

# MIGRAINE IN THE TRIPTAN ERA

## Progresses achieved, lessons learned and future developments

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**Abstract** – Triptans, serotonin 5-HT<sub>1B/1D</sub> receptor agonists, more than revolutionizing the treatment of migraine, stimulated also ground breaking research that provided insights into the anatomy, physiology, and molecular pharmacology of migraine. This knowledge, in turn, is stimulating research on new mechanisms of action for the treatment of migraine. Accordingly, it is opportune to critically review the main advances in migraine science that happened in the triptan era. Herein we first review and conceptualize some of the progresses achieved in migraine science during the triptan era. We then review the class of the triptans – mechanism of action and clinical evidence. We close by briefly discussing the class of CGRP receptor antagonists, which is currently being developed for the acute treatment of migraine.

KEY WORDS: migraine, triptans, CGRP antagonists, emerging drugs.

### Migrânea na era dos triptanos: progressos alcançados, lições aprendidas e desenvolvimentos futuros

**Resumo** – Os triptanos, agonistas serotoninérgicos 5-HT<sub>1B/1D</sub>, revolucionaram o tratamento da migrânea promovendo pesquisas que evidenciaram aspectos da anatomia, fisiologia e farmacologia molecular deste tipo prevalente de cefaléia primária. Esse conhecimento, por sua vez vem estimulando ainda mais a descoberta de novos mecanismos de ação para drogas anti-migranosas. Assim, é oportuno rever de forma crítica, os maiores avanços na ciência das cefaléias ocorridos durante a era dos triptanos. Inicialmente reveremos e conceituaremos alguns dos progressos obtidos nesta fase seguido de uma revisão profunda dos mecanismos de ação e evidências clínicas para o uso desta classe de fármacos. Finalmente, discutiremos a nova classe dos antagonistas dos receptores do peptídeo geneticamente relacionado à calcitonina (CGRP) atualmente em desenvolvimento.

PALAVRAS-CHAVE: migrânea, enxaqueca, triptanos, antagonistas do CGRP.

Migraine is a chronic neurological disorder characterized by episodic attacks of headache and associated symptoms<sup>1</sup>. Attempts to alleviate the suffering caused by migraine span millennia and encompass treatments as primitive as trepanation of the skull, to increasingly specific medications that act on receptor subtypes implicated in the pathophysiology of migraine<sup>2</sup>.

Triptans, serotonin 5-HT<sub>1B/1D</sub> receptor agonists, more than revolutionizing the treatment of migraine, stimulated also ground breaking research that provided insights into the anatomy, physiology, and molecular pharmacology of migraine<sup>3</sup>. This knowledge, in turn, is stimulating research on new mechanisms of action for the treatment of migraine.

Accordingly, it is opportune to critically review the main advances in migraine science that happened in the triptan era. To do so, we divided this views and reviews in two main components. We first review and conceptualize some of the progresses achieved in migraine science during the triptan era. We focus on selective themes, and for each, we briefly discuss the established concept (status quo), as well as the evolving knowledge on the area. We then review the class of the triptans – mechanism of action and clinical evidence. We close by briefly discussing the class of CGRP receptor antagonists, which is currently being developed for the acute treatment of migraine.

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## **PART 1 – LESSONS LEARNED IN THE TRIPTAN ERA**

### **1. The clinical features of migraine**

#### **The established concept**

Migraine is characterized by recurrent attacks of pain and associated symptoms, typically lasting from 4 to 72 hours<sup>1,4,5</sup>. It has features in common with episodic pain disorder (self-limited attacks of pain). It also has features in common with chronic pain disorders in that sufferers have an enduring predisposition to pain. It is therefore best described as a chronic-episodic disorder<sup>6</sup>.

The migraine attack can be divided in four phases: the premonitory phase (or prodrome), the aura, the headache phase, and the resolution phase (the postdrome). The presence or absence of aura distinguishes the two major types of migraine, migraine with aura and migraine without aura. It is worth of notice that migraine is classified based on the features that happen during the headache phase (headache and associated symptoms). This fact leads to misconceptions that are discussed in the next topic.

#### **The evolving concepts**

##### **1. Premonitory symptoms are frequent and may increase the awareness of migraine**

Premonitory symptoms may begin several hours before a migraine attack and extend to the headache phase. Because migraine is so often missed, if the onset of migraine can be predicted by the patients, awareness of the disorder would increase and create opportunities for pre-emptive or for very early treatment. Accordingly, recent interest has focused on headache predictors. Indeed, an electronic diary study demonstrated that a substantial proportion of the migraineurs could accurately predict their migraine attack based on the premonitory symptoms<sup>7</sup>.

The proportion of migraine sufferers with premonitory features ranges from 12% to 79%. In the Dutch population, a prospective study found that at least one premonitory symptom was reported by 86.9%, and 71.1% reported two or more. The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%)<sup>8</sup>. In a multi-national diary study, about 70% of the migraineurs had premonitory symptoms, the most common being feeling tired and weary (72% of attacks with warning features), having difficulty concentrating (51%), and a stiff neck (50%).

Lesson: The identification of premonitory symptoms and contributions to understanding their biology add to an understanding that migraine is much more than simply a pain problem.

##### **2. Migraine often mimics other headache disorders**

As much as 50% of the migraineurs believe that they have tension-type headache, sinus headache or stress-related headaches. This is due to misinterpretation of symp-

toms associated with migraine attacks. For example, neck pain is a common symptom occurring during a migraine attacks. Furthermore, due to the overlap in cervico-trigeminal pain processing<sup>9</sup>, neck pain and tenderness may trigger migraine pain and migraine may be accompanied by neck pain<sup>7</sup>, which may lead to a diagnosis of cervicogenic headache<sup>9</sup>. If a migraine sufferer experiences headaches triggered by stress, with prominent neck pain, the patient may be diagnosed as, suffering from “tension headaches”.

Similarly, referred facial pain with cranial autonomic symptoms, frequently experienced by migraineurs<sup>10</sup>, can explain the “sinus headache” diagnosis. It is well established that trigeminal stimulation leads to cranial autonomic activation with symptoms such as tearing, conjunctival injection and nasal congestion<sup>11</sup>. This may be seen in healthy volunteers with capsaicin injection into the forehead<sup>12</sup>. It is clear that activation of trigeminal afferents through a reflex that traverses the superior salivatory nucleus in the pons<sup>13</sup> and thence is distributed through the facial/greater superficial petrosal nerve pathway is the likely basis for these symptoms<sup>11</sup>. Other symptoms common in migraine include dizziness or vertigo and these can also contribute to an erroneous diagnosis.

Lesson: Awareness that between one quarter and one-third of migraineurs have “atypical” symptoms with normal migraine would reduce misdiagnosis.

### **2. The natural history of migraine**

#### **The established concept**

As previously mentioned, migraine has features in common with purely episodic pain disorders (like post-operative pain or post-traumatic pain), including the occurrence of self-limited “attacks” of pain and associated symptoms. It also has features in common with chronic pain disorders (like osteoarthritis or painful neuropathy) including an enduring predisposition to pain and disrupted health-related quality of life (HRQoL). Because migraine resembles both episodic and chronic pain disorders we currently conceptualize it as a chronic disorder with episodic manifestations or, to use the now preferred term, as a chronic disorder with episodic attacks<sup>6</sup>. However, migraine is largely considered to be a benign disease.

#### **The evolving concepts**

##### **1. Migraine has a variable prognosis and is sometimes a progressive disease**

The natural history and the prognosis of migraine have not been fully characterized but clinical observation and epidemiologic studies suggest 4 non-exclusive patterns<sup>8</sup> (Table 1). Some, migraine sufferers clinically remit, becoming symptom-free for prolonged periods of time (*Clinical Remission*). Other migraine sufferers continue to have headaches with fewer or less typical migraine features; in

Table 1. Population studies assessing the relationship between medication overuse and chronic daily headaches.

Authors/Study	Design	Design	Sample/Methods	Results
Frequent Headache Epidemiology Study <sup>34</sup>	Case-Control	Computer-assisted telephone interview	<ul style="list-style-type: none"> <li>• 206 individuals with CDH and 507 controls (with episodic or no headache).</li> <li>• Medication for headache and other painful conditions was assessed prior to the development of CDH and in an equivalent period of time for controls.</li> </ul>	<ul style="list-style-type: none"> <li>• Aspirin was protective against CDH (OR=0.55, 95% CI=0.3-0.9).</li> <li>• OTC+caffeine was associated with CDH (OR=1.6, 95% CI=95% CI=1.01–2.6).</li> <li>• Opiates more than doubled the chance of developing CDH (OR=2.37, 95% CI=1.1–4.9).</li> <li>• Analyses on barbiturates were limited due to sample size.</li> <li>• Triptans were not assessed.</li> </ul>
The Head-Hunt Study <sup>35</sup>	Longitudinal	Questionnaire-based interview conducted 11 years apart	<ul style="list-style-type: none"> <li>• 32,067 individuals responded to both interviews.</li> <li>• Headache not assessed during the baseline interview.</li> <li>• Assessed development of CDH and other forms of chronic pain.</li> </ul>	<ul style="list-style-type: none"> <li>• Daily or weekly use of analgesics at baseline was associated with a high risk ratio (RR) for chronic migraine (13.3), chronic non-migrainous headache (RR=6.2) and chronic neck pain (RR=2.4) at follow-up.</li> </ul>
American Migraine Prevalence and Prevention Study <sup>36</sup>	Longitudinal	Annual questionnaire based-interviews in representative sample of the US population	<ul style="list-style-type: none"> <li>• 8,219 individuals with episodic migraine drawn from a cohort of 24,000 headache sufferers.</li> </ul>	<ul style="list-style-type: none"> <li>• Incidence of CDH was 2.5% in the follow up interview.</li> <li>• Relative to acetaminophen, barbiturates (OR=2.06, 95%CI=1.3–3.1) and opiates (OR=1.98, 95%CI=1.4–2.2) increased risk of TM.</li> <li>• Overall, NSAIDs and triptans did not induce CDH.</li> <li>• In individuals with less than 10 days of headaches per month, NSAIDs use was protective.</li> <li>• In individuals with 10–14 days of headache per month, NSAIDs and triptans increased the risk of CM.</li> </ul>

these patients, attacks come to resemble probable migraine or even tension-type headache, rather than full-blown migraine (*Partial Clinical Remission*)<sup>14</sup>. Migraine attacks may continue over many years without major changes in frequency, severity or symptom profile (*Persistence*). Finally, in some, migraine attack frequency and disability may increase over time (*Progression*)<sup>15,16</sup>. Typically, progression refers to increases in attack frequency over time leading to chronic migraine (CM); we term this *clinical progression*<sup>17</sup>. Clinical progression is often associated with emergence of cutaneous allodynia and sensitization at the level of the trigeminal nucleus caudalis<sup>18</sup>; we term this *physiological progression*. In addition there are anatomic correlates of attack frequency including stroke and deep white matter lesions, which we term *anatomical progression*<sup>9</sup> (Fig 1). In describing these 4 patterns we do not suggest that each migraine sufferer follows a distinct, rigidly determined pathway<sup>19</sup>. Patients who remit may subsequently experience recurrence. Patients who progress to CM may eventually remit.

Lesson: Because migraine progresses in some but not most individuals, research will increasingly focus on the identification of factors associated with progression<sup>20</sup>. In the future, the assessment of the migraine patient may include an evaluation of risk factors for progression. Risk assessments may include screening for demographic features, concomitant conditions (obesity, depression), environmental risk factors (stressful life events, head injury) and eventually biomarkers and genes<sup>17</sup>. If studies demonstrate benefits, individuals at high risk for progression may be treated more aggressively to prevent progression. In this context, the goals of treatment will be to decrease current burden and prevent future burden.

## 2. Opioids and barbiturates increase the risk of migraine progression

Clinic-based studies, and limited population studies suggest that symptomatic acute medication overuse is associated with migraine progression<sup>21</sup> (Table 1). In patients with coexistent migraine, daily use of opioids to control

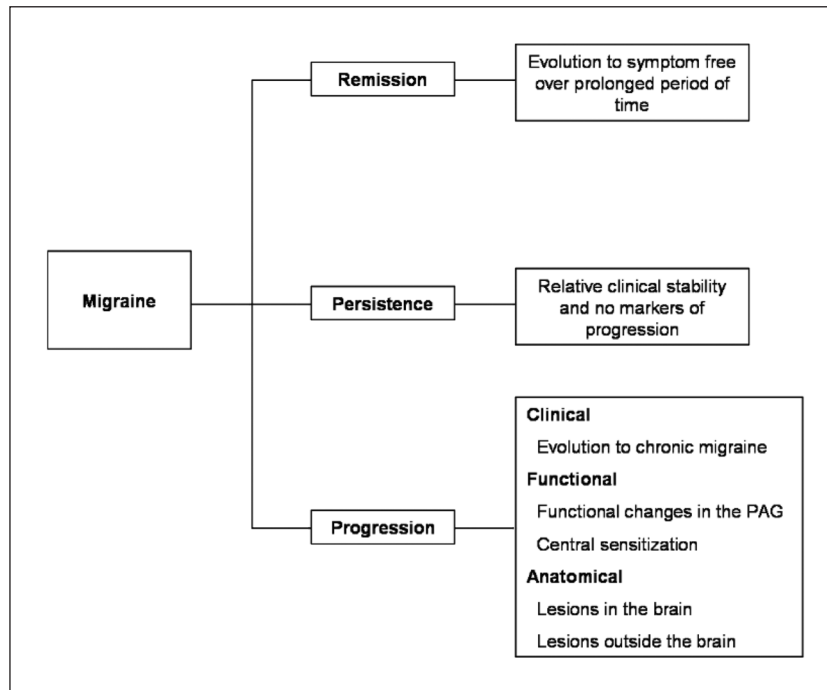


Fig 1. Pathway in the natural history of migraine.

bowel movements<sup>22</sup>, as well as analgesics for arthritis<sup>23</sup> and triptans for cluster headache<sup>24</sup>, are associated with the development of chronic migraine suggesting it is a sub-group of migraineurs who are at risk for this problem<sup>25</sup>. Unanswered questions regarded the causality of the relationship, and if acute medication overuse was a risk factor for chronic migraine overall, or if just specific classes of medication induced transformation.

A recently conducted population-based study (the American Migraine Prevalence and Prevention study) addressed the issue of causality by modeling probability of transition from episodic into chronic migraine over a 1-year period as a function of medication use status at baseline<sup>26</sup>. The most important conclusions of the study were: (1) Opiates are associated with migraine progression; critical dose of exposure is around 8 days per month, and the effect is more pronounced in men; (2) Barbiturates are also associated with migraine progression. Critical dose of exposure is around 5 days per month and the effect is more pronounced in women. (3) Triptans induced migraine progression in those with high frequency of migraine at baseline (10–14 days per month), but not overall; (4) Anti-inflammatory medications were protective in those with <10 days of headache at baseline, and, as triptans, induced migraine progression in those with high frequency of headaches.

Lesson: Specific classes of medications are associated with migraine progression, and high frequency of headaches seems to be a risk factor for chronic migraine.

### 3. Migraine is associated with cardiovascular disease and with subclinical brain lesions

**Migraine and stroke:** Migraine with aura has for long been considered a risk factor for stroke. Relative to individuals without migraine, the risk of stroke is increased in migraineurs [relative risk (RR)=2.16, 95% confidence interval (CI)=1.9–2.5]. This risk is higher for migraine with aura (MA) (RR 2.27; 95% CI: 1.61–3.19), but is also significant in migraine without aura (MO, RR, 1.83; 95% CI, 1.06–3.15)<sup>27</sup>.

Recently, the Women's Health Study assessed the relationship between migraine and a range of prospectively determined cardiovascular end points, using data gathered from nearly 28,000 presumably healthy women<sup>28</sup>. Migraine with aura was also associated with incident ischemic stroke [hazard ratio (HR)=1.70, 95% CI=1.1–2.6]. Similarly, as part of the Physician's Health Study, men with migraine (with or without aura) were at increased risk for major CVD (HR=1.24, 95% CI:1.06–1.46).

**Migraine and coronary heart disease:** Due to the association between MA and ischemic stroke, it is of interest whether migraine is similarly associated with coronary heart disease as well<sup>29</sup>. Three population studies supported the relationship between migraine and coronary disease. In the Atherosclerosis Risk in Communities study, patients with headache were roughly twice as likely to have a history of angina, as compared to controls, with the risk most elevated in MA<sup>30</sup>. In the Women's Health Study, MA but not MO approximately doubled the relative risk of major CVD (ischemic stroke, myocardial in-

Table 2. Putative mechanisms of the relationship between migraine and cardiovascular disease.

Mechanisms of association	Putative mechanisms	Comments
Causal Association (migraine causes CVD)	<ul style="list-style-type: none"> <li>• Repetitive episodes of cortical spreading depression may predispose to ischemia, perfusion changes and chronic inflammation.</li> </ul>	<ul style="list-style-type: none"> <li>• Justifies migraine with aura as a stronger risk factor.</li> <li>• Justifies the relationship with stroke but not with coronary problems.</li> </ul>
Shared predisposition (environmental and/or biological factors predispose to both migraine and CVD)	<ul style="list-style-type: none"> <li>• Migraineurs with aura are more likely to have poor cholesterol profile, elevated Framingham risk score for coronary heart disease, hypertension, and history of heart attack in the family.</li> <li>• A polymorphism of the C677T gene was seen in one study and codes high levels of homocysteine. Not confirmed by a second study</li> </ul>	<ul style="list-style-type: none"> <li>• Accordingly, migraineurs with aura are more likely to present one or multiple risk factors for CVD.</li> </ul>
Common comorbidities	<ul style="list-style-type: none"> <li>• Obesity is associated with increased headache frequency in both migraine with and without aura.</li> <li>• Limited evidence also suggests that metabolic syndrome predisposed to increased headache frequency.</li> <li>• Clinic-based studies suggest that PFO and other congenital heart problems are more common in migraine with aura.</li> </ul>	<ul style="list-style-type: none"> <li>• Likely magnifies the relationship between migraine with aura and cardiovascular disease, since frequency of attacks is associated with number of deep brain lesions. However, in some studies adjustments for body mass index were conducted.</li> </ul>

fraction, coronary revascularization procedures, angina, as well as death related to ischemic cardiovascular events)<sup>31</sup>. Finally, as part of the Physician's Health Study, men with migraine (with or without aura) were at increased risk for major CVD (HR=1.24, 95% CI:1.06–1.46), a finding which was driven by a 42% increased risk of myocardial infarction<sup>32</sup>. Putative mechanisms to explain the relationship between migraine and CVD are displayed in Table 2.

Subclinical changes on brain MRI: Changes in brain imaging that would be consistent with subclinical lesions, found incidentally in neuroimaging exams, have long been reported as happening more frequently in migraineurs. However, most studies did not have a contemporaneous control group and the pathology of these changes have never been studied. In a well designed double-blind population –study, conducted in The Netherlands, individuals with MA had significant increase of sub-clinical infarcts in the cerebellar region of the posterior circulation, although no increase in clinical stroke<sup>33</sup>. The highest risk for these lesions was seen in those with MA and more than one headache attack per month (OR=15.8 [1.8-140]).

Lessons: Migraine, especially migraine with aura, increases the risk of cardiovascular events, and providers should be aware of this association. Possible reasons for this association will be detailed below (pathophysiology of migraine).

### 3. The pathophysiology of migraine

#### The established concept

Migraine is best understood as a primary disorder of the brain<sup>34-36</sup>. There is abundant evidence that migraine is

a familial disorder with a clear genetic basis<sup>37</sup>. Established theories of migraine propose that migraine probably results from dysfunction of brainstem involved in the modulation of craniovascular afferents<sup>38</sup>. Brainstem activation may also lead to activation of ascending and descending pathways, with initiation of a perimeningeal vasodilatation and neurogenic inflammation. The pain is understood as a combination of altered perception (due to peripheral or central sensitization) of stimuli that are usually not painful, as well as the activation of a feed-forward neurovascular dilator mechanism in the first (ophthalmic) division of the trigeminal nerve<sup>39</sup>. Cortical spreading depression (CSD) is the presumed substrate of migraine aura; spreading depression also occurs in migraine without aura<sup>40</sup>, but may not be necessary to trigger the migraine pain (see below).

#### The evolving concepts

##### Cortical spreading depression may have specific consequences

CSD is a self-propagating wave of neuronal and glial depolarization. Cascading depolarization marching across the cortical mantle initiates a series of cellular and molecular events, resulting in transient loss of membrane ionic gradients, as well as massive surges of extracellular potassium, neurotransmitters, and intracellular calcium<sup>41</sup>. This is followed by a long lasting suppression of neural activity. The depolarization phase is associated with an increase in cerebral blood flow, whereas the phase of reduced neural activity is associated with a reduction in flow. This is thought to cause activation of trigeminal nerves and subsequent release of neuroinflammation mediators<sup>42</sup>. During CSD, oxygen free radicals, nitric oxide, and proteas-

Table 3. Generic and brand names (in the United States), and doses of the triptans.

Generic	Brand name in the US	Formulations	Doses	Maximum daily dose
Sumatriptan	IMITREX	Tablets	25 mg, 50 mg, 100 mg	200 mg
		Nasal spray	5 mg and 20 mg	40 mg
		Subcutaneous injection	6 mg	12 mg
		Suppositories	25 mg	50 mg
Zolmitriptan	ZOMIG	Tablets	2.5 mg, 5 mg	10 mg
	ZOMIG-ZMT	Orally disintegrating	2.5 mg, 5 mg	10 mg
	ZOMIG	Nasal spray	2.5 mg, 5 mg	10 mg
Rizatriptan	MAXALT	Tablets	5 mg, 10 mg	30 mg
	MAXALT- MLT	Orally disintegrating, Tablet	5 mg, 10 mg	30 mg
Naratriptan	AMERGE	Tablets	1 mg, 2.5 mg	5 mg
Almotriptan	AXERT	Tablets	6.25, 12.5 mg	25 mg
Frovatriptan	FROVA	Tablets	2.5 mg	7.5 mg
Eletriptan	RELPAX	Tablets	20 and 40 mg 80 mg available in some European Countries	80 mg

es such as the MMPs are increased which may further increase vascular permeability. As a clinical corollary, effective migraine prophylactics seem to share the ability to block CSD in rats despite being from different pharmacological classes<sup>43</sup>.

Lesson: CSD is closely associated with aura and aura progression. Activation the release of neuropeptides, nitric oxides, free radicals and activation of MMP may further contribute to neuroinflammation. Chronic neuroinflammation with the associated vascular changes may explain the deep brain lesions and enduring predisposition to stroke.

#### Glial waves may maintain and support the migraine attack

Recent attention has focused on the ability of astrocytes to propagate long-range calcium signals and actively communicate with each other, as well as with neurons and vascular cells<sup>44,45</sup>. Synaptic activity in neurons triggers an increase in the intracellular calcium concentration ([Ca<sup>2+</sup>]<sub>i</sub>) of neighboring astrocytes, stimulating the release of ATP and glutamate. The released ATP stimulates an increase in [Ca<sup>2+</sup>]<sub>i</sub> in neighboring astrocytes so that a “calcium wave” is propagated from cell to cell. The clinical relevance of astrocyte waves is that, being longer, they maintain the neuronal excitability, therefore predisposing to future migraine attacks and recurrence of migraine pain.

Lesson: Glial waves may maintain the neuronal tonus, predisposing to recurrent CSD and may be facilitating recurrent migraine attacks.

#### Allodynia is common in migraine and arises as a consequence of central sensitization

An interesting event in the pathophysiology of migraine is the sensitization of brain synaptic connections

that transmit nociceptive impulses within the brain since this may be at the basis of the very common symptom of allodynia in migraine<sup>46,47</sup>. Central sensitization (CS) of TNC neurons could account for allodynia and the prolongation of the migraine attack<sup>48</sup>. Alternatively, or in addition, facilitation of trigeminal transmission by central neuromodulatory sites may be the crucial step in sensitization and allodynia.

It has been demonstrated that central sensitization, as determined by cutaneous allodynia, maps onto migraine biology. Its prevalence is higher in chronic migraine than episodic migraine, and is very low in tension-type headache<sup>49,50</sup>. Accordingly, central sensitization may be a risk factor or a marker of migraine progression. It may be hypothesized that repetitive activation of trigeminal neurons and consequently repetitive activation of modulatory pain pathways involving the PAG or hypothalamic regulatory sites may lead to impairment of function or partial neuronal cell damage, through the liberation of free radicals, in the PAG or eventually in areas involved with migraine generation. Iron deposits in the PAG demonstrated using MRI methods are consistent with this concept<sup>51</sup>.

Lesson: Cutaneous allodynia reflects sensitization at the level of TNC. It seems to be a migraine marker, specially a marker of increased chance to develop chronic migraine.

## PART 2 – THE TRIPTANS

### 1. Mechanism of action – what are the triptans?

The most common sites of action for effective serotonergic agonist acute anti-migraine drugs such as the triptans appear to act a several areas both around vasculatures and centrally. 5-HT<sub>1B</sub> receptors on the meningeal vasculature has once though to be the main site of action

Table 4. Quality of evidence and clinical impression of the triptans<sup>85</sup>.

Drug	Quality of evidence	Scientific effect	Clinical impression of effect	Adverse effects
Oral triptans				
Almotriptan	A	+++	++	Infrequent
Eletriptan	A	+++	+++	Occasional
Frovatriptan	A	++	++	Infrequent
Naratriptan	A	++	++	Infrequent
Rizatriptan	A	+++	+++	Occasional
Sumatriptan	A	+++	+++	Occasional
Zolmitriptan	A	+++	+++	Occasional
Nasal triptans				
Sumatriptan nasal spray	A	+++	+++	Occasional
Zolmitriptan nasal spray	A	+++	+++	Occasional
Injectable triptans				
Sumatriptan SC	A	+++	+++	Frequent
Triptan combination				
Sumatriptan plus naproxen sodium fixed-dose combination	A	+++	+++	Occasional

for triptans. However, recent findings suggest that central action of triptans may also contribute to their anti-migraine effects. These include the demonstration of inhibitory 5-HT<sub>1D</sub> receptors on trigeminal nerve terminals projecting peripherally to the dural vasculature and centrally to the brain stem trigeminal nuclei<sup>52,53</sup>. Activation of 5-HT<sub>1D</sub> pre-junctional receptors on nerve terminals seems also to down regulate CGRP release. In addition, co-localization of 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub> and 5-HT<sub>1F</sub> receptors on glutamate positive trigeminal neurons mean that triptans could reduce glutamate release by acting through these receptors, which in turn would contribute to their therapeutic effect<sup>54</sup>. The central actions of triptans is also suggested by their adverse events profile, such as asthenia, dizziness, somnolence, throat tightness and dysaesthesia.

## 2. How were the triptans developed?

Older anti-migraine compounds such as the ergot alkaloids have strong affinity for the “anti-migraine” 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors but they retain high affinity for other serotonin, adrenergic and dopaminergic receptor subtypes that can potentially mediate unwanted nausea, dysphoria, asthenia and vascular effects<sup>55</sup>. The first benchmark Triptan, sumatriptan, was developed by Pat Humphrey and colleagues<sup>52,53</sup>. The receptor pharmacology of second generation triptans was modeled on sumatriptan, with the goal of developing oral formulations with improved bioavailability and rate of drug absorption to potentially speed and improve migraine headache relief<sup>56,57</sup>. The triptan agents are a significant progression from the ergots since they target only the anti-migraine 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors and have reduced or eliminated unwanted activity at most other monoamine receptor subtypes.

Indeed, one view of the triptans is that they are really second generation ergot alkaloids<sup>58</sup>.

The receptor specificity profile of the triptan agents currently in clinical use is broadly similar and although their individual potencies at 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors varies somewhat this is usually reflected in clinical dose<sup>59,60</sup>. This supports the idea that activity at these receptors is primarily responsible for their therapeutic effects.

Although, as mentioned, the triptans are very effective reversing and interrupting the trigeminovascular activation that is postulated to underlie the generation of headache pain, the demonstration that contractile 5-HT<sub>1B</sub> receptors were also present in the coronary arteries caused concern over potential for adverse cardiac events with these drugs<sup>61,62</sup>. Fortunately, the 5-HT<sub>1B</sub> receptor reserve of coronary vessels appears to be low and as a class the triptans lack activity at 5-HT<sub>2A</sub> receptors that mediate most of the serotonergic contraction in coronary blood vessels<sup>63</sup>. Collectively these factors are likely to contribute to their safety profile<sup>64</sup>. Nonetheless, triptans are indeed coronary constrictors and this builds safety concerns among many providers. Subsequent drug discovery efforts in the post-triptan era have been directed to find anti-migraine efficacy without cardiovascular liability.

## Differentiating the triptans

As discussed above, different triptans are available in different strengths and formulations and specific pharmacological differences among the triptans exist.

Two major factors are of importance when differentiating triptans. (1) Because extensive research suggests that oral triptans are preferred by patients, relative to non-oral formulations, a first distinction relates to the relative ef-

ficacy/tolerability of oral triptans<sup>65-67</sup>. (2) Although most patients prefer oral formulations, some do not, and certain situations call for non-oral formulations. Accordingly, a second distinction regards the appropriate use of the formulations.

The first topic was studied by a meta-analysis using data of 24,089 patients in 53 controlled clinical trials of triptans. According to the methods of the study, all triptans were contrasted to sumatriptan 100 mg<sup>68</sup>. The most important conclusion of the meta-analysis is that all the triptans are more effective than placebo in relieving the pain and associated symptoms of migraine. Rizatriptan 10 mg and eletriptan 80 mg were significantly more effective than sumatriptan 100 mg in the primary endpoint of all studies, pain relief in 2 hours (pain improving from moderate or severe intensity to mild or none). Sumatriptan was superior to naratriptan 2.5 mg, eletriptan 20 mg, and frovatriptan 2.5 mg. Pain free-rates at 2 hours and sustained pain-free rates over 24 hours were higher for eletriptan 80 mg, almotriptan 12.5 mg, and rizatriptan 10 mg, compared to sumatriptan 100 mg. The only triptans that presented lower rates of adverse events, compared to sumatriptan 100 mg, were naratriptan 2.5 mg and almotriptan 12.5 mg<sup>69</sup>.

Route of Administration may play an important role in the onset of action and in the preference patterns of triptans. Subcutaneous delivery of sumatriptan offers the most rapid and complete pain relief of the triptans beginning as early as 10 to 15 minutes, yet it also is associated with a higher incidence of adverse events<sup>68</sup>. Nasal deliveries also seem to yield fast relief<sup>70</sup>. Sumatriptan nasal spray is not as effective as the subcutaneous delivery formulation. Zolmitriptan nasal spray demonstrated rapid onset of action and high response rates. All of the triptans are available as conventional tablets, and two (rizatriptan and zolmitriptan) are also available in orally disintegrating tablets (ODT). ODT's are more convenient to use and can be taken when the patient is nauseated; their gastrointestinal absorption means that they will not be absorbed if vomiting occurs soon after ingestion, but they can be swallowed without water.

In selected patients, triptans may be associated to other medications, in order to address specific issues, such as incomplete relieve, recurrence, or slow onset of action<sup>71-73</sup>.

#### **Future developments for the acute treatment of migraine – the CGRP receptor antagonists**

Although triptans improved the lives of millions of migraineurs, several limitations in their use do exist. First, triptans are largely underutilized, especially by primary care doctors who are worried about their potential constrictive effects<sup>74</sup>. Second, up to 30–40% of patients in clinical trials do not response to triptans. The long term adherence to a specific triptan is very low, and this is par-

tially explained by the presence of triptan-specific side effects such as chest pain, chest pressure, paresthesia, throat tightness, fatigue, dizziness and myalgias. Many patients, who do not tolerate or who are contraindicated from taking triptans and/or anti-inflammatory medications, often resort to opiates and/or barbiturate-containing drugs. Use of opiates or barbiturates can lead to dependence and other medical complications. Finally, migraine is one of the most common co-morbid conditions for patients with psychiatric disease, such as depression and anxiety. Recent concern about the rare potential for serotonin syndrome with triptans and serotonergic medications has further limited the use of triptans. Accordingly several unmet treatment needs for the acute treatment of migraine still exist.

The discovery of receptor subtypes located on trigeminal afferents and their pharmacology, as well as the neuropeptides involved in pain transmission, central trigeminal activation, and peripheral activation has led to a host of molecular targets for acute migraine therapy. The class of medications that is closer to reach the market and will likely be available over the near future is the calcitonin gene receptor peptide (CGRP) antagonist. CGRP levels in external jugular venous blood are elevated during migraine and cluster headache attacks and, as in animal models of trigeminal stimulation to be normalized by successful anti-migraine drug therapy with sumatriptan<sup>74,75</sup>.

Intravenous administration of CGRP has been shown to trigger a migraine-like headache in migraineurs. CGRP is involved in sensory neurotransmission and is also one of the most potent endogenous vasodilators in the human body. However, it is not involved in the maintenance of normal major vascular tone<sup>76</sup>. It's antagonism held promise to be a novel strategy to relieve migraine headache pain without overt vasoconstriction. CGRP receptor antagonism would be the first non-serotonergic migraine specific medication (Fig 2).

It was originally proposed that CGRP in the meningeal vasculature could be involved in trigeminovascular activation through vasodilation, but it may be that this is a biomarker that simply reflects trigeminal activation during a migraine attack; focused preclinical studies have indicated that the key sites of action of CGRP and its antagonists may be central rather than peripheral in nature<sup>75,77</sup>. CGRP and its receptor are widely expressed in both central and peripheral nervous systems. CGRP and its receptors have been found in the hypothalamus, amygdala, striatum, hippocampi, auditory, visual pathways, periaqueductal gray, trigeminal nucleus caudalis, and cerebellum<sup>78,79</sup>. It is now postulated that CGRP may act as neuromodulator at multiple area in the nervous system and regulate the flow of nociceptive signals. When CGRP level is elevated, the flows of signals are unimpeded and when CGRP level is de-



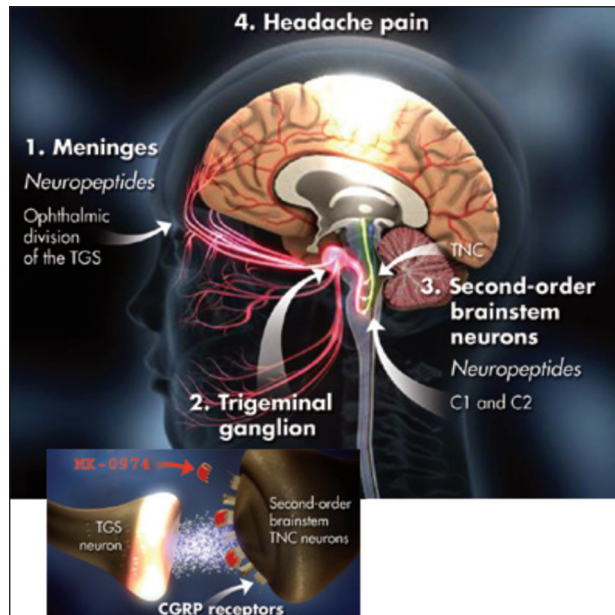


Fig 2. Sites of importance of CGRP in migraine pain.

crease, signals are filtered at multiple brainstem levels and are prevented it from reaching to higher level in the brain.

Investigators found that the only pharmacological agent available to block the effects of CGRP in migraine physiology models was a fragment of the full length peptide containing amino acids 8–37 (CGRP8-37), and this fragment had an excellent anti-migraine profile in the same trigeminovascular assays used to develop rizatriptan.

CGRP receptor antagonism was cracked open with the discovery of a high affinity antagonist BIBN4096 (olcegepant)<sup>80,81</sup>. Positive proof of clinical concept was reported with intravenous administration in spontaneous migraine using an innovative adaptive trial design<sup>82,83</sup>.

Telcagepant was the first oral formulation of CGRP-RA to reach positive proof of concept<sup>84</sup>, and is being tested in an extensive phase 3 program. In a recently published study, 1380 patients were randomly assigned to receive telcagepant 150 mg (n=333) or 300 mg (354), zolmitriptan (345), or placebo (348)<sup>84</sup>. Telcagepant 300 mg was more effective than placebo for pain freedom (95 [27%] of 353 patients vs 33 [10%] of 343 [ $p<0.0001$ ]), pain relief (194 [55%] of 353 vs 95 [28%] of 343 [ $p<0.0001$ ]), and absences of phonophobia (204 [58%] of 353 vs 126 [37%] of 342 [ $p<0.0001$ ]), photophobia (180 [51%] of 353 vs 99 [29%] of 342 [ $p<0.0001$ ]), and nausea (229 [65%] of 352 vs 189 [55%] of 342 [ $p=0.0061$ ]). Efficacy of telcagepant 300 mg and zolmitriptan 5 mg were similar, and both were more effective than telcagepant 150 mg. Adverse events were recorded for 31% taking telcagepant 150 mg, 37% taking telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo.

The CGRP-RA class, accordingly, is the first migraine

specific class of medication that acts through a non-vasoconstrictive and non-serotonergic mechanism of action.

## CONCLUSIONS

In the distant past little was known about the mechanism leading to migraine, and this disease was treated empirically. The vascular theory led to the use of potent vasoconstrictors (ergots). The search for medicines with less adverse events led to the development of the triptans. Science has shown that their important mechanism of action in migraine is on the trigeminal neuronal pathways, not on blood vessels. The triptan era has led to remarkable progress in the diagnosis and treatment of migraine and in our understanding of migraine mechanisms. This in turn opens a new set of scientific questions about the neurobiologic determinants of clinical course and exciting opportunities to develop new therapies for this highly disabling brain disorder.

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