorder characterized by paroxysmal episodes of headache and associated symptoms typically lasting 4–72 hours (ICHD 2004). The migraineur reacts to normal stimuli, which may stem from a state of chronic fluctuating

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neuronal hyperexcitability (Tepper et al 2001; Bussone 2004; Gargus 2006). Migraine phases which may overlap include the prodrome, aura, headache, and postdrome (Saper 1997). The migraine attack may be precipitated by an exogenous or endogenous trigger.

The trigger mechanism, which though not well understood, is most likely a cortical phenomenon. Even though one trigger common to that patient may induce migraine, often this is difficult to pinpoint due to the multiplicity of events (the final event being the “straw that broke the camel’s back”). Common exogenous triggers include exposure to glare, heat, motion, raucous noise, or the ingestion of tyramine containing foods, alcohol, or other neuronally active substances. Endogenous triggers include stress; sleep disturbances, falling estrogen levels and others. Karli et al (2005) found that among 96 Turkish patients, with different headache types, different triggers predominated. Hunger and odors were more significant in typical migraine with and without aura, and nonmigraine headaches. Some foods were more significantly a trigger for migraine without aura rather than other headaches. Head and neck movements triggered episodic tension type headache (ETTH). Stress, anxiety and menstruation were relatively common triggers for both migraine and ETTH, but menstruation is a less frequently reported trigger in ETTH. Once triggered, the excited cortex relays the information to brainstem centers, which continue the process through the migraine phases. Clinical expression of this is variable among patients and from headache to headache.

A prodrome can be present in anywhere from 10–80% of migraineurs (Russell et al 1996), depending on reporting patterns and different definitions. These symptoms may not be reported to the physician without prompting. It is not the same as aura and there are no validated criteria for its diagnosis (Tipper 2001; Evans et al 2002). In the majority prodrome may precede the headache phase by 1–24 hours but in a few can be up to 48 hours early. If it lasts for more than 6 hours and less than 48 hours prior to headache onset, it is nonevolutive prodrome (Tipper 2001; Evans and Mannix 2002; Kelman 2004). Symptoms tend to be vague and nonfocal and can be divided into systemic, neurologic and autonomic. Latter consist of nausea, constipation, yawning, fluid retention, polyuria, feeling cold and diarrhea, whereas systemic symptoms usually are food cravings, anorexia, and feeling tired. Neurologic symptoms range from irritability, malaise, depression, lethargy, disinhibition, photophonophobia, fatigue, and hyperactivity, or musculoskeletal symptoms (muscle tenderness, and stiffness) (Tipper 2001; Evans and

Mannix 2002; Rozen 2004; Kelman 2004). Many patients notice mild cognitive difficulty. Appetite changes may include cravings for starchy or sweet foods; leading to the erroneous idea that chocolate is a trigger factor (Marcus 1997). Rozen (2004) described redness of nose as prodromal symptom in a young woman. Recognition of the prodrome is important in the early treatment paradigm (Evans and Mannix 2002; Kelman 2004), as the attack can be aborted in the pre-headache phase in up to 60% of patients (Luciani et al 2000; Rozen 2004).

An aura is present in 15%–20% of migraineurs. In contradistinction to the prodrome, this is a focal phenomenon which can have both “positive” (extra sensations) and “negative” (lack of sensation) symptoms (Silberstein et al 2002). Each aura symptom typically lasts 5–60 minutes. Ninety nine percent of the migraine patients with aura experience a visual aura in at least some of their auras. The most common is the visual scintillating scotoma, which is a field defect, circumscribed by shimmering lights (Kirchmann 2006). If aura consists of more than one symptom, they come in quick succession. Sensory and visual auras occur on one side of the body. Sensory phenomenon (54%), and speech/aphasic symptoms (32%) are the most common, though motor, (Thomsen et al 2004) and vertiginous symptoms (Eggers 2006) have been described. The two most common of the auras, sensory and the speech, are the only ones that the new International Headache Society classification (ICHD-II 2004) lists. Their criteria for migraine with aura are: gradual development of the symptom over 4 minutes, duration should be less than 60 minutes, consisting of one or more reversible brain symptom and the headache should follow within 60 minutes of it. When the aura occurs without an after following headache, it is called acephalgic migraine. Although variation in duration can occur, prolonged or severe aura type symptoms should alert the physician that a neurologic work-up might be indicated.

Next, in the headache phase, the pain is classically described as an intensely throbbing unilateral headache. It may begin on the face, scalp, or neck and often becomes holocephalic as it peaks. It is variably associated with nausea, vomiting, phonophobia, photophobia, and most importantly is worse with activity (ICHD-II 2004). Patients typically seek a cool, dark and quiet place; and sleep can induce headache resolution. When the headache recedes, the postdrome phase begins, during which the person feels that they have just battled a storm. They feel tired, “hung-over”, and may have cognitive difficulties, GI symptoms, mood changes or weakness. The area of previous headache is now tender and

hypersensitive to touch even combing the hair can become unbearable because of scalp sensitivity. This pain that results from nonnoxious stimuli to normal skin is called allodynia (Burstein 2000). Recently Kellman (2006) showed that 68% of the 827 migraineurs studied reported above mentioned symptoms in the post headache period.

In 2004, the International Headache Society in collaboration with the American Headache Society published a revised classification system for all types of headaches. Originally designed to promote common terminology and diagnosis for headache research studies, it has also fostered a better understanding of migraine symptoms and diagnosis for practitioners (Classification and WHO ICD-10 Codes – IHS ICHD-II 2004).

Despite the vast number of migraine sufferers and disabling features of migraine, only a small percentage of patients see a physician. Lipton et al (2006) found that although half of the migraine patients, identified in random telephone interview, had been to see a physician, one third had never consulted a doctor for their headaches and 21% had not seen one in the last year. Some do not believe they have migraine; others do not have confidence in what medicine has much to offer. Many with migraine instead turn to over-the-counter headache medications, which have proven efficacious only in mild migraine. It has been shown that 94% of patients that present to the primary care physician's office with the complaint of recurrent episodic disabling headache are suffering from migraine or migrainous headache (Newman et al 2002; Tepper et al 2004). A correct diagnosis on the first visit with subsequent corroboration via headache diaries can speed the therapeutic process along.

## The pathophysiology of migraine

The best treatment for any disease comes from understanding its pathophysiology. According to Wolff's original vascular concept, the initial event of a migraine was vascular constriction, giving rise to aura due to focal hypoperfusion of the cortex. It was presumed that this was followed by a reactive vasodilatation, resulting in throbbing headache. This paradigm fits in very nicely with some but not all of the symptoms of migraine. In the latter half of the last century, brain perfusion studies and other data disproved Wolff's theory. Currently, migraine is considered a neurovascular disorder involving the trigeminovascular system (Welch 2003; Silberstein 2004; Goadsby 2005). The genetic predisposition is most certainly multifactorial, autosomal dominant with hundreds of different mutations (Edvinsson and Uddman 2005; Takeshima and Nakashima 2005). The

paroxysmal nature of migraine suggests that it might be related to mutations in the calcium channel gene rendering neurons unstable so they react to normal environmental stimuli abnormally initiating the migraine attack (Bussone 2004; Gargus 2006).

The trigger mechanism, though not well understood, may in many cases be related to hypersensitivity of occipital (Aurora et al 1998; Welch 2003), hypothalamic, and limbic cortex, or other cortical structures affecting parasympathetic pathways (Burstein and Jakubowski 2005a). The prodrome phase of the migraine is possibly related to hypothalamic activation/dysfunction (Tipper 2001; Benjamin et al 2004), and hyperexcitability of central pain processing (Burstein 2000) with, possibly, increased dopaminergic activity (Peroutka 1977).

In the 1940's Brazilian physiologist, Aristides Leão (1944), showed that application of potassium chloride directly to rat cerebral cortex caused a depression of cortical activity that gradually spread to the adjacent cortex at the rate of 3–4 mm/minute. A few years prior Karl S. Lashley (1941), a neurologist, documented the rate of spread of his own visual aura and postulated that this must be due to a spreading cortical phenomenon. The two observations were linked and cortical spreading depression (CSD) has been accepted as possible major underlying mechanism of migraine aura (Dalkara et al 2006). Hadjikhani et al (2001) used functional magnetic resonance imaging (fMRI) to show blood oxygenation dependent signal changes in the cortex of patients with migraine aura occurring from occipital cortex frontally at the rate of 3–5 mm/min in conjunction with decreased visual acuity. CSD as a generator of visual aura has also been supported with transcranial magnetic stimulation (Aurora 1998). Studies show that CSD in migraine is preceded by a brief phase of cortical spreading excitation. This helps to explain why neuromodulators, which inhibit depolarization, decrease the migraine aura frequency (Silberstein 2004).

The trigeminal system innervates the meninges, and provides sensory innervation to the intracranial vessels. The neuronal bodies of these sensory neurons lie within the trigeminal ganglia. Upon stimulation impulses travel antidromically to dural tissue causing dilatation of the meningeal blood vessels and local release of neuropeptides – Substance P, nitric oxide, vasoactive intestinal polypeptide, 5-HT, Neurokinin A and CGRP, a potent vasodilator. This leads to plasma protein extravasation and initiation of sterile neurogenic inflammation. While it is an important factor in causing headache pain, it is not clear if it is by itself sufficient or other stimulatory factors are required to be part of the process leading to pain

in the head (Welch 2003; Goadsby 2005; Edvinsson and Uddman 2005). The nociceptive activation process leads to peripheral sensitization, with further release of excitatory neurotransmitters mediated by opening of sodium channels (Arulmani et al 2004; Edvinsson 2004).

Neurogenic inflammation in the meninges causes reactive impulses from the meningeal first order trigeminal neurons to travel orthodromically back to the brainstem to the trigeminal nucleus caudalis (TNC). From the TNC, second order neurons promote stimulation of central structures responsible for prolongation and wind up of the migraine process. From the TNC the information travels:

- 1) Through second order neuron central projections via the thalamus to cortical third order neurons for central pain perception;
- 2) Through parasympathetic pathways (hypothalamus-superior salivatory nucleus – sphenopalatine ganglion) to give rise to increased secretions in the sinus cavities and tear ducts; and
- 3) Through the upper cervical fibers mediating pain from the back of the head and upper neck area (Ramadan 2005; Goadsby 2005).

Central Sensitization perpetuates the migraine after the initial onset. It involves wide dynamic range neurons at the TNC level to ventral postero-medial nucleus of thalamus and cortex. Once started, it maintains itself without any extraneous input. More than 4/5 of migraine sufferers experience central sensitization as evidenced by prolonged allodynia, which is associated with release of excitatory neurotransmitters in central nervous system (CNS). Thus, there is excessive NMDA receptor activation. Normally it is modulated by brainstem pain modulation centers, (peri-aqueductal gray (PAG) and locus ceruleus) but in migraine and other pain states, these centers may be dysfunctional (Welch 2001; Silberstein 2004).

Serotonin is an important neurotransmitter in migraine. It has been shown that during a migraine attack the excretion of 5-hydroxyindole-acetic-acid increases. Serotonin itself, when given slowly intravenously (IV), can abort a migraine attack. Since it is widely present in the body, with both stimulatory and inhibitory effects, there are many side effects of unadulterated 5-HT so it is not used for migraine treatment. Fortunately, the more selective 5-HT agonists are better tolerated.

There are seven different subsets of 5-HT receptors<sup>(1-7)</sup>, some inhibitory and others excitatory. The receptors for 5-HT<sup>1-4</sup> and 5-HT have been identified. 5-HT<sup>1</sup> has five subgroups: A, B, D, E and F. Triptans are relatively selective agonists at the inhibitory 5-HT<sup>1B/1D</sup> receptor sites, thereby

inhibiting release of vasoactive peptides. Trigeminal nerve endings also have 5-HT<sup>1D/1F</sup> receptors endings, which inhibit the release of CGRP and substance P. 5-HT<sup>1B</sup> receptors are present post-synaptically in cerebral blood vessels and their stimulation leads to vasoconstriction. 5-HT<sup>1F/1B</sup> receptors are known to inhibit the release of acetylcholine, noradrenalin, and serotonin (Villalón 2003; Silberstein 2004).

## Central modulation of pain

During the last decade, the central modulation of pain in migraine has been of major interest. Brainstem centers such as the PAG normally receive and modulate sensory neuronal input. In migraine and other pain states, these centers are dysfunctional resulting in excessive thalamic activity leading to increased pain perception. The initiating trigger in the brainstem may be linked to a familial channelopathy (Kors 2003; Gargus 2006). In patients experiencing migraine with aura, a positron emission tomography study demonstrated activation of the dorsal midbrain, including PAG and pons near the locus ceruleus. These areas were activated immediately after successful treatment of pain (Weiller et al 1995). It was subsequently shown in an fMRI study that the PAG was not activated when the subject was paying attention to the pain stimulus and there was high intensity pain, but was activated during distraction from the pain stimulus when the perception of pain was lessened. The conclusion was that the PAG induces analgesia (Silberstein 2004).

An excitatory modulatory mechanism in migraine is via the neurotransmitter glutamate. Migraineurs have CNS hyperexcitability involving overactivity of excitatory amino acids, such as glutamate and aspartate. Levels of these neurochemicals have been found in the cerebrospinal fluid and plasma of migraineurs. Their presence is associated with hyperalgesia mediated by peripheral and central sensitization (Ramadan 2005). Glutamate action is mediated through both NMDA and non-NMDA receptors; the latter include kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Studies on rats show these receptors mediate the relay of impulses from peripheral trigemino-vascular neurons and spinal cord nociceptive transmission. For example, kainate (KA) injections cause hyperalgesia, which can be reduced by the administration of KA receptor antagonists (Ta et al 2000). Some KA receptors are effective in preventing dural plasma protein extravasation.

Two other modulatory mechanisms are worth mentioning, NMDA antagonists (memantine and MK-801) and non-NMDA antagonists (CNQX and NBQX). They block c-fos expression in the TNC in migraine animal models,

following superior sagittal sinus stimulation. Ketamine, a nonselective NMDA antagonist, has also shown efficacy in the treatment of migraine with aura and other chronic pain states (Kaube et al 2000). Its use in clinical practice is currently limited due to hallucinatory side effects. In the future NMDA antagonists may play a larger role in migraine treatment.

## The role of inflammation

Neurogenic inflammation occurs in migraine, although it is not the usual “wheal and flair” type of inflammatory response. Nonsteroidal anti-inflammatory drugs, (NSAIDs) alleviate inflammation and this appears to be same effect in migraine. The benefit of NSAIDs in migraine could well be a nonspecific analgesic effect. The mechanism for this might involve decreased release of inflammatory proteins, which decrease activation of sensory neurons, by reducing free radicals, which decreases nociceptor activation. Lastly, by blocking prostanoid receptors or prostaglandin synthesis which limits the inflammatory pain response (Waeber and Moskowitz 2005).

## Treatment of acute migraine

Once the diagnosis of migraine has been established, an explanation of the neurologic condition to the patient and family is helpful in establishing the patient’s confidence in the diagnosis and management approaches. During this time, patients should be asked about their goals, to help bring any unreasonable expectations out into the open. For instance, complete freedom from headache may not be attainable, and they need to be aware of the present limitations. The patient is then presented with a plan that helps empower him/her to participate in the management of the headaches. Passive, helpless behavior is discouraged. Patients should know what they should do for their next migraine attack including rescue therapy if needed. To facilitate ongoing communication and determining triggers, a headache and medication diary might be useful (Loder 2001; Rothrock 2006). Avoidance of over use of acute medications to prevent rebound headache or transformed migraines is emphasized. The goal is to improve pain control, quality of life, and daily function through appropriate treatment (Adelman and Adelman 2001).

The details of dealing with prophylactic treatment for migraineurs with two or more days of moderately severe to severe headaches per week will not be detailed here. That is a chapter in itself. Suffice it to say that patients who have two or more days of moderately severe to severe headaches per week, should be prescribed prophylactic medications, taking into account comorbidities and pregnancy risk.

The US Headache Consortium published its recommendations for the treatment of migraine in 2000 (Silberstein 2000). Acute treatment is divided into migraine-specific and nonspecific therapy. Nonspecific therapy is further divided into pharmacological and nonpharmacological modalities, as shown below.

1. Specific migraine treatment
  - a. Triptans
  - b. Ergot and its derivatives
2. Nonspecific pharmacological treatment
  - a. Antiemetics
  - b. NSAIDs and nonnarcotic analgesics
  - c. Narcotics – Opiate analgesics
3. Miscellaneous medications:
  - a. Steroids, isometheptene, lidocaine intranasal (IN),
  - b. valproic acid IV
4. Nonpharmacological treatment
  - a. Biofeedback
  - b. Visual imagery (quite useful in children)
  - c. Icepack
  - d. Relaxation therapy
  - e. Yoga, meditation

## Triptans

Ideally, acute treatment of migraine should work rapidly, with few side effects, be cost effective and get the patient functional as soon as possible. The triptans, selective serotonin 5-HT<sup>1B/1D</sup> agonists, are the closest drugs we have to the ideal drug. Sumatriptan (SUM), the first triptan to be released in the US, was followed by six more releases within a decade. These include naratriptan (NAR), zolmitriptan (ZOM), rizatriptan (RIZ), almotriptan (ALM), eletriptan (ELE) and frovatriptan (FRO). While they all mainly target 5-HT<sup>1</sup> receptors, there are some differences in efficacy and tolerability as shown by meta-analysis (Ferrari 2002). Triptans constrict the dilated meningeal arteries through stimulation of 5-HT<sup>1B</sup> receptors on the blood vessel wall. They also inhibit neurotransmitter release and nociceptive transmission by stimulating 5-HT<sup>1D</sup> receptors on central and peripheral trigeminal sensory nerves. They are unable to block ongoing sensitization in the second order trigeminovascular neurons. Therefore, triptans should be used early in the headache before central sensitization has occurred and allodynia has set in (Burststein and Jakubowski 2005b).

Table 1 shows results of the meta-analysis comparing the different triptans to SUM 100 mg as an arbitrary standard (Ferrari 2001). In practice, responses vary from patient to patient. If one triptan does not work despite taking it early and in adequate doses, then a trial of a 2nd triptan is warranted.

**Table 1** Triptan comparison compared to 100 mgs of sumatriptan. Copyright © 2002. Reproduced with permission from Ferrari MD, Goadsby PJ, Roon KI, et al 2002. Triptans (serotonin 5-HT<sup>1B/D</sup> agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalgia*, 22:633–58.

	Initial 2 h Relief	Sustained Pain relief	Consistency	Tolerability
Sumatriptan 50 mgs	=	=	=/-	=
Sumatriptan 25 mgs	=	=/-	-	+
Zolmitriptan 2.5 mgs	=	=	=	=
Zolmitriptan 5.0 mgs	=	=	=	=
Naratriptan 2.5 mgs	-	-	-	=
Rizatriptan 5 mgs	=	=	=	=
Eletriptan 20 mgs	-	-	-	=
Eletriptan 40 mgs	=/+	=/+	-	=
Eletriptan 80 mgs	+	+	=	-
Almotriptan 12.5 mgs	=	+	+	++

Factors that affect the treatment of a migraine attack include the presence of chronic or medication overuse headache, fast onset migraine, or prolonged migraine. Medication overuse headache may not respond to acute treatment until the patient has withdrawn from the dependence-producing substance. Fast onset migraine may require intranasal administration of SUM or ZOM or subcutaneous (SQ) SUM. Menstrual migraine patients may need to start medicating a day before expected headache as “mini-prophylaxis” with NAR, SUM or FRO tablets (Mannix 2005).

Oral triptan doses are titrated according to efficacy and side effects. Until recently, SQ SUM was available only in a 6 mg dose, but a recent clinical research showed that a 3 mg dose was comparable in efficacy with superior tolerability (Landy et al 2005). Since April 2006, a 4 mg SQ dose is available. Although studies have been published on patients less than 18 years of age showing efficacy and safety (Damen 2005), the triptans are currently not FDA approved for this age group. It is disturbing that despite the availability of effective drugs, less than 50% of migraineurs in the US receive prescription medicine for their headache as of 1999, according to the American Migraine Study II (Lipton et al 2001b). Although it is possible that the current percentage of triptan users has increased in the last six years, but there are no more recent studies from the US. The same situation exists around the world (Dowson 2003; Morillo et al 2005). This is partly due to misunderstanding of the disease by the public and misdiagnosis by physicians. The perceived potential for coronary vasoconstriction has also limited prescribing practices. Patients who experience noncoronary chest pain may be unduly wary of ever taking a triptan again. The Triptan Cardiovascular Safety Expert Panel convened

in 2002 and concluded that it is safe to prescribe triptans in patients with no known coronary artery disease (Dodick et al 2004). The origin of the transient chest discomfort from triptans is unknown. It is not attributed to cardiac ischemia and is without clinical sequelae. A study done involving 75 patients with known coronary artery disease revealed no clinically significant electrocardiographic ischemic changes or arrhythmias after FRO 2.5 mg administration for migraine (Elkind et al 2004).

CNS side effects such as mild sedation, dizziness or cognitive problems can occur depending on lipophilicity and active metabolites. Landy and colleagues found that FRO, RIZ, ZOM and ELE have a higher CNS side effect profile, whereas SUM, NAR and ALM are better tolerated (Dodick and Martin 2004).

Concerning teratogenicity, a study published in 2004 found the same incidence (3–5%) of birth defects in babies born to mothers who took SUM during pregnancy as in babies born to unexposed mothers (Hilaire et al 2004).

### Ergots/ergot derivatives

Ergotamine and ergotamine-caffeine combination pills still play a role in the acute treatment of migraine in those patients who do not respond adequately to triptan therapy. Ergotamine has more side effects (nausea, vomiting, peripheral and coronary vasoconstriction) due to its relatively nonselective adherence to serotonin, dopamine and adrenergic receptors (Villalón et al 2003). Dihydroergotamine (DHE) is a long lasting potent anti-migraine drug that can be given parenterally as SQ, intramuscular (IM), IV, or IN routes, for a severe migraine attack. Pretreatment with an anti-emetic might be necessary. Its venous vascular effects are more potent than arterial, but it should be avoided

in patients with known cardiovascular and peripheral vascular disease (Silberstein 2000).

## Nonspecific pharmacological treatment

This is used, either in addition to selective acute migraine therapy or as a rescue medication, in those patients whose headache continues despite adequate and prompt triptan therapy. The patients are to limit its use to 2 days per week, as a rule, to avoid medication overuse headache. Potential agents may include:

1. Antiemetics
  - a. Chlorpromazine – IV/IM
  - b. Prochlorperazine – IV/IM/Per Rectum (PR)
  - c. Metoclopramide – IV/IM/PR – IM/PR routes have shown inconsistent evidence for efficacy but may help with gastric paresis, which occurs during migraine, thus improving absorption of other oral medications. It is also used IV with DHE to counteract nausea.
2. NSAIDs and nonnarcotic analgesics
  - a. Ketorolac IM, IV
  - b. Oral NSAIDs: aspirin, naproxen, diclofenac, ibuprofen etc are all beneficial in mild migraine (Diener et al 2004; Lipton 2005).
  - c. Combination analgesics
    - i. Acetaminophen, aspirin, caffeine (mild migraine)
    - ii. Butalbital, ASA, caffeine – has shown inconsistent evidence for efficacy in migraine, mainly studied in tension-type headache.
    - iii. Isometheptene mucate, acetaminophen, dichloralphenazone
3. Opiate analgesics – to be used judiciously by experienced physicians, primarily as a ‘reserve’ medication, for acute severe attacks not responsive to selective abortive agents. This can prevent overuse of ER services in patients with difficult to control migraine pain.
  - a. Butorphanol nasal spray
  - b. Acetaminophen with codeine, hydrocodone, hydro-morphone
  - c. Oral transmucosal fentanyl citrate
4. Nonopiate analgesics
  - a. Tramadol – a synthetic analog of codeine, which can cause respiratory depression and has a potential for abuse, even though this is comparatively less than traditional opioid drugs
  - b. Tizanidine – centrally acting muscle relaxant with alpha 2- adrenergic receptor activity
5. Miscellaneous medications
  - a. Steroids (infrequent use)
    - i. Methylprednisolone dose pack
    - ii. Dexamethasone (maximum 4 tabs per month)
  - b. Lidocaine IN – probably more useful in cluster headache
  - c. Valproic acid IV
  - d. Propofol IV

## Use of a preventive medication as an acute therapy

There have been times when a patient has told one of us that they obtain benefit from taking a dose of their preventive medication acutely, outside of the prescribed usage parameters. The usual medications involved are amitriptyline, cyproheptadine, and propranolol. When valproic acid became available in a parenteral form, this treatment was studied for severe acute migraine (Stillman et al 2004; Leniger et al 2005). The reported effective dose for one administration is 500 mg given as a bolus over 15 minutes to 30 minutes (Schwartz 2002; Reiter 2005).

## Opioid analgesics

The use of opiates is restricted to patients who are unresponsive to migraine specific therapies and require frequent emergency room (ER) visits to abort their migraine. The judicious use of opiates can markedly reduce cost and time as well as increase the patient’s sense of self-control in such cases. Opiate dependence and addiction must be screened for before choosing this option for the patient. Its use is best left for the specialists in pain and headache management. Synthetic opioid analogs, like tramadol, are comparatively safer due to lower affinity for opioid receptors. Therefore, they have less potential for abuse or respiratory depression but these problems can still occur. It is recommended that these medications also be used with the same care as opioids (Cicero et al 1999; Grond 2004; Keskinbora and Aydinli 2006).

Nonoral opioid medications are especially helpful in patients who are vomiting too much to keep pills down. Butorphanol nasal spray’s efficacy has been proven (Loder 2005). Most practitioners limit prescriptions to one unit (8–10 sprays) per month. Landy (2004) has documented the successful use of oral fentanyl lozenges in refractory migraine.

## Combination specific/nonspecific pharmacological treatment

In response, to the recent trend in clinical practice towards combination therapy, several studies have been reported.

A Brazilian researcher, AV Krymchantowski, studied 45 patients in an open-label randomized protocol, using a combination of RIZ plus the COX-2 inhibitor rofecoxib (RO) or the NSAID tofenamic acid (TA). Results showed a superior pain-free response at 2 hours with RIZ + RO (62.9%) and RIZ + TA (40.6%) compared with RIZ alone (37.9%) and a better recurrence rate as well (Krymchantowski and Bigal 2004). Smith et al and Wargin et al found superior efficacy of SUM + Naproxen in two separate trials presented at the 2005 American Academy of Neurology (AAN) annual meeting. This combination is being considered for FDA approval to be released by Glaxo Smith Kline under the trade name Trexima.

Dr. Krymchantowski also showed efficacy of the combination of RIZ and trimebutine, an opioid derivative at the 2005 AAN annual meeting. This chemical binds only to the receptors of the Meissner and Auerbach plexi in the gastrointestinal tract and decreases gastroparesis. The combination proved more effective than either compound alone in achieving freedom from nausea, photophobia, and pain at 1 hour and 2 hours.

Migraine pain travels to the back of the head via the C2 pathway. A retrospective study of headache patients in an ER setting showed that bupivacaine injected into the lower cervical paraspinal muscles was effective in providing complete pain relief in 65.9% and partial relief in 18.6% (Mellick and Mellick 2004). Occipital nerve blockade has also been used with some success. Greater occipital nerve blocks and trigger point injections are reported to reduce allodynia and pain in migraine patients (Ashkenazi and Young 2005).

## Nonspecific nonpharmacological treatment

Psychophysiologic management (“biofeedback”), self-relaxation, trigger point massage, acupuncture and visual imagery are some of the current methods in use to help migraine patients. An interesting observation led M. Friedman, DDS, to develop a cooling device for migraineurs. He observed that in the majority of his migraine patients the laterality and intensity of the intraoral tenderness in the maxillary area, was very, closely related to the laterality and severity of their head pain. A cooling device, was developed, which was found to be superior in efficacy to oral SUM 50 mg and placebo in a double-blinded randomized placebo controlled study. Twenty-four hours later, there was some recurrence with SUM treated group but none with intraoral chilling and the side effects were more frequent in the SUM treated group (Friedman 2001).

Many studies demonstrating the effectiveness of a variety of nonpharmacological modalities have been reviewed over the years. Although definite proof of effectiveness through traditional scientific method may be lacking in some instances, they deserve mention due to popularity in some patient groups. Many of these prophylactic treatment modalities, though generally used for prophylaxis of migraine, can benefit patients during their acute migraine attacks. These consist of applying localized pressure on temporal artery (Drummond and Lance 1983), cryotherapy (Robbins 1989; Silberstein 1993; Friedmann 2001), punctate transcutaneous electric nerve stimulation (Heydenreich 1988), acupuncture points used were for gallbladder/large intestine/liver (Melchart et al 2003) or in the ear (Romoli et al 2005), relaxation techniques like visual imagery and progressive muscular relaxation probably for slowly evolving migraine (Pryse-Phillips et al 1998), and biofeedback used mostly in pregnant patients (Silberstein 1993; Pfaffenrath and Rehm 1998). These are of special importance in patients who do not wish to use medications, in pregnant patients and for those patients in whom triptans are contraindicated.

## In search of the ideal antimigraine drug

Although the identification of the triptans as migraine-specific therapy has revolutionized migraine management, they are not the panacea we once thought they were. The potential side effects, recurrence rate (about 1/3), response rate (60%–70%) and contraindications limit their universal use. Therefore, investigators are exploring new migraine targets at initiation, progression and perpetuation of the attack. Among the 5-HT<sup>1</sup> receptors, the 1D and 1F ligands have no effect on the cardiovascular system. Two products recently evaluated (LYT334370-109291 and PNU-142633), are highly selective agonists for 5-HT<sup>1D</sup> receptors. They both inhibit the extravasation of plasma proteins in the dura as shown in animal studies, but have not been shown to possess vasoconstrictive effects. Unfortunately, these agents have not been clinically effective unless used at doses that also effect 5HT<sup>1B</sup> receptors, thereby negating the selectivity of the drug in vivo (Villalon et al 2003).

The 5-HT<sup>3</sup>-receptor is a ligand-gated channel, present in the CNS, peripheral nervous system and other cells. It is known to be involved in pathological processes in which there is increased release of serotonin. It modulates the release of neurotransmitters, and neuropeptides and affects regulatory functions, thus its antagonists

have shown clinical efficacy in studies for controlling vomiting, anxiety, chronic fatigue and pain in migraine, fibromyalgia and rheumatic disease (Farber 2004). Studies are ongoing with the 5-HT<sup>7</sup> receptor agonists testing their potential for treating migraine.

## Calcitonin gene related peptide (CGRP)

Currently CGRP1 antagonists hold promise as new antimigraine drugs. Two recently introduced are: BIBN4096BS and Compound 1. BIBN4096BS was tested in the marmoset trigeminal ganglion and found to inhibit vasodilatation. Other experiments support its possible role as an nociceptor mediator in migraine. Compound 1 has similar properties but is less potent than BIBN4096BS in human tissues. A third smaller CGRP antagonistic molecule is SB-273779. It has similar properties as the other two but may have greater value for the study of migraine and CGRP activity in animal models.

The efficacy of BIBN4096BS has been tested in humans in two studies published in 2004. In the first, the safety, tolerability and pharmacokinetics of BIBN4096BS were tested in healthy volunteers. After a single IV administration of gradually increasing dose, most of the adverse events occurred at the highest administered dose (10 mg) and were relatively mild and transient. (Iovino et al 2004) In another controlled study, moderate or severe headache was treated with 2.5 mg of BIBN4096BS IV vs. placebo. The end-point of pain reduction within 2 hours to mild or no pain was achieved in 66% of BIBN4096BS treated patients vs. 27% of the placebo group (Doggrell 2004). In clinical practice, its potential use will be limited to settings appropriate for IV administration.

## The glutaminergic system

Among other avenues for migraine treatment, attention is being given to blockade of central and peripheral sensitization, which can be done by modulation of the glutaminergic system. One of these is an ampakine-KA receptor antagonist, which blocks signals from these receptors without constricting blood vessels, thereby inhibiting central sensitization. Phase I trials are underway.

Another AMPA-KA receptor antagonist named LY293558 was recently reported by Sang et al (2004) to be efficacious in treating migraine. A randomized triple-blind, parallel group, double dummy, multi-center trial tested LY293558 vs. SUM SC vs. placebo for one acute headache in forty-five patients including women of childbearing age.

They were given LY293558 IV + placebo SC, SUM SC + placebo IV or placebo IV + SC within 8 hours of migraine onset. The pain free rate at 2 hours for LY293558 was 54%, for SUM it was 60% and for placebo, 6%. Three of the patients who responded to treatment had recurrence: one after SUM and two following placebo. Fifteen percent of the LY293558 group had side effects, 53% of the SUM group and 31% of the placebo group.

## New routes of administration

There are some devices in phase I trials, which look promising. Alexza Molecular Delivery Corp. developed a device, called Staccato, for faster delivery of drugs via inhalation. A heating device turns the drug into a mist of micro-particles with rapid uptake from the lungs. Phase I clinical trials using prochlorperazine have been promising. Vyteris, another company, is working on a transdermal delivery system, which includes a low voltage electrical current to help release SUM into the dermal blood vessels. An initial bolus is followed by a sustained release of the drug. Phase I trials with SUM have been positive.

Novartis is developing DHE in a powder form for nasal use. Phase I trials have shown the powder works faster with a longer duration of action than the current spray formulation. Another device is being investigated which will soon start phase II investigation. This machine sends pressurized carbon dioxide up one nostril and out the other. The gas is not inhaled, but after permeating through the nasal mucosa forms carbonic acid, which apparently prevents nociceptor stimulation. It is effective primarily in mild to moderate migraine.

## Conclusion

This review emphasizes the practical treatment of migraine as well as the progress that has been made in defining migraine pathophysiology and in developing new specific therapies. There is room for better efficacy and tolerability. It appears that the pharmaceutical and bioengineering industries, in recognition of the large market of migraine sufferers, is working towards newer and better approaches for affective interventions.

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