Topiramate in Migraine Prevention

a report by
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Migraine is one of the most frequent forms of headache. It is estimated that 6–8% of all men and 12–14% of all women suffer from migraine.[1-4] The lifetime-prevalence in women is >25%. Before puberty the frequency of migraine is 4–5%. Boys and girls are affected equally. The highest incidence of migraine attacks occurs between the 35th and 45th years of life. During this phase of life women are affected three times more frequently than men. Migraine attacks lead to severe, frequently unilateral pulsating and pounding headaches, increasing with physical activity.[5] This can lead to a severe disruption in quality of life and the World Health Organization (WHO) has rated migraine as one of the top 20 leading causes of disability worldwide.[6] The individual attacks are accompanied by a loss of appetite (almost always), nausea (80%), vomiting (40–50%), light sensitivity (photophobia 60%) noise sensitivity (phonophobia 50%) and odour hypersensitivity (10%). If the headaches are unilateral they can change sides within an attack or from attack to attack. The duration of the attacks, depending on the definition of the International Headache Society, varies between four and 72 hours.[5] In children the attacks are shorter and can also occur without headaches, and with only severe nausea, vomiting and giddiness.[6]

Migraine Prophylaxis

The pharmacological treatment of acute migraine attacks is based on the 5-HT1B/1D agonists (triptans), non-opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). If the patient suffers from three or more migraine attacks per month, migraine attacks regularly last longer than 72 hours and if the attack frequency increases and the intake of analgesics or antimigraine agents occurs on more than 10 days per month, then prophylactic treatment is recommended. Pharmacological prophylaxis is also indicated for migraine attacks that do not respond to acute therapy or if side effects render acute therapy intolerable.

The aim of prophylaxis is to reduce the frequency, severity and duration of migraine attacks and to prevent the development of medication overuse. Migraine prophylaxis is considered effective if headache frequency is reduced by at least 50%.

Pharmacological Prophylaxis of Chronic Migraine

In Europe, beta-blockers (e.g. propranolol and metoprolol) are the most widely prescribed drugs for the prevention of migraine. Although the anti-epileptic drug (AED) sodium valproate has also been widely used in an off-label setting for migraine prophylaxis, the approval of topiramate represented the first AED to be indicated for migraine prevention. The tricyclic antidepressant amitriptyline, the calcium channel blocker flunarizine and the serotonin antagonist methysergide have also been used in the prophylaxis setting. Despite evidence of efficacy, the mechanism or site of action of these drugs is uncertain. Cortical spreading depression (CSD) has been implicated in migraine and as a headache trigger. In experimental animals CSD can be evoked by electrical or chemical stimulation. A recent study in the rat model suggests that CSD provides a common therapeutic target for migraine prophylactic drugs.[7] In the study, rats were treated either acutely or chronically over weeks and months, with either topiramate, sodium valproate, propranolol, amitriptyline, methysergide, vehicle or D-propranolol, a clinically ineffective drug. The impact of treatment was determined on the frequency of evoked CSDs after topical potassium application or on the incremental cathodal stimulation threshold to evoke CSD. Chronic daily administration of migraine prophylactic drugs dose dependently suppressed CSD frequency by 40–80% and increased the cathodal stimulation threshold. Importantly, acute treatment was ineffective.

Currently, the recommended first-line agents for migraine prophylaxis include the beta-blockers metoprolol and propranolol, the calcium antagonist flunarizine and the AED topiramate.

Normally patients are treated prophylactically for 9–12 months. Then patients are slowly titrated down from drug treatment under managed supervision. If improvement is maintained during the drug withdrawal, treatment is stopped and the need for further treatment reviewed. However, if the patient experiences an increase in attack frequencies as the

drug dose is decreased, the patient is advised to continue treatment for another 6–9 months, before attempting to titrate down therapy again. From experience, half of the patients are able to terminate drug therapy after intervention for one year and half will have to continue a longer period of drug therapy.

The most commonly used drugs for the prevention of migraine are the beta-blockers propranolol and metoprolol. Their use is supported by a good body of evidence from several placebo-controlled trials.[8-13] However, they have a disadvantage of significant side effects, such as sedation, decreased blood pressure and, especially in women, weight gain, which can make adherence to treatment a problem for many patients.[14] The success rate for beta-blockers is around 50%, with half of the patients experiencing significant decreases in the number and severity of migraine attacks.

In some European countries where the drug is licensed, another first-line choice is flunarizine, a calcium channel blocker. This drug is as effective as beta-blockers[15-17] but can lead to even greater weight gain than beta-blockers.

Certain AEDS have also shown efficacy in migraine prophylaxis. In Europe, topiramate is an AED that has been approved for the prevention of migraine. Sodium valproate, another AED that has shown evidence of efficacy in more than one placebo-controlled trial, is not licensed for this indication in Europe.[18-20]

The efficacy of topiramate in migraine prophylaxis has been confirmed in three large placebo-controlled studies.[21-23] Whilst sodium valproate has been shown to be effective in terms of the frequency of migraines, topiramate also influences the intensity and duration of attacks. Moreover, sodium valproate is also associated with weight gain. In contrast, topiramate is associated with no weight change or weight loss.[25]

In one US randomised, double-blind, placebo-controlled trial, topiramate demonstrated significant efficacy in migraine prevention within the first month of treatment, an effect that was maintained for the duration of the double-blind phase.[21] The 483 patients enrolled in the trial were aged 12–65 years, with a six-month history of migraine (International Headache Society criteria), and three to 12 migraines a month but no more than 15 headache days a month during a 28-day prospective baseline period. In the study, following a washout period, patients meeting the entry criteria were randomised to topiramate (50, 100, or 200mg/d) or placebo. Topiramate was titrated by 25mg per week for eight weeks to the assigned or maximum tolerated dose, whichever was less. Patients continued receiving that dose for 18 weeks. Mean monthly migraine frequency decreased significantly for patients receiving topiramate at 100mg/d and topiramate at 200mg/d vs placebo. In another US randomised, double-blind, placebo-controlled study, with a similar design and patient population, topiramate, 100 or 200mg/d, was shown to be effective as a preventive therapy for patients with migraine. Significantly more topiramate-treated patients exhibited a 50% or more reduction in monthly migraine frequency than placebo-treated patients.[23] A multinational randomised, double-blind, multicentre trial evaluated the efficacy and safety of topiramate (100 or 200mg/d) vs placebo for migraine prophylaxis, with propranolol as an active control. The study population included patients with episodic migraine with and without aura. In the study, the lower dose of topiramate and propranolol exhibited similar efficacy profiles.[22] Topiramate was also superior to placebo. The efficacy of results from eight-month open-label extension phases of two pivotal, six-month, randomised, double-blind, placebo-controlled trials with topiramate, demonstrated there was persistent reduction in monthly migraine frequency that was consistent with the initial six-month maintenance period.[24]

Topiramate demonstrated good tolerability across all three pivotal trials in migraine prevention at the target dose of 100mg/d. A common side effect seen with topiramate is paresthesia, however, this will normally go away after a few days. Cognitive side effects appear in 8–10% of patients, which can potentially restrict the use of topiramate. These persistent cognitive problems include memory problems and problems with concentration. If these situations arise, then treatment should be stopped. However, careful titration of topiramate can help ameliorate side effects. A typical titration would begin with an initial low dose of 25mg/day for the first week. The dosage should then be increased at one- or two-week intervals. This will help to improve tolerability.

Summary

Migraine is a severe disruption to everyday life. Moreover, it has a major economic impact, in terms of absence from work, particularly in women. The indirect costs in terms of work days lost are much higher than direct costs related to drug treatment.

Currently the number of patients receiving migraine prophylaxis treatment is still too low compared to the real need. The statistics show that only 15–20% of all migraine patients that fulfil the criteria for migraine prophylaxis treatment receive the appropriate treatment. This is partly due to some doctors not being aware of the treatment options available. Another problem is that patients may underestimate the impact of migraine.

In terms of drug class of choice, if there are no contra-

indications, then beta-blockers should be used, especially as these drugs are backed by good clinical data and are readily available as cheap generics.

However, if the patient has contra-indications for beta-blockers (asthma, fatigue, obesity, depression) or beta-blockers do not appear to be effective, then topiramate offers new hope for patients with frequent migraine in terms of controlling their condition and improving their quality of life. ■

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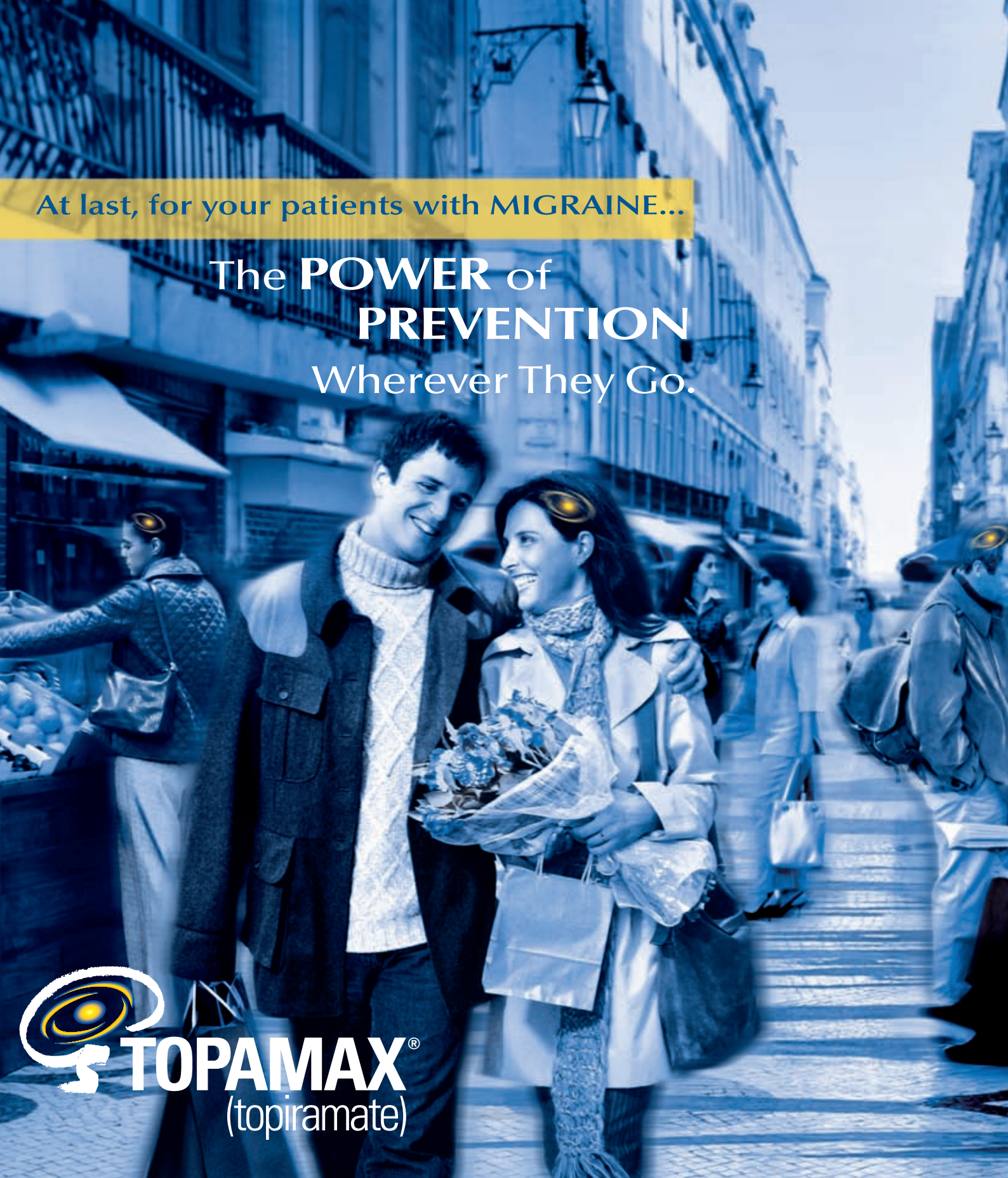

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