Patient Related Outcome Measures

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REVIEW

Patient outcome in migraine prophylaxis: the role of psychopharmacological agents

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Introduction: Migraine is a serious illness that needs correct treatment for acute attacks and, in addition, a treatment prophylaxis, since patients with migraine suffer during acute attacks and also between attacks.

Methods: A systematic review of the most relevant clinical trials of migraine headache and its epidemiology, pathophysiology, comorbidity, and prophylactic treatment (medical and nonmedical) was carried out using "Medline" and "PsychINFO" from 1973 to 2009. Approximately 110 trials met our inclusion criteria and were included in the current review.

Results: The most effective pharmacological treatment for migraine prophylaxis is propranolol and anticonvulsants such as topiramate, valproic acid, and amitriptyline. Nonmedical treatments such as acupuncture, biofeedback, and melatonin have also been proposed. Peripheral neurostimulation has been suggested for the treatment of chronic daily headache that does not respond to prophylaxis and for the treatment of drug-resistant primary headache. The majority of the pharmacological agents available today have limited efficacy and may cause adverse effects incompatible with long-term use.

Limitations: The review was limited by the highly variable and often insufficient reporting of the complex outcome data and by the fact that migraine prophylaxis trials typically use headache diaries to monitor the course of the disease. The results of the different studies were also presented in different ways, making comparison of the results difficult.

Discussion: An adequate prophylaxis is crucial in reducing disability and preventing the evolution of the problem into a chronic progressive illness. The implications of the present findings were discussed.

Keywords: migraine, prophylaxis, pharmacological agents, nonmedical treatments, outcome

Introduction

Chronic daily headache is defined as a group of disorders in which headache occurs 15 or more days per month for at least 3 months.[1] These disorders include: chronic migraine (which affects approximately 2.4% of the general population),[2] migraine with or without aura and migraine aura without headache, chronic tension-type headache, hemicrania continua, and daily persistent headache.[3]

Migraine is usually a genetic disorder, often associated with other medical conditions such as depression (80%),[4] major depressive disorder,[5,6] anxiety (70%),[7] insomnia (71%),[8] chronic fatigue (66%),[9] and fibromyalgia (35%).[10]

Factors such as stressful life events, contraceptive pill use, hypertension, mood changes, and the use or overuse of certain drugs may increase the frequency of headache,[10] while dietary factors, regular sleep, physical activities, and relaxation

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technique are associated with a decrease in the frequency of headache.[11] An untreated migraine attack may last from 4 to 72 hours. Often it is related to autonomic nervous system dysfunction and, in certain cases, it is associated with aura and can result in neurological symptoms.[6] Migraine is a fluctuating disorder in which worsening and spontaneous improvements are common.[12] In up to 25% of patients, pain may be preceded or accompanied by aura, which is usually characterized by visual disturbances, neurological events, fatigue, mood changes, and food cravings. The pain of migraine may be accompanied by phenomena such as photophobia, nausea, and vomiting.[13] Studies conducted in Europe show that one out of five people are absent from work for 11 days or more due to migraine headache during any 3-month period, and experience a 50% or more reduction in productivity or an inability to participate in social activities.[14] It has been estimated that migraine is the most costly neurological disorder in Europe and one of the most costly in the United States.[15,16] It has been estimated that the cost of migraine in Europe per patient is €579, or €27 billion for the 41 million patients aged between 18 and 65 years.[14]

Migraine is an issue for both individuals and the society and causes reduced productivity at work and impaired family and social life.[17] Early and accurate diagnosis is fundamental in optimizing treatment and in preventing progression. However, only a minority of migraine sufferers receive preventive treatment because of the cost.[17,18] Additional problems for prophylactic medication involve the limited efficacy and the incidence of side effects of medications.[5,19–21]

The present paper analyzes the epidemiology and physiopathology of migraine, focusing on the need for and the efficacy of both medical and nonmedical therapeutic approaches for long-term preventive management of migraine and its role in patient outcome.

Method

A systematic review of the most relevant clinical trials about migraine headache and its epidemiology, physiopathology, comorbidity, and prophylactic treatment (medical and nonmedical) was carried out using "Medline, PsychINFO, Embase, Cinahl, and Pubmed databases" from 1973 to 2009 in order to maximize the chance of finding trials. We limited our research to articles in English, using as keywords the following terms: "migraine epidemiology," "migraine pathophisiology," "migraine comorbidity," "migraine treatment," "migraine prevention," "migraine AND disorders," "migraine AND prophylaxis," "migraine AND psychiatric disorders," and "migraine AND outcome". We included both open and double-blind trials. Trials exploring acute treatment for migraine were not included because we focused on long-term treatment of migraine.

The combined search strategies yielded 1,890 abstracts. After a complete analysis of the abstracts, 350 full-text articles were reviewed. Approximately 110 trials met our inclusion criteria and were included in the current review and 240 were excluded because they focused primarily on acute migraine and headache treatments, pharmacological approaches, or management in pediatric populations.

Migraine: epidemiology and pathophysiology

Migraine is a vascular headache characterized by periodic unilateral pulsating headaches associated with changes in the size of the arteries within and outside the brain. Several studies have demonstrated that the overall prevalence of migraine is 6%–8% for men and 15%–18% for women in Europe and America.[18,22,23]

Epidemiological data indicate that there are about 28 million patients suffering from migraine in the United States.[24] The overall prevalence of migraine is roughly similar in industrialized countries. In a very recent study, Benamer, Deleu, and Grosset reported that the migraine prevalence was 2.6%–5% in Saudi Arabia and 7.9% in Qatar, while the 1-year migraine prevalence was 10.1% in Oman similar to that estimated worldwide.[25] Migraine without aura is more common than is migraine with aura. In a Danish study of a representative sample of the general population, the lifetime prevalence of migraine with aura was 6%, whereas the prevalence of migraine without aura was 9%. Importantly, 1.2% of the population reported having both types of migraine.[26]

A migraine begins when hyperactive nerve cells send out impulses to the blood vessels, causing constriction, followed by the dilation of these vessels and the release of prostaglandins, serotonin, and other inflammatory substances that cause the pulsation to be painful. Cortical spreading depression (CSD) is a spontaneous neuronal depolarization moving slowly (3 mm/min) on the occipital cortex, which has a clinical counterpart in positive scotoma (a dark spot in the visual field) and teichopsia (transient visual sensations of bright shimmering colors). CSD activates the brainstem and gives rise to depolarization of ascending and

descending pathways, perimeningeal vasodilatation and neurogenic inflammation.[27,28] Therefore, in migraine, the excitatory events are believed to be proximal, whereas the neurovascular events that lead to pain production are distal.[29] Repeated episodes of hyperexcitability could parallel, or cause, dysmodulation of nociceptive pathways, with a resultant chronic state, potential disease progression, and a refractoriness to therapy that some patients experience.[27] Central sensitization, associated with abnormal neuronal excitability in the trigeminal nucleus caudalis, may also play a critical role in migraine pathogenesis, especially in the latter stages of an acute attack, and in the development of chronic forms of the disorder.[30,31]

Moskowitz suggested that some components of migraine pain are related to dural plasma protein extravasation with sterile neurogenic inflammation.[32] Electrical stimulation of the trigeminal ganglion induces plasma protein extravasation which may be blocked by sumatriptan, a substance active in acute migraine attacks.[33]

However, a blockade of neurogenic plasma protein extravasation is not completely predictive of anti-migraine efficacy.[34] Plasma protein extravasation may be an epiphenomenon rather than a pivotal mechanism of trigeminal activation and migraine generation.[35]

Migraine might be also explained by a dysfunction of neuromodulatory structures in the brainstem, such as the locus coeruleus or periaqueductal grey matter, which have a critical role in the regulation of cortical function and in modulating responses to afferent traffic.[36]

Such dysfunction might explain not only the somatosensory components of migraine, but also the auditory, olfactory, and visual components. Additionally, a locus coeruleus dysfunction may also explain the distractibility and anxiety often observed in migraine sufferers.[36]

An overview of the literature indicates that stress may be a predisposing factor for headache onset, acute headache trigger, and potential contributor to migraine progression.[37]

However, the relationship between migraine, stress, psychological symptoms, and response to treatment is complex and largely unknown. Géraud et al found that the majority of 5,417 migraine patients exhibited significant psychological symptoms, and most of patients were classified as anxious.[38] Two-thirds of patients (67%) suffered from anxiety (28% from anxiety alone, 39% from anxiety and depression), and 2% from depression alone. Stress, avoidance, and catastrophizing, along with the number of headache days/month, the number of drugs taken during attacks, and migraine chronicity were the strongest predictive factors of migraine.

Several causal factors (low concentrations of glutamate, mitochondrial abnormalities, dysfunctions related to nitric oxide and calcium channelopathy, plasma protein extravasation, and dysfunctions of neuromodulatory structures in the brainstem) may converge onto a common hyperexcitable brain state, which constitutes the fundamental susceptibility to migraine attacks.[39]

Migraine and prophylaxis

Migraine is a cyclical pathology in which acute treatment is crucial for the patient's health during migraine-free intervals. It has been demonstrated that patients suffer not only in the acute episodes but also during the inter-critical period.[13] Migraine sufferers are impaired in daily activities,[32,33] and their health-related quality of life is generally poor compared both with the general population and with sufferers from other chronic disorders.[40–42]

Preventive therapy is essential in order to reduce recurrences and relapses and may be measured in terms of the reduction in the frequency of acute attacks, the impact of acute treatment on headache recurrence within the next 24 hours, as well as in a reduction in overall functional impairment.

Recent guidelines for the treatment of migraine suggest that patients who are candidates for prophylaxis should have the following features: more than two migraine attacks per month or migraine refractory to acute therapy, strong side effects of acute therapy, contraindication, failure of acute medication, use of acute medication more than twice per week,[43,44] and a risk of overusing acute medication.[22] Disability level, future pregnancy status,[17] and the costs of acute and preventive therapy are aspects to be considered in initiating prophylaxis.[22]

The first goal of prophylactic treatment is to reduce the frequency and intensity of attacks, and, thereby, improve the quality of life.[6,17,20,45] The prophylactic therapy may cause problems in relation to adverse effects (fatigue, dizziness, reduced concentration, loss of appetite, weight gain, hair loss, changes in libido, and drowsiness), tolerability, cost, frequency of the dosage, the patient's compliance, and failure to complete treatment.[18,21] Exploratory efficacy outcome measures should include: number of migraine attacks per four weeks, number of headache days, pain intensity, headache index, and global response.[14,18,46]

Several migraine preventive treatments have been recommended for improving negative disease outcome related to migraine.[47]

Treatment options: medications

There is a general agreement that propranolol, valproic acid, and topiramate are first-line treatments for migraine prophylaxis.[48] Other drugs that are frequently used are flunarizine, amitriptyline, other betablockers, gabapentin, and methysergide. In addition, vitamins, natural medications, SSRIs such as paroxetine and fluvoxamine, tricyclic antidepressants (TCAs), and botulinum toxine have been tried. Evidence exists from several randomized controlled studies of the efficacy of anti-epileptic drugs, antidepressants, β-blockers, and calcium channel blockers in migraine prophylaxis.[49] Combining pharmacological agents is useful if depression is present, but the side effects and patient dissatisfaction argue against the use of antidepressants for patients who suffer from migraine but without depression.[6]

An important issue here is the frequent abuse of medications such as nonsteroidal anti-inflammatory drugs and other analgesics, especially given their long-term side effects such as reduction of renal function. Headaches can be so frequent that patients use analgesics daily or nearly daily. Patients who abuse medications are particularly difficult to treat because prophylactic treatments are usually ineffective with these patients.[50] Withdrawal from analgesics abuse is essential in order to improve both the patient's clinical condition and the analgesic abuse itself.[51]

Antiepileptic drugs

It is well demonstrated that anticonvulsants are effective in migraine treatment and prophylaxis. They reduce both the frequency of attacks (up to 1–2 attacks per month) as well as the number of attacks. Anticonvulsants are also well tolerated, and they cause fewer adverse effects.[22,39] Topiramate (TPM) and valproic acid (VPA) are the most important treatment options for migraine and are now approved for migraine prevention in several countries.[52,53] Table 1 summarizes the most relevant studies on the efficacy of pharmacological agents in migraine prophylaxis.

VPA increases GABA levels in the brain and potentiates GABA-mediated responses. One possibly important action of VPA is the blockade of the degradation of GABA by GABA transaminase, thereby increasing GABA concentrations in both axons and glial cells.[54] VPA has been found to block voltage-dependent sodium ion channels, thereby modulating the release of excitatory amino acids, and has also been found to block low threshold T-type calcium ion channels.[55] The efficacy of VPA in migraine prevention has been shown in several double-blind, randomized, placebo-controlled studies.[56,57]

However, Apostol et al investigated the efficacy, tolerability, and safety of different doses of divalproex sodium extended-release vs placebo in the prophylaxis of migraine headaches in a 12-week, randomized, placebo-controlled, double-blind, parallel-group study in approximately 300 adolescents.[58] They found that, although well tolerated, it did not differ from placebo in the prophylactic treatment of migraine headaches.

TPM is generally used to treat epilepsy, psychiatric disorders, and migraine prophylaxis and to suppress CSD frequency by 40%–80%. Longer treatment durations produce stronger suppression. Direct and indirect effects on the inhibition of glutamate release and on blocking NMDA receptors may also be relevant for modulating migraine susceptibility.[59]

Large, multicentre, randomized, double-blind, placebo-controlled trials have demonstrated the efficacy of TPM in migraine prophylaxis in adults.[60,61] A recent study showed a significant improvement in health-related quality of life in adult migraine patients.[62–64] In four randomized placebo controlled trials, 6 months of TPM (100mg/d) administration was associated with a significant decrease in monthly migraine frequency.[50,60,61,65] However, a recent study suggests that a lower dose of TPM (45.7 mg/d) may also reduce migraine days and pain intensity.[14] (For more details see Table 1). Feliu et al found significant reductions in acute migraine medication and medical resource use in 1,749 migraine sufferers in the six months following initiation of TPM preventive therapy.[66] Vuković et al assessed the efficacy and safety of gabapentin at 900–1800 mg of drug in 3 doses in 67 migraine patients refractory to other prophylactic treatments, of which 52 completed the prospective, open-label study.[67] They found a significant reduction in the number of days with headache, the use of acute medications and pain intensity in the prophylaxis of migraine.

Finally, in a cost-effectiveness analysis from three, double-blind, placebo-controlled, clinical trials of antiepileptic drugs studied for migraine prevention, Adelman, Adelman, and Von Seggern found that divalproex sodium was cost-effective in patients with 10 migraines per month, whereas gabapentin and topiramate became cost-effective for more than 10 migraines per month.[68]

Table 1 Most relevant literature studies reporting findings about the effectiveness of the majority of pharmacological agents in migraine prophylaxis

Study	Design	Sample size	Conclusions
Gomersall and Stuart[114]	Double-blind controlled clinical trial.	20 subjects treated with amitriptyline.	Amitriptyline reduces both migraine attacks characterized by short warning and with no specific cause and those with long warning and recognized as due to fatigue. Amitriptyline was effective, irrespective of severity, only in reducing attacks with shorter duration.
Hering and Kuritzky[57]	Double blind study, valproate vs placebo for 8 weeks.	29 patients divided into 2 groups; group 1: valproate 400 mg daily and group 2: placebo.	More effectiveness of valproate than placebo in reducing severity and frequency of migraine attacks in 86.2% of patients.
Linde et al[115]	Review including twenty-two randomized trials with a post-randomization observation period of at least 8 weeks comparing clinical effects of acupuncture intervention with a control group.	4419 participants.	Additional benefits with acupuncture in acute migraine attacks only or to routine care.
Schrader et al[90]	Double blind, placebo controlled, crossover study.	Sixty patients aged 19–59 years with migraine with two to six episodes a month. Treatment period of 12 weeks. First treatment period 10 mg lisinopril/daily (one week) 20 mg lisinopril/daily (11 weeks) Two week wash out period Second treatment period One placebo tablet/daily (one week). Two placebo tablets/daily (11 weeks).	Lisoprinil vs placebo: Hours with headache reduced by 20% Days with headache reduced by 17% Days with migraine reduced by 21% Headache severity reduced by 20% Days with migraine were reduced by at least 50% in 14 participants for active treatment vs placebo. Days with migraine were fewer by at least 50% in 14 participants for active treatment vs placebo.
Freitag et al[56]	Double blind randomized, placebo controlled, parallel-group study.	Subjects with 2 or more migraine attacks in 4 weeks, divided into 2 groups receiving valproate 500–1000 mg daily or placebo.	Mean reductions in 4-week migraine headache rate 1.2 (from baseline 4.4) in the extended-release (ER) divalproex sodium group and 0.6 (from baseline 4.2) in the placebo group ($P = 0.006$). Significantly greater reductions in all three 4-week segments of the treatment period with ER divalproex sodium than with placebo.
Linde and Rossnagel[79]	Review included 58 randomized and quasi-randomized clinical trials of at least 4 weeks duration comparing clinical effects of propranolol with placebo or another drug in adult migraine sufferers.	26 participants with placebo and 47 participants with other drugs.	Propranolol is more effective than placebo in the short-term interval treatment of migraine. Evidence on long-term effects is lacking. Propranolol seems to be as effective and safe as a variety of other drugs used for migraine prophylaxis.
Lewis et al[116]	Review of 166 controlled, randomized, and masked trials.	Treatment options were separated into medications for acute headache and preventive medications. For preventive therapy, 12 agents were evaluated.	Flunarizine is presumably effective and may be considered for prophylaxis but is not available in USA.
Dahlöf et al[47]	Longitudinal and responder analysis from 3 topiramate-placebo-controlled clinical trials.	756 patients: 384 recived topiramate 100 mg/daily and 372 received placebo.	Significant improvement of topiramate 100 mg/daily activities and patient functioning. Significant improvement of daily functioning and health status for those achieving ≥50% migraine frequency reduction.

(*Continued*)

Table 1 (*Continued*)

Study	Design	Sample size	Conclusions
Keskinbora and Aydinli[6]	Single-center, double-blind, randomized and controlled trial.	73 patients with migraine with or without aura.	Amitriptyline and topiramate in combination may be beneficial for patients with migraine and comorbid depression, particularly in terms of side effects and associated displeasure due to monotherapy.
Dodick et al[46]	Multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority study.	331 subjects (172 topiramate, 159 amitriptyline).	Topiramate was at least as effective as amitriptyline in reducing the rate of mean monthly migraine episodes and all pre-specified secondary efficacy end points. Topiramate was associated with improvement in some quality of life indicators compared with amitriptyline, with weight loss and improved weight satisfaction.
Mullally et al[105]	Randomized, prospective, single blind, controlled trial for more than one year. Biofeedback + education in pain theory + relaxation technique vs education in pain theory + relaxation techniques alone.	Sixty-four migraine patients aged 18–55.	Decrease in the frequency and severity of the headaches in the first 12 months that continued to 36 months in education in pain theory and relaxation techniques group. Decreased number of medications used and utilization of medical care. No additional benefit in the biofeedback group when compared to simple relaxation techniques alone in the treatment of migraine and tension type headaches in adults.

Triptans

These agents are a major option for migraine management, but only about 50%–60% of patients consistently respond to this type of medication.[69] In most cases, they provide only partial relief. Prophylactic treatment is indicated if other treatments are inadequate and if patients experience two or more migraine attacks per month.[70]

Antidepressants

Antidepressants have shown evidence for efficacy in the prophylactic treatment of migraine.[27,71] Serotonin (5-HT) and norepinephrine (NE) signalling play a role in some models of migraine pathophysiology. In general, among the antidepressants, amitriptyline (a tricyclic antidepressant) has well-demonstrated efficacy in migraine treatment.[27,71]

In evidence-based guidelines developed by Japanese Headache Society and the American Neurological Association, amitriptyline is classified as a Group 1 drug (an effective drug for the prevention of migraine attack).[72] Moreover, amitriptyline is especially useful where there is comorbidity with depressive disorders. Administration of amitriptyline at low doses may reduce the frequency of side-effects such as sleepiness. Several clinical trials of this drug have also shown the remarkable benefits of amitriptyline in the prophylactic treatment of migraine attack.[27,71] Table 1 summarizes the most relevant studies on the efficacy of amitriptyline in migraine prophylaxis.

Landy et al measured the baseline migraine frequency and severity over a 4-week period in twenty-seven subjects and found that sertraline, fluoxetine, fluvoxamine, and paroxetine are not as effective as conventional migraine prophylaxis medications such as beta-blockers, tricyclic antidepressants, or divalproex sodium whereas they may be effective in patients with comorbid depression who have failed conventional therapy.[73]

β-blockers

The improvement of migraine in patients who were given propranolol for angina pectoris revealed the effectiveness of propranolol in migraine prophylaxis. Available guidelines commonly recommend beta-blockers as the first choice for migraine prophylaxis.[74] It is not certain how beta-blockers decrease the frequency of migraine attacks,[74] but they may affect the central catecholaminergic system and serotonin receptors in the brain. The central action of β-blockers is probably mediated by inhibition of central β-receptors interfering with the vigilance-enhancing adrenergic pathways, interaction with 5-HT

receptors and cross-modulation of the serotoninergic system.[75] Propranolol inhibits CSD in rats by blocking glutamate release.[76]

Other beta-blocking drugs, such as nadolol, metoprolol, atenolol, timolol, and bisoprolol, have also been demonstrated to be effective in the prophylaxis of migraine. In contrast, several beta blockers with intrinsic sympathetic activity (ISA), such as alprenolol, oxprenolol, pindolol, and acebutolol, have not been demonstrated to be effective in migraine prophylaxis.[77] Some case reports in the literature have reported successful treatment with amlodipine, a slow calcium-channel blocker in migraine prophylaxis.[78] In a systematic review of 26 clinical trials,[79] propranolol was shown to be more effective than placebo in reducing migraine frequency among adults. Seventeen trials out of 26 showed a significant superiority over placebo, while 7 showed a trend in favor of propranolol, and 2 showed no differences. In 13 clinical trials comparing propranolol with a calcium antagonist (flunazarizin in 7 cases), no difference was found in favor of propranolol in 12 clinical trials, while one found a trend in favor of flunarizin. In the same review, no difference was found in 7 of ten studies comparing propranolol with other beta-blockers, while in 3 trials a trend in favor of beta-blockers was seen. Comparisons of propranolol with other drugs such as femoxetine, tolfenamic acid, and 5-hydroxytryptophan, have shown that propranolol appears to be superior for the treatment of migraine patients.[79] In a double-blind placebo-controlled cross-over study of migraine prophylaxis with propranolol 80 mg once daily, 160 mg once daily or placebo for two months in thirty migraine sufferers, al-Qassab and Findley found no significant differences between the three treatments in headache frequency, headache severity, nausea frequency, or severity.[80]

Pascaul et al explored treatment combining a beta-blocker plus topiramate in migraine patients previously resistant to either medication in monotherapy, and found that the combination of beta-blocker plus topiramate demonstrated a benefit in 60% of patients who had not previously responded to monotherapy.[81]

Flunarizine

The primary pharmacological mechanism of flunarizine on burst potentials has been attributed to the blockage of calcium or sodium ion channels. Flunarizine has been used frequently (32%) for prophylactic treatment, and it has been considered to be a first-choice medication for the management of patients with migraine.[82] It has also been reported that flunarizine might be a useful add-on treatment in therapy-resistant forms of epilepsy.[83,84]

Both flunarizine and propranolol have demonstrable efficacy in the prophylaxis of migraine,[79,85] but no significant difference in efficacy was observed between sodium valproate at 1000 mg versus flunarizine at 10 mg daily maintained for 4 weeks.[86] Diener et al reported that 10 mg flunarizine daily is at least as effective as 160 mg propranolol in the prophylaxis of migraine after 16 weeks of treatment, and 5 mg flunarizine proved to be at least as effective as 160 mg propranolol when looking at the mean attack frequency for both the whole double-blind period and the last 28 days of treatment.[87]

Lucetti et al found that family history, a high intensity of pain, frequent attacks and a history of analgesic abuse were the most important predictive factors for a positive response to flunarizine in migraine prophylaxis.[88]

Wöber et al reported that therapeutic success with flunarizine and beta blockers dramatically decreases in the majority of patients several months after discontinuation of treatment, and further long-term prophylaxis is more effective if the substance class is changed.[89]

Pizotifen and naproxen

There is consistent evidence to support pizotifen's efficacy in migraine prevention.[90,91] In a comparative study, pizotifen was more effective than naproxen sodium and placebo in migraine prophylaxis. However, in a recent review of 16 published randomized controlled trials of naproxen in the treatment of migraine, naproxen sodium was more effective than placebo in reducing pain intensity and providing a pain-free state within 2 hours in adults with moderate or severe migraine attacks.[92]

The mechanism of action of pizotifen is not known for certain, but pizotifen has additional antagonistic effects on 5-HT2, histamine H1, muscarinic cholinergic, α-1-adrenergic, α-2-adrenergic, and dopamine receptors.[90,91,93]

Angiotensin II receptor blockers

The angiotensin-converting enzyme (ACE) inhibitor lisinopril has been found to be an effective prophylactic treatment for migraine attacks.[94] In addition, candesartan is a long-acting angiotensin II type 1 (AT1) receptor blocker with a high affinity for the AT1 receptor that has demonstrated efficacy in migraine prophylaxis.[95] However, the mechanism of action of ACE inhibitors in migraine prevention is poorly understood.

Other drugs

Other options for migraine prophylaxis exist, but the evidence in support of their use is not robust or well-documented.

All of these drugs have varying degrees of adverse effects, and some of these effects may limit their use.[95] There are additional agents such as vitamins, natural medications, and botulinum toxine, which have shown to have possibilities in migraine prophylaxis.

Botulinum toxin type A (BoNTA)

Patients whose migraines are poorly controlled by traditional preventive therapies may be treated with Botulinum Toxin type A (BoNTA).[5,18,21] BoNTA is more effective in patients with chronic migraine. It may be used in migraine patients with the following features: muscular stress as a migraine trigger, craniocervical dystonia, pericranial painful muscular trigger points, and oromandibular dysfunction. BoNTA is highly recommended for patients with poor compliance because of its method of action, its long duration of action and for the lack of the usual side-effects caused by prophylaxis.[5,18,21] BoNTA has beneficial effects on the frequency of migraine but not in lowering the severity of pain.[5,18,21]

Jakubowski et al found that exploding headaches (a build-up of pressure inside the head) were impervious to extracranial BoNTA injections consistent with the prevailing view that migraine pain is mediated by intracranial innervation.[96] The response of imploding headaches (feeling crushed by external forces) and ocular headaches to BoNTA treatment suggests that these types of migraine pain involve extracranial innervation.

Feverfew

Feverfew (Tanacetum Parthenium) is derived from dried chrysanthemum leaves. Some studies have demonstrated that Feverfew showed greater benefits than placebo in two-third of patients, and that adverse effect were greater with placebo (10.2%) than with feverfew (8.4%).[19,97,98]

In a randomized, double-blind, multicentre, controlled trial, Pfaffenrath et al compared the clinical efficacy and safety of three dosages of feverfew (2.08, 6.25, and 18.75 mg) with placebo.[99] They found that feverfew showed a significant migraine prophylactic effect, but only in a small subgroup of patients with at least four attacks during the 28-day baseline period. The most favorable benefit-risk ratio was observed with a dosage of 18.75 mg of feverfew daily.

Petasites hybridus, magnesium, riboflavin, coenzyme Q10

Petasites hybridus is a European wild herb, and extracts of the roots are used for the treatment of pain. It seems to be effective in reducing migraine attack frequency if administered in doses $>$ 50 mg bid.[19] Petasites hybridus's adverse effects are similar to those of a placebo.

Magnesium has been shown to be effective in acute treatment, while no significant improvement has been shown in preventive treatment.[19] However, in a randomized double-blind placebo-controlled trial in 120 patients of a compound providing a daily dose of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg, Maizels, Blumenfeld, and Burchette found that riboflavin 25 mg showed an effect comparable to a combination of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg.[100]

Schoenen, Jacquy, and Lenaerts found that riboflavin is an interesting option for migraine prophylaxis because of its high efficacy, excellent tolerability, and low cost.[101]

However, there is also conflicting scientific evidence with regard to the efficacy of these compounds for migraine prophylaxis, but the combination of these various natural drugs might bring some improvement in migraine frequency and number of headache days.[19]

Nonmedication treatment

Therapy that does not involve medications may provide symptomatic relief. Biofeedback and relaxation techniques may be helpful for stopping an attack once it has started, and better sleep is another possible outcome. Preventing migraine requires motivation on the part of the patient to make some life changes. Patients can be educated as to triggering factors that can be avoided, including smoking cessation[102] and avoiding certain foods, especially those high in tyramine or those containing sulphites or nitrates.[103] Generally, leading a healthy life style, with good nutrition, adequate water intake, sufficient sleep and exercise, may be useful. Acupuncture has also been suggested as useful.[20]

Biofeedback and relaxation therapy

Behavioral interventions, particularly biofeedback and relaxation therapy, have demonstrated their effectiveness in controlled trials for the treatment of both adults and older children with migraine, often permitting patients to decrease their dependence on medication. The physiological basis for their effectiveness is unclear, but data from one trial suggest that levels of plasma beta-endorphin can be altered by relaxation and biofeedback therapies. Biofeedback is an established nonpharmacologic technique commonly used in the treatment of migraine and tension-type headaches. Research has also suggested that biofeedback may result in a decrease in medical utilization.[104,105]

Biofeedback and relaxation therapy can also be important tools in migraine prophylaxis in terms of the frequency of attacks and drug reduction, but biofeedback is more costly and does not have any additional benefit when compared to simple relaxation techniques alone.

Sleep and melatonin

The quality and quantity of sleep is decreased in patients with migraine.[106,107] The pineal gland involved in the sleep-wake cycle may be involved in migraine physiopathology. Specifically, pineal gland irregularity may be the physical origin of migraine headaches, with subsequent physiological changes being secondary. Research has found that the level of the pineal hormone melatonin is low in migraine patients.[108] According to this theory, the administration of melatonin may normalize this circadian cycle, and it may play a role in re-synchronizing biological rhythms to lifestyle and in relieving migraines and other forms of headaches.[108] Research testing the administration of melatonin found that it was safe for migraine sufferers, with few or no side-effects. Additionally, several studies have found administering melatonin to migraine sufferers relieved pain and decreased headache recurrence in some cases. It has been suggested, therefore, that melatonin may play an important therapeutic role in the treatment of migraines and other types of headaches.[109]

Acupuncture

Acupuncture is often used for migraine prophylaxis as it reduces the frequency and intensity of attacks and does not have side-effects.[20] It has been demonstrated that the addition of acupuncture to active treatment is beneficial for the three months after the migraine attack.[20] Acupuncture may, therefore, be an effective adjunct to basic care and prophylactic treatment when used together with drugs that are superior to placebo.[20]

New treatments

New therapies have been proposed for the treatment of drug-resistant primary headache. For example, peripheral neurostimulation has been proposed for the treatment of a number of types of chronic daily headache that do not respond to prophylaxis.[15,16,109–112] Experimental studies indicate that it may have an antidolorific effect,[92,113] and may affect brain areas involved in pain modulation.[111] However, a recent study suggests that the use of the neurostimulation technique may increase analgesic overuse (including opioids). The role of psychiatric disorders or other comorbidities and uncertainty as to which types of headaches respond to this type of treatment argue against its use at the present time.[67]

Limitations of this review

The major problem encountered in undertaking this review was the highly variable and often insufficient reporting of the complex outcome data. Additionally, migraine prophylaxis trials typically use headache diaries to monitor the course of the disease. From these headache diaries, a variety of outcomes can be extracted including: headache days, migraine days, migraine attacks, days with a defined headache intensity, attack intensity, mean headache intensity, headache indices, headache hours, days with medication and use of analgesics. The outcomes were assessed over different time frames ranging from 3 to 8 weeks. Patient outcomes were also presented in different ways such as means with standard deviations, standard errors, confidence intervals; medians with range or quartiles; and as mean or median percent change compared to baseline.

Discussion

Migraine is a cyclical illness that needs correct treatment of acute attacks, but also an adequate treatment prophylaxis to reduce the intercritical pain. The benefits of preventive pharmacotherapy for migraine should be measured over time in terms of changes in the frequency of acute attacks, the impact of acute treatment on headache recurrence within the next 24 hours, and the reduction of overall functional and psychosocial impairment. Although most data reported in the studies reviewed were heterogeneous, we may conclude that the most effective pharmacological treatment for migraine prophylaxis includes propranolol, some anticonvulsants such as topiramate, valproic acid, and amitriptyline. There was a suggestion of some benefit from alternative therapies such as riboflavin and coenzyme Q10, but they appear to have little effect, and only a combination of various natural drugs might bring some improvement in terms of migraine frequency and number of headache days. Other nonmedications approaches may play a role in migraine prophylaxis, and they have been proposed for the treatment of chronic daily headache that does not respond to prophylaxis.

Another consideration that should be taken into account is related to the complex relationship between migraine, stress, psychological symptoms, and response to treatment. The majority of migraine patients exhibit significant psychological symptoms, particularly stress, anxiety, and a combination of both anxiety and depression. Stress is

considered to be one of the most relevant predictive factors for migraine reoccurrence. Anxiety, depression, and stress often have negative consequences on patient outcome. Most migraine sufferers do not treat themselves in anticipation of the headache, and they often returned unused quantities of drugs to physicians. The correct assessment of anxiety, depression, and stress appear critical for developing an adequate preventive treatment strategy.

Conclusion

Optimizing the treatment outcome and reducing the frequency of episodes may help to alleviate the cycle of migraines. Several studies were identified that clearly supported the importance of pharmacotherapy in migraine prophylaxis. Combining comprehensive care and preventive therapy in adult migraine sufferers is presumably the most appropriate strategy for improving long-term outcome in migraine. An adequate prophylaxis is crucial for reducing disability and preventing the evolution of migraine into a chronic progressive illness.

Disclosure

No conflicts of interest were declared in relation to this paper.

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