

# New advances in prevention of migraine

## Review of current practice and recent advances

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### ABSTRACT

بالرغم من أن الصداع النصفي أحد أكثر أنواع الصداع الأولية المسببة للعجز، إلا أنه لا يُشخص ولا يُعالج بالقدر الكافي بعد . لا يُشكل الصداع النصفي تحدياً لمصابيه فحسب، بل للأطباء أيضاً؛ خاصة في تمييز مرشحي العلاج الوقائي واختيار العلاج الوقائي الملائم . هناك تطورات حديثة مهمة في تشخيص وعلاج الشقيقة وارشادات علاجية مختلفة من أنحاء العالم . في هذا البحث، نراجع أدوية الصداع النصفي المثبتة والوقائية، بناءً على مجموعاتها الصيدلانية، مُشيرين إلى الجرعة الموصى بها، فعاليتها وآثارها الجانبية . بالإضافة لذلك، نلفت النظر إلى العلاج الوقائي لمجموعات محددة من مصابي الصداع النصفي ونعرض أساليباً علاجية مقترحة لاختيار العلاج الوقائي الأمثل من منظور التوصيات العلاجية العالمية الحديثة والتي تأخذ بعين الاعتبار عوامل إضافية غير فعالية الدواء . أخيراً، نطرح أدوية في مراحل مختلفة من التطوير الدوائي؛ ذات آلية العمل المبتكرة أو ذات أهداف علاجية جديدة .

Despite being one of the most common disabling primary headaches, migraine continues to be under-diagnosed and under-treated. A migraine challenges not only the patient suffering from the migraine, but also physicians; especially in recognizing candidates for prophylaxis and selecting the appropriate preventive medication. Recently, there have been major advances in the diagnosis and treatment of migraine, with different guidelines of migraine management across the world. Here, we review migraine's abortive and prophylactic medications, based on their pharmacologic category, citing their recommended doses, efficacy, and side effects. Additionally, we highlight the prophylactic treatment of specific patient populations and present suggested treatment approaches in view of recent international treatment guidelines that consider factors other than drug efficacy when choosing the optimal preventive therapy. Finally, we introduce drugs in different stages of development, which have novel mechanisms of action or have new therapeutic targets.

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Headache disorders are classified into primary and secondary. Migraine is one of the most common disabling primary headaches. It affects 18% of American women, and 6% of American men.<sup>1</sup> Locally, a systematic review in 2010<sup>2</sup> estimated that the prevalence of headache in the Saudi population ranges from 8-12%, with migraine headache ranging from 2.6-5%. Migraine is further classified into: migraine with aura, and migraine without aura, and is recognized through the International Classification of Headache Disorders (ICHD) criteria (Table 1).<sup>3</sup> However, these criteria have a poor sensitivity, so strict adherence may lead to migraine under diagnosis. Therefore, "probable migraine without aura" is used for patients who fulfill all criteria except one.<sup>4</sup> Migraine disorders also include hemiplegic migraine, chronic migraine, menstrual-related migraine (MRM), and complicated migraine.

The diagnosis is often made clinically, depending on a patient's history.<sup>5</sup> A headache diary in which a patient records headache frequency, severity, associated symptoms, trigger factors, and medications is very

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**Table 1** - Major clinical characteristics of migraine (migraine without and with aura).

Migraine without aura	Migraine with typical aura
A. 5 attacks or more	A. 2 attacks or more
B. Headache attacks lasting 4-72 hours	B. Aura (no motor weakness): 1. Fully reversible visual symptoms
C. Headache characteristics (2 of the following): 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravated by or causing avoidance of routine physical activity	2. Fully reversible sensory symptoms 3. Fully reversible dysphasic speech disturbance
D. Associated symptoms: 1. Nausea and/or vomiting 2. Photophobia and phonophobia	C. At least 2 of the following: - homonymous visual symptoms - unilateral sensory symptoms - aura symptom develops gradually over $\geq 5$ minutes D. Headache (migraine without aura) begins during the aura or follows aura within 60 minutes

helpful in diagnosing headache disorders and evaluating the effectiveness of treatment.<sup>6</sup> In addition, a detailed history is necessary to distinguish migraine from other headaches, such as tension or cluster headaches, for which they are frequently confused. Tension headache, unlike migraine, is bilateral, has a pressing character, and is not aggravated by ordinary activities. However, a single patient may have both migraine and tension headache.<sup>4</sup> Cluster headaches are differentiated from migraine in that they are commonly unilateral, surrounding an eye and associated with eye redness or nasal congestion.<sup>6</sup>

Professional consensus does not support brain imaging or EEG for diagnosing migraine or distinguishing it from other primary headaches in patients identified through ICHD criteria. Nevertheless, some situations require further evaluation, as in patients presenting with: sudden onset headache, first presentation after age of 50, atypical aura, neurological deficit, impaired level of consciousness, progressive headache, or change from a preexisting pattern, or headache with unexplained fever.<sup>4-6</sup>

In this review, we will discuss different pharmacological therapies for migraine prophylaxis that have been recommended by different international guidelines, which will help clinicians to choose appropriate treatment options during patient care and may help to develop a local guideline for treatment of migraine. Furthermore, we will discuss the new advances in pharmacological and non-pharmacological modalities that may help researchers interested in the field migraine.

**Treatment modalities.** Migraine can be managed pharmacologically or non-pharmacologically. Its pharmacological treatment encompasses abortive drugs and prophylactic drugs. Additionally, the US Food and Drug Administration (FDA) have recently approved new therapies. Recent research data has enhanced our understanding of migraine pathophysiology and provided a promising background for the manufacture of new therapies. Non-pharmacological treatment of migraine includes a variety of psychological interventions with varying levels of evidence supporting their use. Relaxation, biofeedback, and cognitive behavioral therapy are recommended and effective (grade A evidence). They can improve the patient's quality of life.<sup>4,6</sup> Studies evaluating acupuncture are inconclusive, while homeopathy is proved to be ineffective (grade A evidence).<sup>4</sup>

**A. Acute (abortive) treatment.** Abortive medications for migraine can be classified into; first line and second line drugs, or specific and nonspecific drugs. Nonspecific drugs are analgesics and anti-inflammatory drugs, while specific treatments include drugs like ergots or triptans, which target 5HT<sub>1</sub> receptors specifically. These abortive agents are summarized in (Table 2).

**Non steroidal anti-inflammatory drugs (NSAIDs)** recommended for treating acute migraine include: naproxen, ibuprofen, diclofenac (grade A methodology).<sup>4</sup> Their efficacy increases when combined with triptans. They are excellent in treating young individuals who can tolerate their gastrointestinal side effects, and ibuprofen can be used safely in children. Gastrointestinal side effects are more common with naproxen. Both naproxen and ibuprofen can be used for menstrual migraine.<sup>5</sup> Aspirin can be used as a single abortive agent or combined with metoclopramide (grade A methodology).<sup>4</sup>

**Paracetamol.** Only grade C recommendations are available for the use of paracetamol as a single abortive agent.<sup>4</sup>

**Triptans.** Triptans are highly effective in alleviating both migraine headaches and its associated digestive symptoms, especially if taken early after the headache onset. There are few differences among the triptans regarding efficacy or tolerability (grade A methodology). Sumatriptan is the most effective abortive medication for severe headache. Sumatriptan combined with naproxen is more effective than using one of them separately (grade A methodology). Hypertensive patients should not receive sumatriptan. Considering the individual variability in the response to triptans in clinical practice, a triptan must be used for at least

3 months before discontinuing it for ineffectiveness (grade A methodology).<sup>4,5</sup>

**Ergot derivatives.** Ergot derivatives are the oldest compounds used for treatment of migraine. Their use is supported now by level B methodology.<sup>4</sup> Dihydroergotamine is well tolerated and can be given intramuscularly (IM), intravenously (IV), or nasally; ergotamine is available in tablet format. These compounds are contraindicated in patients with hypertension, coronary artery disease, or other cardiovascular risk conditions.<sup>5</sup>

**Corticosteroids.** Oral, IM, or IV corticosteroids are beneficial in treating prolonged migraine attacks and menstrual migraine. However, their use carries the usual risk of steroid side effects.

**Opioids.** Opioids like codeine, fentanyl, meperidine, and tramadol are employed in the acute treatment of migraine, but they should be kept as a last resort as they may cause drug dependency or addiction.<sup>5</sup>

**Antiemetics.** Antiemetic medications should be used for patients who complain of disabling nausea and vomiting. Several antiemetics are available for use in migraine. Promethazine is effective but sedating, while ondansetron is not. Prochlorperazine has extrapyramidal side effects. Metoclopramide is generally well tolerated and commonly used.

Patients using abortive medications should be counselled to limit their use of medications to 2 days per week, or 10 days per month. This is necessary to guard against the development of medication overuse headache, which is more resistant to treatment than episodic migraine.<sup>7</sup> French guidelines on headache, revised in 2014,<sup>4</sup> recommend an NSAID with a triptan be used as a rescue medication if a patient's migraine is not relieved within 2 hours of using his abortive medication, requires more than a dose per day, or the abortive medication is ineffective in 2 out of 3 attacks. The treatment should be reviewed if NSAIDs fail to control the headache and typically triptans are prescribed as a first line agent. Lastly, NSAID and triptans can be used simultaneously if none of the above strategies is effective.

**B. Prophylactic treatment.** Migraine is known to cause varying degrees of functional impairment, activity restriction, decreased productivity, and work absence. European countries estimate €27 billion are lost due to migraine, and the equivalent amount in U.S. dollars as well.<sup>8-10</sup> This suggests an urgent need for prophylactic treatment among a subset of migraineurs. However, many candidates for prophylaxis are not receiving prophylactic treatment. Migraine, as available data indicates, is not only under-diagnosed, but also under-treated. Lipton et al<sup>7</sup> reports that only 13% out

**Table 2** - Summary of medications used in treatment of acute attacks of migraine.

First line medications			Second line medications		
Triptans			Ergot derivatives		
Specific Rx	Dose	Side effects	Drug	Dose	Side effects
Almotriptan	12.5 mg, max 25 mg/day	Dizziness, weakness. Hot flushes, nausea, and vomiting	Ergotamine	2 mg, max 6 mg/day	Nausea, vomiting, rebound headache
			Dihydro-ergotamine	1 mg IM or IV, max of 2 mg/day	Nausea, leg cramps at site of injection
Eletriptan	40 mg, max 5 mg/day				
Frovatriptan	2.5 mg, max 5 mg/day				
Naratriptan	2.5 mg, max 5 mg/day	Pins and needles sensation, elevated blood pressure			
Rizatriptan	5 or 10 mg, max 20 mg/day				
Sumatriptan	50 mg, max 200-300 mg/day				
Zolmitriptan	2.5 mg, max 10 mg/day				
NSAID			Other classes		
Non-specific Rx	Dose	Side effects		Dose	Side effects
Diclofenac	50 mg, max 150 mg/day	GI upset	Butalbital	Max 4 tablets/day	Weakness, addictive potential
Ibuprofen	400 mg, max 2400 mg/day		Opioids	Limits for each individual drug	Addiction or drug dependency
			Steroids	Limits for each individual drug	Usual steroid adverse effects
Rx -prescription, max - maximum, IM - intramuscular, IV - intravenous, GI - gastrointestinal					

of 38% of migraineurs who qualify for prophylaxis are on preventive therapy. It was estimated that one in every 4 migraineurs who are candidates for migraine prophylaxis are not getting it.<sup>7,11</sup>

Physicians face several challenges when it comes to prescribing prophylactic medication for migraine sufferers, such as recognizing the candidates for prophylaxis, and the selection of the appropriate preventive medication.<sup>12</sup> Additionally, the American Academy of Neurology (AAN) and the American Headache Society (AHS) believe physicians are not aware and/or confident in the clinical guidelines of migraine preventive treatment.<sup>13</sup> The aim of preventive therapy is to reduce the severity, frequency, and duration of headache attacks. Moreover, preventive therapy can enhance patient's response to abortive therapy, resulting ultimately in a better quality of life.<sup>14</sup>

The Canadian Headache Society and the U.S. Headache Consortium both recommend, based on expert consensus, considering prophylactic therapy whenever one of the following is present: a headache profile with a significant impact on daily life, having a contraindication to or an adverse effect with acute treatment, risk of medication overuse headache, patient preference, and the presence of one of the uncommon, unpleasant migraine varieties like; hemiplegic migraine, basilar migraine, or migrainous infarction.<sup>14,15</sup>

This section reviews the most important prophylactic treatments, based on their pharmacologic category:

**Antiepileptics. Sodium valproate/divalproex sodium.** At least 6 clinical studies, reviewed in the recent AHS and AAN guidelines, provided consistent evidence for the effectiveness of valproate in reducing headache frequency at a dose of 500 to 1000 mg/day.<sup>13</sup> There is no statistically significant difference between valproate and propranolol in preventing migraine without aura.<sup>14,16</sup> The high efficacy of valproate may be limited by its adverse effects profile, as it can cause weight gain, hair loss, tremors, bone marrow dysfunction, and pancreatitis. Women of childbearing age should avoid valproate because of its teratogenicity.<sup>12,15</sup>

**Gabapentin.** Clinical studies on the use of gabapentin for prevention of migraine provide conflicting results. The new U.S. guidelines mention a single recent study<sup>13</sup> supporting its use at a dose of 2400 mg/day, while Canadian guidelines consider it a preventive drug of moderate quality of evidence at a dose of 1200 mg/day.<sup>15</sup>

**Topiramate.** Topiramate for migraine prevention is supported by approximately 11 clinical trials reviewed in the new AHS & AAN guidelines.<sup>13</sup> Its target dose is 100 mg/day.<sup>15</sup> Topiramate has equal efficacy to that of propranolol and valproate.<sup>12,17,18</sup> Adverse effects include

paresthesia, gastrointestinal (GI) upset, and memory issues.

**Lamotrigine.** Lamotrigine has failed to demonstrate any clinical efficacy in migraine prevention. Its side effects may include rash and GI upset.<sup>13,14</sup>

**Carbamazepine.** Carbamazepine may have a weak effect in migraine prevention, as suggested by the U.S. Headache Consortium 2000 review.<sup>14</sup>

**Antidepressants. Amitriptyline.** Consistent evidence supports the use of amitriptyline in migraine prevention. Its target dose ranges from 10-100 mg/day.<sup>15</sup> Amitriptyline is probably as effective as venlafaxine, topiramate, and propranolol.<sup>13,15</sup>

**Venlafaxine.** A dose of 150 mg/day of venlafaxine is recommended as preventive therapy for migraine.<sup>15</sup> As mentioned earlier, venlafaxine has equal efficacy to amitriptyline. It may cause nausea, and drowsiness.<sup>12</sup>

**Fluoxetine.** Studies investigating the use of fluoxetine for migraine prevention found it better than placebo, the AHS & AAN guidelines review suggested in 2000 and 2012.<sup>19</sup> However, this evidence is inadequate or controversial.<sup>12-14</sup>

**Beta blockers. Propranolol.** Since 2000, clinical studies have provided consistent evidence for the efficacy of propranolol as a preventive therapy at a dose of 80-240 mg/day.<sup>12,14</sup> Propranolol may cause drowsiness and weight gain.

**Metoprolol.** Metoprolol was reclassified and upgraded in the 2012 U.S. guidelines to be a preventive drug "of established efficacy."<sup>19</sup> It is recommended at a dose of 100-200 gm/day. One study showed it is more effective than aspirin in reducing headache frequency.<sup>20</sup>

**Timolol.** Timolol was the highest rated group of preventive medications in the U.S. guidelines in 2000 and 2012.<sup>19</sup> It is recommended for use in patients eligible for preventive therapy at a dose of 10-15 mg bid.<sup>19</sup>

**Calcium-channel blockers. Verapamil.** Verapamil is an old agent for migraine prevention; however studies on verapamil provide conflicting evidence. Therefore, it has been downgraded in the latest U.S. guidelines.<sup>19</sup>

**Nimodipine.** Nimodipine also has inadequate evidence to support its use, in the latest drug reviews.<sup>13</sup>

**Angiotensin receptor blockers/angiotensin converting-enzyme inhibitors.** Lisinopril can be considered, and the recommended dose is 10-20 mg/day. Side effect includes cough or fainting. Serious side effects are uncommon.<sup>15</sup>

**Candesartan.** Candesartan is possibly effective mainly in reducing headache frequency. The recommended dose is 16 mg/day. Side effects include dizziness, and muscular fatigue.<sup>13</sup>



**Triptans.** Frovatriptan, zolmitriptan, and naratriptan are recommended for use in short-term prevention of MRM. Frovatriptan and zolmitriptan are given at a dose of 2.5 mg bid perimenstrually; naratriptan's dose is 1 mg bid perimenstrually.<sup>12</sup>

**Non steroidal anti-inflammatory drugs (NSAIDs).** The 2012 U.S. guidelines<sup>21</sup> reviewed 23 trials of a number of NSAIDs evaluated for their prophylactic effect. It concluded that fenoprofen, ibuprofen, ketoprofen, and naproxen are probably effective preventive medications. Reviewing aspirin trials, results were conflicting in both 2000 and 2012<sup>19,21</sup> versions of the guidelines. Therefore, the evidence supporting aspirin use is inadequate.<sup>14,21</sup>

**Treatment approaches.** Current guidelines provide recommendations to prevent migraine prophylactically based on drug efficacy, but evidence on how to choose the optimal therapy for a patient is still lacking. Reaching optimal therapy requires considering efficacy, side effect profile, patient's comorbidities, and his personal preferences.<sup>13</sup> Canadian guidelines suggest using a beta blocker or a tricyclic (amitriptyline or nortriptyline) as an initial prophylactic drug for most patients because of their combined efficacy and tolerability. They also present a number of treatment strategies depending on a patient's condition or comorbidity. For example, they recommend topiramate for overweight patients, amitriptyline or venlafaxine for patients suffering from anxiety or depression, propranolol, nadolol, metoprolol, candesartan, or lisinopril for hypertensive migraineurs.<sup>15</sup> Targeting migraine and the comorbid disease with a single medication improves adherence to treatment and decreases the likelihood of drug interactions.

A preventive medication should be used for no less than 2 months at the optimal dose or maximum dose tolerated before concluding that it is ineffective. The patient should be started on a low dose that is increased gradually until reaching the optimal dose. Meanwhile, treatment should be followed up periodically to detect possible side effects. Preventive therapy is considered effective when headache frequency decreases by 50% or more. Headache severity and migraine disability may also be included when judging drug efficacy. A preventive medication can be tapered gradually and discontinued following 6 to 12 months of successful therapy. However, the dose should be increased again if the headache frequency rises with tapering.<sup>15,22</sup> On the other hand, patients who are refractory to preventive monotherapy could benefit from drug combinations. The following combinations are recommended by the Canadian guidelines: beta blockers and topiramate, beta blockers and divalproex, beta blockers and amitriptyline, and amitriptyline and topiramate.<sup>15</sup>

**Prophylaxis in specific populations.** Menstrual-related migraine is defined as a migraine attack that starts 2 days before menstruation and lasts until the third or the last day of menstruation. Usually, this diagnosis is given when the migraine appears in 2 out of 3 consecutive cycles, and when no other attacks are reported other than those related to menstruation.<sup>4,7</sup> For women whose MRMs are not effectively controlled by abortive medications, a short-term prophylactic therapy can be given. Evidence supports the use of NSAIDs, triptans (frovatriptan, naratriptan and zolmitriptan; specifically), and 1.5 gm dermal patches of estradiol. These should be given the second day of menstruation and continued through it.<sup>4,7</sup>

Many women experience varying degrees of migraine remission during pregnancy.<sup>4</sup> If migraine persists, paracetamol is the first line abortive drug. Aspirin and NSAIDs can also be used during the first and second trimesters only.<sup>4,6</sup> Prophylactic therapy is not advised during pregnancy and lactation. However, if prophylaxis is necessary, magnesium, beta blockers or amitriptyline may be considered. Ergot derivatives and divalproex sodium are absolutely contraindicated during pregnancy for their teratogenicity and better avoided in women of childbearing age unless appropriate contraception is ensured.<sup>4,15</sup>

It is estimated that around 3-10% of children suffer from migraines. Unfortunately, diagnosis is more difficult because migraine diagnostic criteria are less sensitive in children. For abortive treatment in children, ibuprofen is the first line drug. French guidelines<sup>4</sup> also cite the use of the following agents: aspirin, paracetamol, and diclofenac in children weighing more than 16 kg, naproxen in children older than 6 years or heavier than 25 kg, and sumatriptan nasal spray for severe migraine in children older than 12 years or heavier than 35 kg. In 2014, topiramate was the first FDA-approved drug for the prevention of migraine in 12-17 year olds.<sup>23</sup> Several other agents are in use for migraine prevention in children according to the professional consensus. One systematic study found evidence on the efficacy of topiramate, valproic acid, flunarizine, amitriptyline, and cyproheptadine, and found conflicting data on the use of propranolol and pizotifen.<sup>24</sup>

**Migraine prophylaxis guidelines worldwide.** Five distinguished guidelines on migraine pharmacological prevention were published: the European Federation of Neurological Societies (EFNS) guideline on the treatment of migraine, revised in 2009,<sup>25</sup> the Canadian Headache Society guideline in 2012,<sup>15</sup> the report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society, revised in 2012,<sup>13</sup> the UK's National Clinical

Guideline report on the diagnosis and management of migraine, funded by the National Institute for Health and Clinical Excellence (NICE), in 2012,<sup>6</sup> and the revised French guidelines for the diagnosis and management of migraine in 2014.<sup>4</sup>

The scope of disease/disease syndromes covered by these published guidelines is variable. The Canadian, American, EFNS, and French guidelines focus primarily on the treatment and prevention of episodic migraine - EFNS discusses status migrainosus, and French and U.S. guidelines add MRM too - while the UK's guidelines have a broader scope. The UK guidelines deal with a variety of primary and secondary headache syndromes, namely, primary headaches, including: migraine, MRM, chronic migraine, tension headache, cluster headache, medication overuse headache. The EFNS addresses migraine in children and/or adolescents.<sup>25</sup>

The U.S. guidelines<sup>13,19</sup> were more interested in investigating and assessing the scientific literature

for drug safety and efficacy. Neither cost analysis nor side effect profiles were used to assign each drug to a recommendation class. It is worth noting this guideline reviewed a large number of drugs for their efficacy in prevention of migraines.

Table 3 presents a comparison of the level of recommendations for a number of prophylactic agents, according to US, Canadian, French and EFNS guidelines.<sup>4,13,15,19,25</sup>

**New advances in treatment and future direction.** In the past, migraine mechanism-based drug development was a remote possibility. Today, many of these types of drugs are in different stages of drug development, as we better understand the complex pathophysiology of migraine. These drugs have novel mechanisms of action or have new therapeutic targets.

Triptans are well-established abortive migraine treatments. They have an affinity to 5-hydroxytryptamine receptors: 5-HT1B, 5-HT1D, and 5-HT1F. The

**Table 3** - Level of recommendation and evidence for prophylactic medication used for migraine according to the U.S.,<sup>13,19,25</sup> Canadian,<sup>15</sup> French<sup>4</sup> and EFNS<sup>25</sup> guidelines.

Drug	2012 U.S. guidelines	Canadian guidelines	French guidelines	EFNS
Valproate*	Level A	Weak recommendation, HQE	DE, Grade A methodology	Level A
Topiramate*	Level A	Strong recommendation, HQE	DE, Grade A methodology	Level A
Carbamazepine*	Level C	Not rated	Not rated	Not rated
Gabapentin*	Level U	Strong recommendation, MQE	Doubtful efficacy, Grade B or C methodology	Level C
Lamotrigine*	Ineffective	Not rated	Not rated	Not rated
Amitriptyline <sup>†</sup>	Level B	Strong recommendation, HQE	PE, Grade B or C methodology	Level B
Venlafaxine <sup>‡</sup>	Level B	weak recommendation, LQE	PE, Grade B or C methodology	Level B
Fluoxetine <sup>‡</sup>	Level U	Not rated	Not rated	Not rated
Pizotifen <sup>†</sup>	Not rated	Weak recommendation, HQE	PE, Grade B or C methodology	Not rated
Metoprolol <sup>†</sup>	Level A	Strong recommendation, HQE	DE, Grade A methodology	Level A
Propranolol <sup>†</sup>	Level A	Strong recommendation, HQE	Not rated	Level A
Timolol <sup>‡</sup>	Level A	Not rated	PE, Grade B or C methodology	Not rated
Atenolol <sup>‡</sup>	Level B	Not rated	PE, Grade B or C methodology	Not rated
Nadolol <sup>‡</sup>	Level B	Strong recommendation, MQE	PE, Grade B or C methodology	Not rated
Nebivolol <sup>‡</sup>	Level C	Not rated	Probable efficacy, Grade B or C methodology	Not rated
Acebutolol <sup>‡</sup>	Ineffective	Not rated	Not rated	Not rated
Verapamil <sup>§</sup>	Level U	Weak recommendation, LQE	Not rated	Not rated
Candesartan <sup>§</sup>	Level C	Strong recommendation, MQE	PE, Grade B or C methodology	Level C
Lisinopril <sup>§</sup>	Level C	Weak recommendation, LQE	Not rated	Level C
Naproxen <sup>§</sup>	Level B	Not rated	PE, Grade B or C methodology	Level B
Aspirin**	Level U	Not rated	Not rated	Level C
Feverfew**	Level B	Not recommended	Not rated	Not rated
Petasites**	Level A	Not rated	Not rated	Level B
Butterbur**	Not rated	Strong recommendation, MQE	Not rated	Not rated
Coenzyme 10**	Level C	Strong recommendation, LQE	Not rated	Level C
Riboflavin**	Level B	Strong recommendation, LQE	Not rated	Level C
Magnesium**	Level B	Strong recommendation, LQE	Not rated	Level C

HQE - high quality evidence, LQE - low quality evidence, MQE - moderate quality evidence, DE - demonstrated efficacy, PE - probable efficacy, EFNS - European Federation of Neurological Societies, U.S. - United States of America, symbols represent different groups of medications

5-HT<sub>1F</sub> receptors have particular interest as they do not have a vasoconstrictor effect, rather, they hyperpolarize the trigeminal nerve.<sup>8</sup> Lasmiditan is an oral 5-HT<sub>1F</sub> receptor agonist currently in phase II development.<sup>26</sup>

Several pain-producing inflammatory mediators, which act unfavorably on the neurovasculature were identified; including glutamate, substance P, and calcitonin gene related peptide (CGRP). Drugs acting on CGRP as a target molecule are promising. Olcegepant was the first CGRP antagonist recognized, but its development was halted. Telcagepant is another CGRP antagonist that could be effective in acute migraine treatment, but faces some safety concerns.<sup>8</sup> Moreover, LY-2951742 is an antibody that binds to CGRP, inhibiting its vasodilator effect. It is now in later stages of development as an injectable therapy.<sup>26</sup>

Human provocation studies have given us valuable insights into the role of prostaglandins in migraine. Both EP<sub>2</sub> and EP<sub>4</sub> are 2 prostaglandin receptors that can be a more selective drug target with a better side effect profile than NSAIDs.<sup>8</sup> One EP<sub>4</sub> receptor antagonist, AP-1531, is already in stage II clinical trials.<sup>26</sup>

The need for developing abortive migraine treatments is as great as the need for prophylaxis, especially since most prophylactic treatments already in use are not specific for migraine and only cite it as a secondary indication. Tonabersat is one of these prophylactic drugs under development. It inhibits cortical spreading depression, thus preventing migraine with aura.<sup>8</sup>

Botulinum toxin A is now approved for the treatment of chronic headache, defined as headache for more than 15 days/month for at least 3 months, with at least 8 days with migraine headache. It is also recommended for use in patients who are refractory or intolerant to therapy.<sup>7</sup> The NICE guidelines<sup>6</sup> recommend stopping botulinum toxin A if the number of headache days does not decrease by at least 30% after 2 courses of treatment or if chronic migraine converts to episodic.<sup>27</sup> Many authors still doubt its efficacy as it only has a therapeutic gain of 10%.<sup>8</sup>

Transcranial magnetic stimulation (TMS), a noninvasive procedure, has been experimented with for use in acute and chronic migraine treatment and prevention. It delivers magnetic pulses either during the aura/early in the headache episode to treat it, or at planned intervals to prevent it. The optimal dose of pulses and their frequency is still uncertain. The data showed that the use of TMS is effective and safe in the short-term use; however, there is still no evidence for its long-term safety.<sup>28</sup> Similarly, transcutaneous electrical nerve stimulation is another noninvasive procedure

that could have potential benefit for migraineurs. A recent randomized clinical trial<sup>28</sup> investigated the safety and efficacy of trigeminal supraorbital transcutaneous stimulation (STS) as a preventive therapy for migraine. It showed STS significantly decreasing mean number of migraine days. No side effects were observed.

In conclusion, although migraine is a common disorder it is frequently under-diagnosed. Furthermore, some patients who suffer from migraine and eligible for prophylactic treatment do not receive it properly. These treatments if offered, it might reduce the physical and functional impairment of migraine and enhance the quality of life. The current international guidelines recommend a good number of abortive and prophylactic medications that are effective with good safety profile. More advanced treatment modality with mechanism-based therapies including transcranial magnetic stimulation and supraorbital transcutaneous stimulation and other showed a potential role in migraine treatment and prevention with promising results. A limited local data are available for migraine in Saudi Arabia which require farther studies and research that address different aspect of disease characteristics and burden as well as pharmacogenetics that may help to improve patient care and develop a national guideline for treatment of migraine.

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