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EXPERT REVIEW

Update on Therapeutic Options for Acute Migraine

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Abstract: Migraine is a common disabling disorder that affects approximately 12% of the population. Migraine treatment requires the avoidance of triggers, acute treatment to control individual attacks, and preventive treatment for patients with frequent headaches. The choice between the different drugs available for the acute management of migraine is based on the severity of the attacks and associated symptoms. Migraine-specific acute therapies, such as triptans, are recommended in patients with moderate or severe migraine attacks and also for mild episodes that do not respond to simple analgesics. The use of simple analgesics is appropriate for mild attacks or patients who cannot use triptans. Currently, ergotics are not recommended in de novo migraine patients mainly because of their lower efficacy compared to triptans and their side-effect profile. Novel methods for delivering triptans and ergotics will increase the efficacy and reduce the side effects of current formulations. New acute migraine therapies without vasoconstrictive activity and a better side-effect profile than triptans are under investigation. This review focuses on drugs to treat acute migraine attacks and covers a comprehensive selection of emerging therapies.

Keywords: migraine, triptan, CGRP, ergotics, acute, treatment

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Introduction

Migraine is a common disabling illness in which sufferers are predisposed to recurrent headache attacks that interfere with their ability to function and their productivity and which significantly lower their quality of life.[1,2]

The prevalence of migraine headache ranges between 8% for men and 17% for women,[3] figures which have remained stable for decades.[4] According to World Health Organization data, migraine is 12th on the list of the most frequent causes of disability for women and 19th in the population as a whole.[5] More than half of patients with migraine report severe impairment or the need for bed rest during their headache attacks.[4,6,7] Furthermore, the disability seen during a severe migraine attack is considered to be on a level with the disability caused by quadriplegia. The economic repercussions of migraine associated with the cost of care, absenteeism and reduced workplace productivity are considerable.[8]

Treatment of migraine attacks should be prescribed to all patients to relieve pain and associated symptoms (such as nausea, vomiting, phonophobia and photophobia), regardless of the frequency of the attacks. For those patients in whom migraine episodes are frequent, disabling, and do not respond to symptomatic treatment, preventive treatment is recommended. This review focuses on the current treatment for migraine attacks and covers a comprehensive selection of emerging therapies.

Pathophysiology

The pathophysiology of migraine has not been completely clarified. Experimental and neuroimaging studies show that brainstem and diencephalic structures modulate the activation of the trigeminovascular system.[9] Activation of the trigeminovascular system induces the release of inflammatory and vasodilatory mediators from the primary sensory nerve terminals that innervate the meningeal blood vessels. The pain is caused by a sterile neurogenic inflammatory process and dilatation of meningeal arteries in the dura mater.

The aura is caused by a neuronal dysfunction called cortical spreading depression.[10] Cortical spreading depression is a transient, spreading disturbance in cortical function that usually starts in the occipital cortex and depolarizes meningeal nociceptors, giving rise to migraine pain.[11] Various studies suggest that neuronal hyperexcitability is the predisposing factor that initiates spreading depression.[11]

General Principles of Migraine Treatment

The primary goal of acute therapy in patients with migraines is the rapid and complete suppression of pain and accompanying symptoms and reduction in the disability and loss of productivity associated with the attack in order to improve the patient's quality of life.

The efficacy in oral symptomatic treatment of migraine attack is usually measured by speed of action and non-recurrence of pain. Specifically, the most commonly used efficacy parameters in clinical trials are the percentage of pain-free patients after two hours (which reflects speed of action), and the percentage of pain-free patients on a sustained basis, which is defined as pain-free patients after two hours who do not require the use of rescue medication or who do not present recurrence in the first 24 hours (patients with sustained freedom from pain).[12] From the patient's perspective, rapid and long lasting pain relief with no adverse events is one of the most highly valued efficacy parameters.

It is recommended that after diagnosis of migraine with or without aura, and before prescribing drugs, the causes of migraine and the aims of treatment should be explained in a comprehensible manner. It is important to have the patient understand that migraine is a recurring, episodic disorder with no cure, which can generally be controlled to permit acceptable quality of life, and to clarify the differences between treatment of acute attacks and preventive treatment.

The selection between the different available drugs for the acute management of migraine is based on the severity of the attacks and associated symptoms. The choice of acute treatment should also be guided by the side effect profile and the patient's comorbid conditions. There are several sets of recommendations for the acute treatment of migraine published by European Societies, the American Academy of Neurology and the Spanish Society of Neurology.[13–15]

Treatment of migraine attacks should be individualized for each patient and each episode. Patients with migraine may present different attacks in terms of intensity and accompanying symptoms (nausea, vomiting). Moreover, the disability produced by

each episode is not always similar. For this reason, prescribing the same treatment for every attack does not seem to be reasonable. Patients may suffer mild attacks that can be treated with non-steroidal anti-inflammatory drugs (NSAIDs) and moderate or severe attacks that require the use of triptans. Furthermore, a non-oral route of administration or the early administration of prokinetic and anti-emetic drugs is recommended in the presence of nausea or vomiting. Finally, symptomatic treatment of migraine attacks should be taken when the attack is in its early stages, whilst the migraine is mild, before central sensitization occurs.[16]

Symptomatic treatment (Table 1) may be undertaken with non-specific drugs (paracetamol, non-steroidal anti-inflammatory drugs—NSAIDs, opiates), specific drugs (ergotics or triptans) and co-adjuvant drugs (such as prokinetics or anti-emetics).[2,15,17]

Acute Migraine Treatment

Non-specific drugs

Non-migraine-specific drugs include paracetamol, NSAIDs and opiates. These treatments are usually indicated in mild attacks, migraine in childhood and adolescence, attacks during pregnancy—although NSAIDs are not recommended during the third trimester—and in patients for whom vasoconstrictors use (ergots or triptans) are contraindicated. Because of the risk of inducing medication overuse headache, most guidelines[13–15] recommend restricting the use of certain treatments such as the combination of analgesics with barbiturates, codeine, and caffeine, especially in patients with frequent migraine attacks.

In a recent Cochrane meta-analysis, paracetamol (with a usual dose of 1000 mg) was found to be significantly superior to placebo and the addition of 10 mg metoclopramide was found to increase its efficacy.[18] Other meta-analyses showed that ibuprofen[19] (with a dose between 400–800 mg), aspirin[20] (1000 mg) and naproxen[21] (500 mg) were superior to placebo for acute migraine attacks.

Opiates are not generally used for headache except when pain cannot otherwise be treated. The opioids most frequently studied (meperidine and tramadol) are superior to placebo in relieving migraine pain.[22,23] They may induce nausea and vomiting, in addition to sedation, dizziness and constipation.[23] These drugs are not usually recommended because they do not act on the pain mechanisms of migraine and may cause medication overuse headache and addiction.

Table 1. Treatment options for acute migraine treatment.

Drugs	Usual dose
Simple analgesics/NSAIDs	
Paracetamol	650–1000 mg PO, IV
Aspirin	500–1000 mg PO
Ibuprofen	400–800 mg PO
Naproxen	275–550 mg PO
Desketoprofen	25–50 mg PO, 50 mg IV
Diclofenac sodium	75 mg IM
Prokinetic and antiemetics	
Domperidone	10–20 mg PO
Metoclopramide	
Tablets	10–20 mg PO
Suppository	20 mg suppository
Injections	10 mg IV, SC or IM
Ergotic drugs	
Ergotamine	1–2 mg PO/1 mg as suppository
Dihydroergotamine	0.5–1 mg SC, IM, IV
Opiates	
Codeine	15–30 mg PO
Meperidine	50–100 mg IM or IV
Triptans	
Sumatriptan	
Tablets	50–100 mg PO
Nasal spray	10–20 mg
Injections	6 mg SC
Suppository	25 mg
Zolmitriptan	
Tablets	2.5–5 mg PO
Nasal spray	5 mg
Rizatriptan	10 mg PO
Naratriptan	2.5 mg PO
Almotriptan	12.5 mg PO
Eletriptan	40–80 mg PO
Frovatriptan	2.5 mg PO

Abbreviations: IM, Intramuscular; IV, Intravenous; PO, oral; SC, subcutaneous.

Serotonin 5HT1B/1D agonists or triptans

Triptans are migraine-specific drugs for acute treatment. Different guidelines recommend the use of triptans in patients with moderate or severe migraine attacks as well as for mild episodes that do not respond to simple analgesics, as long as their use is not contraindicated.[13–15] It is recommended that each triptan should be tried in three attacks before it is rejected for lack of efficacy.[24]

Triptans are serotonin agonists with high affinity for 5-HT1B and 5-HT1D receptors. Triptans cause vasoconstriction through an action in the postsynaptic 5-HT1B receptors on blood vessels but also block the release of vasoactive peptides through their action at presynaptic 5-HT1D receptors on the nerve terminals.[25] All 7 triptans on the market are 5-HT1B/1D agonists and some are also agonists at 5-HT7 (frovatriptan) and 5-HT1F (almotriptan). Unlike ergotic drugs, triptans are selective 5-HT1B/1D/1F receptor agonists and they have a better side-effect profile.[26] They are contraindicated in patients with vascular problems (ischemic cardiopathy, stroke, and peripheral arterial disease) and uncontrolled hypertension, and are not recommended for some subtypes of migraine such as basilar migraine and migraine with prolonged aura.

Triptans may also be administered orally (sumatriptan, zolmitriptan, rizatriptan, naratriptan, frovatriptan, almotriptan and eletriptan), subcutaneously (sumatriptan) and by inhalation (sumatriptan, zolmitriptan), and in some countries there are also forms for rectal administration (sumatriptan).

The efficacy of triptans has been evaluated against placebo, studied in patients not responding to NSAIDs or simple analgesics, and compared to ergotic drugs.[24,27,28] Treatment with any of the triptans on the market is clearly superior to placebo and, in general, controls other migraine-associated symptoms such as nausea, vomiting, photophobia and phonophobia.[24,25] In several trials, triptans were superior to treatment with NSAIDs and combinations of simple analgesics (paracetamol, aspirin with caffeine). Several studies have shown that the use of triptans was superior to ergotamine, either alone or combined with caffeine.[24,27,28]

Clinical data have suggested that an important factor accounting for the variable efficacy of triptans within patients and between attacks might be the time of treatment intake relative to headache onset. Several studies have indicated that early triptan intake is more efficacious than late treatment on various clinical endpoints, including pain-free state after 2 hours and sustained pain-free state.[16,29–33] Therefore, early triptan administration is strongly recommended because pain is aborted while the headache is still mild.

All oral triptans were effective and well tolerated and a meta-analysis of 53 trials suggests that almotriptan, eletriptan, and rizatriptan are the most effective.[34] In terms of the percentage of pain-free patients after two hours, 80 mg of eletriptan, 12.5 mg of almotriptan and 10 mg of rizatriptan were more effective than 100 mg of sumatriptan. On the other hand, 25 mg of sumatriptan, 2.5 mg of naratriptan and 20 mg of eletriptan were less effective than 100 mg of sumatriptan. Efficacy in sustained freedom from pain was greater with 10 mg of rizatriptan, 80 mg of eletriptan and 12.5 mg of almotriptan than with 100 mg of sumatriptan.[25,34]

The seven oral triptans on the market are more alike than different on the basis of their receptor profiles but present relevant pharmacokinetic differences that make triptans more suitable for different types of attacks (Table 2). On the basis of these differences, the triptans are chosen and targeted toward specific patient and migraine characteristics such as time to peak intensity, duration of headache, associated symptoms such as nausea and vomiting, time to associated symptoms, co-morbid diseases, and concomitant treatments.[35] Indirect comparisons between the different oral triptans[34] have shown that rizatriptan is the triptan with the fastest action, almotriptan the best tolerated, and eletriptan the one with the lowest rate of recurrence. Naratriptan and frovatriptan have slower onset and slightly lower efficacy than the other

Table 2. Pharmacokinetic characteristics and dosage of triptans.

Variable	Sumatriptan	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Zolmitriptan
Half-life (h)	2.0	3.5	5.0	25.0	5.0–6.3	2.0	3.0
Time to maximal concentration (h)	2.5	2.0–3.0	2.8	3.0		1.0	4.0
Oral bioavailability (%)	14	69	50	24–30	63–74	40	40
Dosage PO (mg)	50–100	12.5	40–80	2.5	2.5	10	2.5–5

Abbreviation: h, hours.

triptans but both possess lower rates of adverse events and recurrence than sumatriptan. In those patients with severe migraine and early vomiting, non-oral administration with subcutaneous sumatriptan is appropriate. Sumatriptan or zolmitriptan nasal spray provides a faster onset of action than oral triptans.

Recently, the combinations of triptans (sumatriptan) and NSAIDs (naproxen 500 mg) have been found to improve efficacy and reduce headache recurrence in a significant proportion of patients when compared to sumatriptan alone.[36] This combination may be particularly useful in those patients with poor response to triptans.

Another possible combination is the use of triptans with dexamethasone.[37] This combination could be considered for those subjects with incomplete relief or recurrence of pain with triptan monotherapy.

Ergotic drugs

Ergotics are also specific drugs for treating migraine attacks.[36,37] As with triptans, ergotics have an agonist action on 5-HT1B/D receptors—they produce vasoconstriction and pain relief—but they also act on several other serotonin receptors (including 5-HT1A, 5-HT2, 5-HT5) and adrenergic receptors, which favors the appearance of side effects. Because of their vasoconstrictor action, they should not be used for patients with a history of vascular disease or uncontrolled hypertension and should never be combined with triptans. Among their side effects, it should be noted that they could lead to nausea and vomiting. In recent years and with the introduction of triptans, their use has declined due to their side effects and tendency cause medication overuse headache. Currently, ergotics are not recommended for de novo migraine patients mainly because of their lower efficacy compared to triptans and their side-effect profile.[38]

A serious disadvantage is their low bioavailability,[37] which is below 1% when administered orally, possibly because of incomplete passage through the small bowel mucosa and significant first-pass metabolism in the liver. The bioavailability reaches a maximum of 3% when given rectally. The bioavailability of nasal dihydroergotamine (DHE) is around 40%. Intramuscular and intravenous DHE are 100% bioavailable, but these formulations are unavailable in many European countries, including Spain.

Symptomatic Treatment in Special Situations

Children, adolescents and pregnancy

Children and adolescents may benefit from simple analgesics such as paracetamol or Ibuprofen.[39] In children under 16 years of age aspirin should be avoided. If simple analgesics are not effective, triptans may be used. The possible alternatives with demonstrated efficacy and safety are nasal sumatriptan and oral almotriptan. Almotriptan is the first triptan to be approved for treatment of migraine in adolescents by the FDA.[15] Other triptans such as zolmitriptan (nasal) and rizatriptan also appear to be safe and effective.[15,39–44] Ergotamine is not recommended in children and adolescents.

During pregnancy, management of migraine should first focus on minimizing risk to the developing baby. The FDA lists five drug risk categories in pregnancy.[45] These pregnancy categories provide information about the risk of fetal injury due to the drugs commonly used for treating acute attacks of migraine. In pregnant women paracetamol (Category B), and NSAIDs (Category C) could be used, although the administration of NSAIDs should be avoided in the third trimester of pregnancy (Category D in the third trimester). As demonstrated by the record of pregnancies with sumatriptan, this 5-HT1B/1D agonist is not associated with a higher than expected incidence of miscarriages or foetal malformations, but it is not recommended because insufficient data are available (Category C). Based on expert consensus, EFNS guidelines stated that administration of triptans in the first trimester of pregnancy is permitted if the child is more at risk by severe attacks with vomiting than by the potential impact of the triptan.[13] Opioids (meperidine) are safe, except when pregnancy is prolonged or at term, and ergotamine is contraindicated in pregnancy (Category X).

Acute migraine in the emergency room and status migrainosus

The drugs that are usually used in the emergency setting and in status migrainosus include NSAIDs (such as intravenous aspirin or ketorolac), metoclopramide, subcutaneous sumatriptan, steroids, and chlorpromazine. Intravenous DHE is also very useful but this presentation is unavailable in several European countries.

Intravenous paracetamol was not effective in a placebo-controlled trial in acute migraine attacks.[46]

We initially recommend intravenous hydration and NSAIDs with or without metoclopramide as an adjunct treatment for nausea and vomiting. Ketorolac (30–60 mg IM or IV) is an effective cyclooxygenase COX1/COX2 inhibitor to relieve a migraine attack in the emergency room.[47]

Steroids can be useful in patients with severe migraine attacks that are unresponsive to other treatments and are recommended in patients with a status migrainosus by expert consensus.[13] In those patients treated in an outpatient setting, a course of oral steroids (dexamethasone, prednisone) for 3 to 5 days may be useful.[48–49] In the emergency room the optimal regimen includes intravenous dexamethasone (4–20 mg) followed by oral dosing for several days after discharge or prednisone. Single-dose dexamethasone is usually well tolerated.

The neuroleptics (dopamine antagonists) currently used in migraine patients include the phenothiazines (prochlorperazine, chlorpromazine), and metoclopramide.[50] Prochlorperazine and chlorpromazine administered intravenously or by intramuscular injection are at least as effective as ketorolac and may be useful in status migrainosus.[51] Hypotension, may occur, especially if the drug is administered intravenously and for that reason patients should be pretreated with normal saline to reduce the incidence of this side effect. Other commonly reported adverse events include drowsiness and akathisia. Metoclopramide has analgesic activity in migraine attacks, although it is currently used as a coadjuvant therapy to control nausea and vomiting.[52]

In several studies, intravenous sodium valproate provided substantial relief during a migraine attack. At doses between 300 and 1500 mg, it represents an alternative in those patients who do not respond to other treatments.[53]

In some cases, the use of diazepam (5–10 mg, IM/IV) may be useful as adjunct treatment to terminate a headache attack, although evidence of the use of diazepam is based on personal observations.

New therapeutic approaches for acute migraine attacks

The development of new therapeutic options for acute migraine attacks is keenly awaited because triptans are not effective in 25% of patients and only one third of patients in clinical trials are pain-free 2 hours after taking a triptan orally.[26] Furthermore, triptans and ergotics may induce intolerable side effects and are contraindicated in patients with myocardial infarction, peripheral arterial disease and stroke.[24,25,34,54] For these reasons, new methods of delivering triptans and ergots to increase their efficacy and reduce their side effects have been developed, and new drugs without vasoactive properties and a better tolerability profile are under investigation (Table 3).

Recently, an iontophoretic patch that delivers sumatriptan transdermally was developed.[55] Current data suggest that transdermal iontophoretic delivery of sumatriptan may offer significant clinical utility for those migraine patients with severe digestive symptoms. The most common adverse events for transdermal sumatriptan were the appearance of skin reactions at the patch site and therefore this drug may also be potentially useful in patients who cannot tolerate the usual adverse events with triptan, such as chest pain.

Intranasal DHE can be used for the treatment of acute migraine attacks for patients with moderate to severe migraine and may be given in patients with nausea or vomiting. However, it has slow absorption, low bioavailability and unpredictable pharmacokinetic properties that may result in a poor clinical response in different patients and even in the same patient in repeated administrations.[56] For all of these reasons, a new route of administration of DHE delivered by oral inhalation through the lungs to the systemic circulation using a device called the TEMPO inhaler was developed.[57] MAP0004 is an orally

Table 3. New treatments for acute migraine.

Compounds	Mechanism of action
Lasmiditan	5-HT_{1F} receptor antagonist
Telcagepant	CGRP receptor antagonist
BI 44370	CGRP receptor antagonist
BMS 927711	CGRP receptor antagonist
NXN-188	Neuronal nitric oxide synthase inhibition &5-$HT_{1B/D}$ agonist
Tezampanel (LY-293558)	AMPA and kainite receptor antagonist
BGG492	AMPA receptor antagonist

Abbreviations: AMPA, α-amino-3-hydroxy-5 methyl-4-isoazolepropionic acid; CGRP, Calcitonin gene-related peptide; 5HT, 5-hydroxytryptamine.

inhaled formulation of dihydroergotamine delivered to the systemic circulation that was effective for the acute treatment of migraine, providing significant pain relief and freedom from photophobia, phonophobia, and nausea, compared with placebo.[57] Orally Inhaled formulation of DHE provides rapid therapeutic levels of DHE (and similar efficacy) but with lower rates of adverse effects compared with intravenous DHE.[58]

A new formulation or Diclofenac using potassium or epolamine salt has been developed for rapid absorption. It has a faster onset of action (within 30 minutes) than the usual tablet and could be used in moderate and severe migraine attacks.[59]

The expression of 5-HT1F receptor mRNA in neurons of the trigeminal ganglia led to the suggestion that 5-HT1F receptors could be a therapeutic target for migraine. Lasmiditan, a highly selective 5-HT1F agonist, was recently evaluated in a multicenter, double-blind, parallel-group dose-ranging, which confirms that selective activation of 5-HT1F receptors with lasmiditan reduces headache severity in migraine attacks compared with placebo, without triptan-specific side effects.[60] Both efficacy and nervous system-related adverse effects showed a clear dose response. Nevertheless, further assessment in larger placebo-controlled and triptan-controlled trials is needed to evaluate the potential role of lasmiditan in acute migraine therapy.

Calcitonin generelated peptide (CGRP) may play a role in the pathophysiology of migraine. The possible use of selective CGRP receptor antagonists (or gepants) in migraine patients has been tested with intravenous olcegepant[61] and the oral CGRP receptor antagonist telcagepant.[62] The efficacy of both drugs appears comparable to that of triptans but with fewer overall adverse side-effects. In a recent large, multicenter, randomized, controlled trial of telcagepant (150 mg or 300 mg) versus zolmitriptan (5 mg) or placebo, telcagepant at higher doses (300 mg) was more effective than placebo for pain freedom and pain relief at 2 hours.[63] The efficacy of telcagepant 300 mg is comparable to that of zolmitriptan 5 mg, but with fewer associated adverse effects.

The clinical tolerability of gepants in terms of vascular side-effects seems to be more favorable than for triptans. In a randomized, double-blinded, placebo-controlled, cross-over study, it was proven that telcagepant was generally safe and well tolerated in a small cohort of migraine patients with stable coronary artery disease,[64] as there were no consistent treatment-related changes in cardiovascular parameters. However, a preventive study of telcagepant in migraine resulted in liver toxicity in some participants. Although other gepants are under evaluation (BMS-927711, BI 44370), more studies to delineate the security profile of selective CGRP receptor antagonists are needed.

NXN-188 is a novel oral drug that inhibits neural nitric oxide synthase and binds to 5-HT1B/1D receptors.[65] A recent phase II, multicenter, randomized, controlled study showed positive results. NXN-188 appeared to be well tolerated.[66]

Tezampanel is an AMPA/kainate receptor antagonist that may be useful for treating migraine attacks[67] and supports the importance of glutamate in the pathogenesis of migraine.

Transcranial magnetic stimulation (TMS) is a non-invasive method that can transiently modulate the excitability of cerebral cortex. Experimental studies showed that the inhibition of cortical spreading depression may decrease the progression of a migraine with aura attack.[68] Promising results have been obtained with TMS when applied to patients with acute migraine with aura in the occiput, just below the occipital bone, and the procedure is usually well tolerated.[59]

Conclusion

Triptans are recommended for patients with moderate or severe migraine attacks. NSAIDs are usually indicated in mild attacks, migraine in childhood and adolescence, and in patients for whom vasoconstrictors use (triptans) are contraindicated. Novel methods for delivering triptans and ergotic will increase the efficacy and reduce the side effects of current formulations and may be particularly useful in patients who have severe digestive symptoms precluding oral drug intake. New acute migraine therapies without vasoconstrictive activity and triptan-related adverse effects are currently under investigation.

Author Contributions

Analysed the data: MCA, PI, EMV. Wrote the first draft of the manuscript: MCA, PI. Contributed to the

writing of the manuscript: MCA, PI, EMV. Jointly developed the structure and arguments for the paper: MCA, PI, EMV. Made critical revisions and approved final version: MCA, PI, EMV. All authors reviewed and approved the final manuscript.

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