



## Preventive and abortive treatment of migraine with traditional drugs - the state of the art

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### Abstract

#### Introduction

Migraine is a chronic neurological disease, with a prevalence of 15.2% in Brazil. It is 2.2 times more prevalent in women, predominantly in the 18-50 age group. Its pathophysiological mechanism is still not completely understood. Possibly headache attacks and symptoms are associated with cortical spreading depression, the trigeminovascular system, neurogenic inflammation, vasodilation and genetic vulnerability.

#### Objective

This is a narrative review of preventive and abortive treatment of migraine.

#### Comment

Migraine treatment is based on three pillars: patient education, treatment of the disease itself or prevention of attacks, and acute treatment of headache attacks. The therapeutic classes of traditional drugs used in migraine prevention are beta-blockers, tricyclic antidepressants, calcium channel antagonists or blockers, and anticonvulsant neuromodulators. Specific drugs used in the treatment of headache attacks are triptans or serotonergic 5-HT<sub>1B/1D</sub> receptor agonists, ditans or 5-HT<sub>1F</sub> receptor agonists, and gepants or CGRP receptor antagonists.

#### Conclusions

Traditional drugs used in the preventive or abortive treatment of migraine are considered to be effective. Through modulation of the disease mechanisms, there is a reduction in the frequency, intensity and duration of headache attacks, and also in the disability caused by the headache. All this to improve the quality of life of patients. The therapeutic classes of traditional drugs used in migraine prevention are beta-blockers, tricyclic antidepressants, antagonists or blockers of calcium channels and anticonvulsant neuromodulators. Specific drugs used in the treatment of headache attacks are triptans or serotonergic 5-HT<sub>1B/1D</sub> receptor agonists, ditans or 5-HT<sub>1F</sub> receptor agonists, and gepants or CGRP receptor antagonists.



## Introduction

Migraine is a chronic neurological disease, with a prevalence of 15.2% in Brazil.<sup>1</sup> It is defined as an abnormal neurovascular reaction that occurs in a genetically vulnerable individual. Clinically manifests itself in recurrent episodes of headache associated with other symptoms, dependent on triggering factors.<sup>2</sup>

According to the diagnostic criteria of ICHD-3,<sup>3</sup> headache lasts from 4 to 72 hours, presenting some characteristics, such as unilateral location, pulsatile character, moderate to severe intensity and worsening with routine physical activities. In addition, headache is accompanied by nausea and/or vomiting, photophobia and phonophobia (Table 1).

Table 1. Diagnostic criteria for migraine, according to ICHD-3

- |    |  |
|----|--|
| A. | At least five attacks <sup>1</sup> fulfilling criteria B–D   |
| B. | Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)   |
| C. | Headache has at least two of the following four characteristics: <ol style="list-style-type: none"> <li>1. unilateral location</li> <li>2. pulsating quality</li> <li>3. moderate or severe pain intensity</li> <li>4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)</li> </ol> |
| D. | During headache at least one of the following: <ol style="list-style-type: none"> <li>1. nausea and/or vomiting</li> <li>2. photophobia and phonophobia</li> </ol>   |
| E. | Not better accounted for by another ICHD-3 diagnosis   |

According to the number of headache days per month, migraine can be classified as episodic, when there are less than 15 headache days per month in the last three months; or chronic, if the headache is present 15 or more days per month, also in the last three months.<sup>4</sup> Patients diagnosed with chronic migraine have a more impaired quality of life and are more incapacitated for daily activities.<sup>5,6</sup>

Migraine is a highly prevalent disease, affecting 15.2% of the Brazilian population.<sup>1</sup> About one billion people worldwide, including more than 30 million Brazilians and 40 million Americans, suffer from migraines.<sup>7</sup> The disease is 2.2 times more prevalent in women, predominantly in the 18-50 age group, in individuals with higher education, with lower income and in those who do not practice regular physical activity, regardless of body mass index.<sup>1</sup>

In most patients, migraine attacks are sporadic, but a subgroup of individuals experience a gradual increase in frequency over time; among these, up to 1% to 2% of the global population develop chronic migraine. Regardless of the frequency of attacks, migraine interferes with quality of life and is among the most disabling diseases in the world. According to the Global Burden of Disease, it is the second leading cause of disability among young adults aged between 18 and 50 years.<sup>8</sup>

As a result, the socioeconomic impact is enormous, as it affects the quality of life of patients and impairs work, social activities and family life. It constitutes the major

cause of absenteeism and decreased productivity at work, especially among women who are the most affected by this disease.<sup>9-11</sup>

The pathophysiological mechanisms of migraine are still not completely understood. There are multiple origins to explain headache attacks and associated symptoms, such as cortical spreading depression (CSD), the trigeminovascular system, neurogenic inflammation, vasodilation and genetic vulnerability. Evidence suggests that the fundamental physiological disorder is central neuronal hyperexcitability, involving peripheral or brainstem trigeminovascular pathways, or both. Some factors can increase or decrease neuronal excitability, constituting the threshold for triggering headache attacks.<sup>12,13</sup>

Initially, certain internal or external triggering factors trigger CSD, an electrophysiological phenomenon that plays an important, but not exclusive, role in the generation of migraine attacks. This wave of depolarization propagates from the occipital cerebral cortex to the frontal region, at a speed of 2-3 mm/min, causing cerebral ionic dysfunction (increased intracellular calcium), release of neurotransmitters and vasoconstrictor vascular events, responsible for the phase premonition and aura symptoms.<sup>12,14</sup> CSD can activate the trigeminal nociceptive system, both peripheral and central, with the release of nitric oxide and inflammatory neuropeptides, such as substance P, neurokinin A and calcitonin gene-related peptide (CGRP), responsible for vasodilation and related to the headache stage.<sup>12,15</sup>

Finally, the genetic abnormality of calcium channels is a potential mechanism of interictal neuronal excitability. Voltage-gated P/Q-type calcium channel genes likely influence presynaptic neurotransmitter release, possibly from excitatory or inhibitory amino acid systems.<sup>12</sup> A genetic vulnerability was observed in relatives of patients with migraine without aura, who have a 1.9 times greater risk of having this disease and a 1.4 times greater risk of suffering migraine with aura.<sup>16</sup>

### Drug treatment of migraine

Migraine treatment is based on three pillars: patient education, treatment of the disease itself or prevention of attacks, and acute treatment or headache attacks. Education must be carried out with any patients from any instances of care. In emergency or tertiary outpatient services, it is essential to inform and reiterate the chronic biological, genetic and chemical nature of migraine for adherence to other treatment components. Any patient who seeks medical help due to migraine needs to receive clear and objective information about the disabling, but benign, nature that the disease and its symptoms can



cause frequently or infrequently, depending on the patient and their moment in life.<sup>17</sup>

Furthermore, the impossibility of curing the disease must be reiterated, although effective treatment results in reduced impact by controlling a decrease in headache attacks. Simple, objective physical activity programs such as brisk one-hour walks for at least four days a week, as well as pragmatic stress management, also represent fundamental items for patient improvement.<sup>17,18</sup>

The main basis of the approach is the treatment of the disease or the prevention of symptoms. It must be emphatically explained that this is only achieved with medication or biological therapies and the objective is not to cure migraine, but to greatly reduce the frequency and intensity of attacks. This goal is achieved by modulating disease mechanisms and not just with pain medication. There are general criteria for opting for migraine prevention with drugs or other therapeutic agents.<sup>17,18</sup>

Patients with three or more headache attacks a month that interfere with functional capacity or require use of symptomatic medications should be approached with caution. In patients with a lower frequency of attacks, but with significant impairment of their daily activities, this option should also be used. We exemplify here the patient suffering from migraine with aura whose crises occurred every three months, but who exercised the profession of commercial pilot of large airplanes. In this patient, occasional attacks characterized by total visual loss or a visual field loss occurred in landing and takeoff situations. In cases like this, the need to prevent even infrequent crises is unquestionable. In addition, migraines can progress with frequency, even spontaneously, and prevention becomes an important weapon to avoid compromising the quality of life and productivity of sufferers.<sup>17-19</sup>

As fundamental general principles of the treatment, essential for its success, we must always start with low doses, increase them slowly and gradually every 1-2 weeks, wait for at least 2 months in the planned therapeutic doses and require the patient to complete of pain diaries, which prove the behavior of headache attacks during the use of the prescribed treatment. Failure to observe such principles greatly compromises adherence and the evaluation of the effectiveness of what was chosen.<sup>17,18</sup>

Another practical aspect is to carefully evaluate treatment options in women planning to become pregnant or who are pregnant. Thus, clear guidelines and effective contraceptive measures should be in use when starting migraine prevention and only proven non-teratogenic options should be suggested in these cases. Monotherapy is preferred for patients who have never received preventive pharmacologic agents, and whenever possible, options with better tolerability should be selected.<sup>18,20</sup>

## Preventive treatment for migraine

The therapeutic classes of traditional drugs used in migraine prevention are beta-blockers, tricyclic antidepressants, antagonists or blockers of calcium channels and anticonvulsant neuromodulators.

### Beta-adrenergic blockers

Beta blockers have been used to prevent migraines for over 35 years (Table 2) and for many, they still represent the first choice of treatment for non-asthmatic patients.<sup>21</sup> The first beta-blocker to be used clinically was propranolol in 1964.<sup>22</sup> The mechanisms of action are related to its ability to act centrally on the serotonergic and noradrenergic neurotransmitter systems. The various beta-blockers differ in terms of selectivity for  $\beta_1$  and  $\beta_2$  receptors, their lipophilic capacity and blood-brain penetration. In addition, regarding its agonistic properties at other sites and its ability to stabilize neuronal membranes.<sup>21</sup>

All beta-blockers, to a greater or lesser degree, inhibit the release of noradrenaline by blocking pre-junctional or presynaptic beta-receptors, reduce neuronal firing from the locus coeruleus (the most important noradrenergic nucleus in the brainstem) and decrease the synthesis of norepinephrine by reducing the activity of the enzyme tyrosine hydroxylase. In addition, they interact with serotonergic 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors, promoting their down regulation.<sup>18,20,23</sup>

The most used beta-blockers with proven efficacy are propranolol (the oldest),<sup>22</sup> at doses from 30 to 180 mg/day; metoprolol, at doses of 50 to 200 mg/day; atenolol, at doses of 50 to 120 mg/day; and nadolol, at doses from 80 to 240 mg/day (Table 2). Nadolol is the only one with predominantly renal excretion, without hepatic metabolism and more present in breast milk.<sup>20,23</sup> Doses should always be individualized and started low with slow and gradual progression until the effect manifests itself and/or side effects appear.

Table 2. Effective beta-blockers in migraine prevention

Drug	Doses (mg/day)	Effectiveness	Side effects	Number of doses per day
Propranolol	30 to 180	+++	+ to ++	3
Atenolol	50 to 120	+++	+ to ++	1 to 2
Nadolol	80 to 240	++ to +++	+ to ++	1 to 2
Metoprolol	50 to 200	++ to +++	+ to ++	1 to 2

The side effects most observed in beta-blockers are fatigue, depression, memory disorders, sexual impotence, reduced tolerance for physical activities, bradycardia, arterial hypotension, weight gain, peripheral vasoconstriction, bronchospasm and elevation of glycemia and cholesterol. Major contraindications are congestive heart failure, asthma, uncompensated diabetes, bradycardia, hypotension, moderate or severe hyperlipidemia, vertebrobasilar disease, basilar or hemiplegic migraine,



and cerebrovascular disease.<sup>20,23</sup>

### Tricyclic antidepressants

The tricyclic antidepressants amitriptyline, nortriptyline and doxepin are the most used in migraine prevention, with different actions on neurotransmitter systems (Table 3). Amitriptyline was first suggested for migraine prevention in 1968. Its effectiveness compared to the use of placebo has been evidenced for over 40 years.<sup>24,25</sup> There is wide variation in the absorption, distribution and excretion of tricyclics, but beneficial effects can begin three to seven days after starting treatment, although some patients require up to three to four weeks to show improvement.<sup>24,25</sup>

Table 3. Relative potency of the most used tricyclic antidepressants in the different neurotransmitter systems

Tricyclic antidepressants	Neurotransmitter systems		
	serotonergic	noradrenergic	dopaminergic
Amitriptyline	+++	++	++
Nortriptyline	++++	++++	++
Doxepin	+++	++	++

There are important variations in the individual metabolism of tricyclics. They will likely be ineffective for migraine treatment outside the therapeutic window. Some patients will need 150 to 200 mg/day, in divided doses; while others will show improvement with 10 to 20 mg/day.<sup>24-26</sup> The mechanisms of action for migraine are down regulation, antagonism of central 5-HT<sub>2A,B,C</sub> receptors, decrease in the density of postsynaptic beta-adrenergic receptors, inhibition of synaptic reuptake of serotonin and noradrenaline and the improvement of central antinociception through a functional increase in endogenous opioid mechanisms.<sup>24-26</sup> Tricyclics are highly lipid soluble and avidly bound to plasma proteins. Recommended doses vary over a wide range and are usually between 10 and 200 mg/day.<sup>26,27</sup> They should be started at low doses but gradually increased every 5 to 7 days.

Tricyclics are not well tolerated and side effects are frequent and generally related to their interaction with various neurotransmitter systems and their receptors (Table 4). These can manifest even before the headache improves and the most observed side effects are the result of its antimuscarinic activity, such as dry mouth, metallic taste, epigastric discomfort, intestinal constipation, vertigo syndrome, mental confusion, tachycardia, palpitations, blurred vision and urinary retention. Elderly patients may develop tremor, mental confusion and even delirium. The side effects resulting from the antihistamine action (at H<sub>1</sub> and H<sub>2</sub> receptors) and the unwanted activity in the noradrenergic system may also represent a limiting factor to the use of these drugs. They usually manifest as an increased desire for carbohydrate intake and consequent weight gain, drowsiness, postural hypotension, reflex tachycardia and palpitations<sup>24,26,27</sup>

Table 4. Most common side effects of tricyclic antidepressants in relation to their action on the various neurotransmitter systems

Neurotransmitter systems	Side effects
Cholinergic	Blurred vision, dry mouth, sinus tachycardia, constipation, urinary retention, memory disturbances, speech disorders, and decreased sweating
Serotonergic	Nausea, increased intestinal motility, sweating
Histamine (type 1 receptor)	Sedation, vertigo syndrome, hypotension, weight gain, potentiation of other CNS depressant drugs
Histamine (type 2 receptor)	Mental confusion
Adrenergic (α1 receptor)	Postural hypotension, reflex tachycardia
Dopaminergic	Tremor, increased muscle tone, myoclonic jerks, dyskinesia

Note: CNS - central nervous system

### Antagonists or calcium channel blockers

Antagonists or calcium channel blockers are drugs that are frequently used to prevent migraines. Calcium, in combination with binding proteins such as calmodulin or troponin, regulates diverse cellular and neuronal functions. Muscle contraction (including arterial wall), hormone and neurotransmitter release, and enzymatic activity are just a few examples of the importance of calcium ions in cell function. Knowledge of the role of calcium and the various types of neuronal calcium channels is crucial to understanding the recent evidence that points to genes associated with the expression of different types of calcium channels and their possible practical implication in genetic inheritance and pathophysiology from the migraine. Furthermore, the notion that different classes of calcium channel antagonists act on different types of channels as, for example, verapamil does on L-type voltage channels is important.<sup>28</sup>

The components of this group of drugs have varied chemical structures. They differ in clinical efficacy, side effect profile and contraindications. Flunarizine, a diphenylpiperazine derivative, is the most used in Brazil. It is recommended at a dose of 10 mg/day, although studies have shown that doses of 3 to 5 mg/day at night may have the same efficiency, without the undesirable side effects of weight gain, drowsiness, tremor and extrapyramidal symptoms.<sup>29,30</sup> Flunarizine requires 4 to 6 weeks to demonstrate efficacy and has a residual effect for up to 4 weeks. Several comparative studies between flunarizine and other drugs for the prevention of migraine have been carried out and there was no statistical difference between their effectiveness and propranolol, metoprolol or pizotifen.

Verapamil, a phenylalkylamine substance effective for the prevention of cluster headaches,<sup>31</sup> is the most widely used calcium antagonist in the United States. Although little effective in migraine, it has been shown to be superior to placebo and should be used in doses of 80 mg three



to four times a day. Its most frequent side effect was constipation, which affected 43% of patients.<sup>31,32</sup>

The components of this group of drugs exert blocking effects on the release of platelet serotonin, interfering with neurovascular inflammation, in the initiation and propagation of spreading depression, in the inhibition of calcium-dependent enzymes used in the synthesis of prostaglandins and, finally, in the inhibition of contraction vascular wall smooth muscle.<sup>33,34</sup>

The most common side effects are constipation, A-V block, congestive heart failure and hypotension with verapamil and weight gain, drowsiness, dizziness, hypotension and extrapyramidal reactions with flunarizine. Contraindications are congestive heart failure, heart block and moderate to severe bradycardia, hypotension, atrial fibrillation, and severe constipation. The best candidates for the use of calcium antagonists are patients with a history of prolonged aura, migraine infarction, and migraine with vertigo or other vestibular symptoms.<sup>35</sup>

### Anticonvulsant neuromodulators

Anticonvulsant neuromodulators play a prominent role in migraine prevention due to their action on cortical hyperexcitability and the imbalance between GABAergic inhibition and glutamatergic excitation observed in migraineurs. The main anticonvulsant neuromodulators are sodium valproate and divalproate. They began to be studied for migraine prevention in 1992 with subsequent studies starting in 1999.<sup>30,36,37</sup>

Divalproex sodium is an oligomeric complex of valproate and valproic acid in a 1:1 molar ratio and dissociates into valproate ion in the mucosa of the gastrointestinal tract. It is made from a simple fatty acid with eight carbon atoms and two main chains and is 80% bioavailable after an oral dose. Its plasma half-life is 8 to 17 hours and it is highly bound to plasma proteins. It acts peripherally, including reducing experimental neurogenic inflammation in the trigeminovascular system through agonism at GABA<sub>A</sub> receptors.<sup>38</sup>

Several mechanisms of action of divalproex sodium are known. It increases gamma-aminobutyric acid (GABA) levels in presynaptic storage vesicles and brain parenchyma through inhibition of the GABA acid transaminase enzyme, but also increases the postsynaptic response to GABA. It increases membrane conductance to potassium, promoting neuronal hyperpolarization, in addition to decreasing the firing rate of serotonergic neurons in the dorsal raphe nucleus (an important center involved in the pathophysiology of migraine and located in the brainstem), which are implicated in the control from headache.<sup>30,36,37</sup>

Cognitive functions are rarely affected by divalproex.

However, hematological effects are important and platelet count must be monitored, especially in doses greater than 1,500 mg/day. Serious side effects are infrequent and hepatitis and pancreatitis can occur, but this is usually related to the concomitant use of other medications, the patient's age, the presence of metabolic or genetic diseases and general health. Although rare, these idiosyncratic reactions are unpredictable, but tend to occur more in children under 2 years of age, on concomitant use of multiple anticonvulsant drugs, with metabolic disorders or epilepsy accompanied by mental retardation and organic brain disease.<sup>39</sup>

Fatal hepatotoxicity is extremely rare in patients with migraine, but liver dysfunction may be more common and not predicted by laboratory monitoring alone, as liver function tests may be normal while clinical symptoms are developing.<sup>30</sup> In the real world of treatment, alternating daily doses of 250 mg and 500 mg reveal efficacy with fewer side effects.<sup>40</sup>

Topiramate (TPM) is probably the most studied neuromodulator in migraine prevention. It is an anticonvulsant with a unique chemical structure with a chain similar to a chemical radical found in acetazolamide. This raised the possibility of exerting an intrinsic anticonvulsant action, which was confirmed in subsequent studies with epileptic patients.<sup>30</sup>

It has multiple mechanisms of action and can influence the function of some subtypes of calcium and sodium voltage channels, in addition to GABA<sub>A</sub> receptors and the Kainate/AMPA receptor subtype, which is involved in the excitatory glutamatergic system. In addition, TPM inhibits carbonic anhydrase isoenzymes II and IV.<sup>41</sup> As a result of this action at various molecular sites and at receptors for various neurotransmitters, TPM modulates GABAergic action, increases GABA-induced chloride ionic currents, and exerts variable antagonizing effects on Kainate-evoked ionic currents in the glutamatergic system. The result is stabilization or modulation of neuronal activity. Thus, TPM and other drugs in this category began to be called neuromodulators, representing a more current concept in the preventive treatment of migraine.<sup>42</sup>

TPM is rapidly absorbed after oral administration, with plasma concentrations rising linearly with dose. Its metabolism is dependent on hepatic microsomal enzymes of the P<sub>450</sub> system, increasing its clearance in the presence of other enzyme-inducing antiepileptic drugs. TPM readily penetrates the central nervous system and 70% to 80% is eliminated unchanged in the urine. Its half-life is 21 hours with normal renal function and the time required to reach a stable concentration is 4 to 5 days. Após 1 hora de administração oral, a concentração do TPM no parênquima cerebral pode atingir um terço dos níveis plasmáticos.<sup>43</sup>

Edwards et al. carried out the first evaluations of TPM in



migraine, in 2000. These authors studied 30 patients with migraine with or without aura who used TPM (n=15) or placebo (PL) (n=15). The patients underwent progressive dose adjustments, with increments of 25 mg per week, up to a maximum dose of 100 mg twice a day, and remained on regular use for 12 weeks. Mean frequencies per 28-day period were compared between the two groups of patients and with baseline periods ( $3.00 \pm 2.60$  vs.  $3.78 \pm 1.99$ ;  $p=0.10$ ), revealing a trend of superiority in reducing headache attacks for the TPM group. The percentage of patients who responded (i.e., experienced at least a 50% reduction in seizure frequency) during the 18-week study period was 46.7% for TPM and 6.7% for PL ( $p=0.035$ ). Sete pacientes em uso de TPM abandonaram o estudo (4 por efeitos colaterais e 3 por outras razões) e 6 pacientes do PL também o fizeram (3 por falta de eficácia e 3 por outras razões). The most reported side effects of TPM were paresthesia of the extremities, diarrhea, altered taste and drowsiness.<sup>44</sup>

Two subsequent studies supported the use of TPM as an effective drug for migraine prevention.<sup>45,46</sup> In addition, and contrary to what was imagined, the target dose of 100 mg was shown to be the best cost-effective action, since doses of up to 200 mg did not achieve better results than those of 100 mg/day.

TPM is well tolerated when its doses are started low (15-25 mg/day in a single dose) and increased slowly and gradually (25 mg every 14 days). Its administration should always be in two daily doses, during breakfast and dinner. Still, there may be undesirable side effects in a portion of patients. Slowing of psychomotor activity, difficulty concentrating, changes in memory, language and speech, drowsiness, asthenia, weight loss, acute angle glaucoma and formation of kidney stones (due to the activity of inhibiting carbonic anhydrase) may occur.<sup>47</sup>

Table 5 presents the efficacy and side effect profile of migraine prophylaxis substances used in clinical practice,

before the advent of anti-CGRP therapies.

### Treatment of headache attacks

Migraine attacks have four distinct phases: (1) prodromal phase with premonitory symptoms; (2) aura phase with transient neurological signs and symptoms; (3) headache phase with associated symptoms that include nausea, vomiting, photophobia, phonophobia, and osmophobia; and (4) recovery or postdromic phase, often associated with rest and sleep.<sup>48</sup>

Only headache phase symptoms can be treated and there is no effective treatment for aura symptoms.<sup>49</sup> Existing drugs for the treatment of headache attacks are divided into specific and non-specific. Specific ones are serotonergic 5-HT<sub>1B/1D</sub> receptor agonists or triptans, 5-HT<sub>1F</sub> receptor agonists or ditans, and CGRP receptor antagonists or gepants.

Preference, degrees of effectiveness, doses, routes of administration, formulations and associations with other substances such as caffeine, muscle relaxants and even barbiturates make the treatment of headache attacks something to be individualized. It should be chosen based on the physician's personal experience, the patient's headache behavior and aspects related to medication availability. These variations are characterized by intense national, cultural and economic differences. There are patients who report the effectiveness of simple, non-specific and low-cost commercial preparations, while others require injectable triptans. Gepants and ditans are not yet available in Brazil until the end of 2022, but international studies have shown efficacy in the parameter of absence of pain in 2h, lower than that of some oral triptans and below 20% when compared to placebo.<sup>50</sup>

Table 6 summarizes the effective drug options for the acute treatment of migraine that are available in Brazil in December 2022.

Table 5. Efficacy and tolerability profile of the most used drugs in migraine prevention

Drug	Effectiveness*	Side effects
Beta blockers	++ to +++	++ to +++
Propranolol	+++	++ to +++
Atenolol	++	++
Nadolol	++	++
Metoprolol	++	++
Tricyclic antidepressants	+++ to ++++	+++ to ++++
Amitriptyline	+++	++++
Nortriptyline	+++	+++
Doxepin	++	+++
Anticonvulsants	+++	+++ to ++++
Sodium divalproex	+++	++ to +++
Topiramate	+++	++ to +++
Calcium channel antagonists	++ to +++	+++
Flunarizine	++	+++
Verapamil	+	+

\*Based on the literature and the personal experience of the authors.



Table 6. Names, recommended doses per headache attack and formulations of substances used for the acute treatment of migraine

Drugs	Available doses (mg)	Formulations	Recommended doses (mg/per 24h)
Non-specific analgesics			
Simple analgesics			
Dipyrrone	500 and 1000	tablets/ injection	2000 to 4000
Paracetamol	500 and 750	tablets	2000 to 4000
NSAIDs			
Salicylate derivatives	500	tablets	1500 to 3000
Naproxen sodium	550	tablets and suppositories	550 to 1100
Tolfenamic acid	200	tablets	400 to 600
Diclofenac	50	tablets and suppositories	50 to 100
Ibuprofen	400 and 600	tablets	800 to 1200
Ketoprofen	100	tablets	100 to 200
Ketorolac	10	tablets	10 to 20
Celecoxib	100 and 200	tablets	200 to 400
Specific analgesics			
Ergotamine (tartrate)	1-2	tablets and suppositories	1 to 2
Ergotamine	0.25-0.5	SC or IM injections	0.25 to 0.5
Dihydroergotamine	1	SC, IM or IV injections	1 to 2
Dihydroergotamine (mesylate)	0.5	intranasal spray	0.5 to 1
Triptans			
Sumatriptan	25-50-100	tablets	maximum: 300mg
Sumatriptan	6	SC injection	6 to 12
Naratriptan	2.5	tablets	2.5 to 7.5
Zolmitriptan	2.5	tablets	2.5 to 7.5
Rizatriptan	5 and 10	tablets	5 to 15
Rizatriptan	10mg	dissolution discs	10 to 30

Note: NSAIDs – non-steroidal anti-inflammatory drugs; SC – subcutaneous; IM – intramuscular; IV – intravenous.

### Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs)

Some patients benefit from the use of common analgesics such as salicylate derivatives and paracetamol. These substances have restricted efficacy in more intense attacks and their association with caffeine or barbiturates does not reveal evidence of superiority over salicylates or paracetamol alone.<sup>49</sup> Many of these drugs act centrally, in the caudal trigeminal nucleus and in the thalamus. Its use or prescription for patients with severe, disabling or rapidly progressive headache attacks is not warranted. Salicylate derivatives also have anti-inflammatory action and inhibition of prostaglandin synthesis when used at higher doses, such as 70 to 100 mg/kg.

Nonsteroidal anti-inflammatory drugs (NSAIDs) with proven efficacy in migraine are naproxen, tolfenamic acid, diclofenac, ibuprofen, ketoprofen, ketorolac, lysine clonixinate, and indomethacin.<sup>49</sup> They act by blocking the cyclooxygenase enzyme and inhibiting the synthesis of prostaglandins, notably prostaglandins G<sub>2</sub>. NSAIDs also exert a relevant central action that includes inhibition of neuronal prostaglandin synthesis, prolongation of the turnover of catecholamines and serotonin in neurons, and blockade of serotonin release upon painful stimuli.<sup>51</sup> They are useful and well tolerated and may represent the first treatment option for patients with moderate or slower-progressing attacks, when used correctly.

### Triptans

Triptans represent the first specific drugs for the treatment of migraine attacks. They act as a selective 5-HT<sub>1B/1D</sub> serotonergic receptor agonists. The first, sold in 1990, was sumatriptan. Its effectiveness has been well established with over 180 million seizures treated worldwide.

Sumatriptan is structurally related to serotonin with potent selective action on 5-HT<sub>1B/1D/1F</sub> receptors. It has no significant action on other serotonin receptors, such as 5-HT<sub>2,7</sub> and on non-serotonergic receptors (adrenergic,

dopaminergic, histaminergic), as well as on ion channels. It has a vasoconstrictor effect on the basilar, parent and dura mater arteries, through an agonistic action on 5HT<sub>1B</sub> receptors. In peripheral vessels, there is no vasoconstrictor action, since there is little or no action on the 5-HT<sub>2A</sub> receptors, which mediate this process. Triptans produce a mild and equivalent degree, at therapeutic concentrations, of contraction in coronary arteries.<sup>52</sup>

The oral bioavailability of sumatriptan in 25, 50 and 100 mg tablets is low, around 14%. Mean T<sub>max</sub> values range from 1 to 2.3 hours after oral administration. However, 80% of plasma C<sub>max</sub> is reached within 45 minutes of oral ingestion in healthy patients. With subcutaneous administration of a dose of 6 mg, there is rapid absorption, T<sub>max</sub> of 0.17-0.23 hours and high bioavailability, around 96%. Sumatriptan has proven efficacy in acute treatment with initially recommended doses of 6 mg subcutaneously and 100 mg orally, which reach therapeutic levels with plasma concentrations of 72 µg/L in 10 minutes and 54 µg/L in 1.5 hours, respectively. It is observed that 14% to 21% of the drug binds to plasma proteins and weakly crosses the blood-brain barrier due to its poor lipophilicity.<sup>52,53</sup>

Approximately 55% to 65% of patients show improvement after 2 hours, while 70% after 4 hours of an oral dose. Subcutaneous administration is most effective, providing significant headache relief in 80% of patients after 1 hour, and in 86% after 2 hours.<sup>52,53</sup>

Zolmitriptan was developed to be superior to sumatriptan. It has high affinity for 5-HT<sub>1B/1D</sub> receptors, moderate affinity for 5-HT<sub>1A/1F</sub> receptors, and has both central and peripheral actions, which may be relevant to its antimigraine effect. It acts centrally by modulating serotonergic neurotransmission, even outside of headache attacks. This leads to changes in cortical excitability that are shown in changes in cortical potentials evoked by auditory stimulation without affecting global cortical processing.<sup>54</sup> It provides pain relief after 1 and 2 hours in 24% to 51% and 62% to 75% of patients, respectively.



After the use of zolmitriptan, the absence of pain within 2 hours is achieved by 25% to 45% of patients and recurrence varies between 20% and 37% of patients.

Naratriptan is also a selective 5-HT<sub>1B/1D/1F</sub> agonist and was synthesized to achieve greater bioavailability than sumatriptan. In fact, naratriptan has an oral bioavailability of 63% to 74% and a high plasma half-life, around 6 hours, when compared to sumatriptan. It has high affinity for 5-HT<sub>1B/1D/1F</sub> receptors and low affinity for 5-HT<sub>1A/1E</sub> receptors. There is no affinity for 5-HT<sub>2A</sub> receptors, which mediate peripheral vasoconstriction, nor for 5-HT<sub>7</sub> receptors, which mediate vascular relaxation and hypotension. The 2.5 mg dose reduces headache intensity to mild or absent in 48% of patients (ranging from 45% to 51%), with a therapeutic gain over placebo of 21% (17% to 25%).<sup>52,55</sup> Clinical studies compared naratriptan 2.5 mg with sumatriptan 100mg and revealed a lower therapeutic gain, equivalent to 33% (ranging from 27% to 39%).

Naratriptan is the best tolerated and least efficient of the currently available triptans. Its percentage of side effects is similar to placebo in several evaluated studies, but its effectiveness is even lower than that of other non-selective drugs such as some NSAIDs, for example. Contraindications for the use of naratriptan are similar to those for other triptans. The fact that this drug is the best tolerated among the available oral triptans does not remove the impediment to its use in patients with coronary artery disease, previous myocardial infarction, Prinzmetal's angina, coronary vasospasm, peripheral vascular disease, previous history of accident ischemic stroke or transient ischemic attacks. It is the only triptan not contraindicated for concomitant use with MAO inhibitor antidepressants.<sup>56</sup>

Rizatriptan is a potent 5-HT<sub>1B/1D</sub> agonist with high oral bioavailability, around 40% to 45%, which demonstrates efficacy far superior to placebo already after 30 minutes. Its T<sub>max</sub> is 1 hour and the plasma half-life is 2 hours. It is available as 10 mg oral tablets and orally disintegrating tablets (ODT), which can be used without fluid intake. The beginning of its beneficial effect is already manifested after 30 minutes and can be observed even after 4 hours in studies that evaluated efficacy versus time. Therapeutic gain reached 34% for rizatriptan at a dose of 10 mg and the absence of pain after 2 hours occurred in 33% of patients.<sup>52,57</sup>

Rizatriptan, at a dose of 10 mg, provides pain relief in 70% of headache attacks, being greater than 100 mg of sumatriptan. However, subcutaneous sumatriptan is clearly superior to other oral triptans.

In several other countries, three other triptans (almotriptan, frovatriptan, eletriptan) are available, as well as the triptan presentations found in Brazil. All triptans that have ever been synthesized are shown in Table 7.

Table 7. Triptans used in the treatment of migraine attacks.

Substance name	Commercial name	Formulation/ administration	Doses (mg)	Max. dose (mg/24h)
Sumatriptan	Sumax™	Tablet orally	25, 50, 85 and 100	300
	Sumax™	Spray nasal	10 and 20	40
	Sumax™	SC injection	6	12
Zolmitriptan	Zomig™	Tablet orally	2.5 and 5	10
	Zomig ODT™	ODT	2.5 and 5	10
	Zomig™	Spray nasal	2.5 and 5	10
Rizatriptan	Maxalt™ / Maxalt RPD™	Tablet orally/ RPD	5 and 10	30
Naratriptan	Naramig™	Tablet orally	2.5	7.5
Almotriptan*	Axert™	Tablet orally	6.25 and 12.5	25
Frovatriptan*	Frova™	Tablet orally	2.5	7.5
Eletriptan*	Relpax™	Tablet orally	40 and 80	160

\*Not yet available in Brazil; ODT - orally disintegrating tablets; RPD - dissolving freeze-dried; SC - subcutaneous

### Ditans e gepants

New drugs are emerging for the treatment of migraine attacks: ditans and gepants. Lasmiditan is a ditan that acts as a 5-HT<sub>1F</sub> receptor agonist. Gepants (ubrogepant, rimegepant, atogepant and zavegepant) are small molecule CGRP receptor antagonists, but they are not available and/or approved for use in Brazil.

From the analysis of studies with these new therapeutic options for migraine attacks, none stands out absolutely or has superior efficacy to the most efficient triptans.<sup>50</sup> However, there is the recent and promising concept that some gepants can be used every other day and do not induce medication overuse headache. In this way, migraine as a disease and headache attacks could be treated with the same medication. Real-world studies are needed to confirm these observations.

### How to treat correctly and effectively?

It is fundamental that the patient be treated according to the profile of his crises, frequency, usual intensity, speed of progression, co-morbidities, personal preferences and drug efficacy parameters. After decades of empiricism with which these patients were treated, we now have specific drugs that act selectively on serotonergic receptors and on CGRP, leading to objective, rapid and consistent improvement in headache, associated symptoms and productivity in some patients. In addition, the growing evidence that migraine is a multifactorial disease and that headache attacks involve several circuits, mediators and mechanisms simultaneously, it is not difficult to understand why rational combinations are chosen in both prevention and symptomatic treatment.<sup>58-64</sup>

The combined use of a triptan, a non-steroidal anti-inflammatory and a gastrokinetic drug is the best way to obtain the best results of efficacy, persistence of pain relief



and improvement of the associated symptoms of nausea, photophobia, phonophobia and osmophobia that characterize the migraine headache attack. The use of subcutaneously injectable sumatriptan (3 mg) with rectal indomethacin (50 mg) (even in lower doses than those available in commercial presentations, respectively 6mg and 100 mg) proves to be effective in severe crises even after the lack of response to the options oral treatment with triptans and NSAIDs.<sup>65</sup>

For the preventive treatment of migraine, rational combinations, especially in more complex patients or in tertiary centers, is the general rule and if it does not result in worse tolerability, it should be chosen or considered in the treatment plan.<sup>58,59,63</sup>

## Conclusions

Traditional drugs used in the preventive or abortive treatment of migraine are considered to be effective. Through modulation of the disease mechanisms, there is a reduction in the frequency, intensity and duration of headache attacks, and also in the disability caused by the headache. All this to improve the quality of life of patients. The therapeutic classes of traditional drugs used in migraine prevention are beta-blockers, tricyclic antidepressants, antagonists or blockers of calcium channels and anticonvulsant neuromodulators. Specific drugs used in the treatment of headache attacks are triptans or serotonergic 5-HT<sub>1B/1D</sub> receptor agonists, ditans or 5-HT<sub>1F</sub> receptor agonists, and gepants or CGRP receptor antagonists.

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