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REVIEW

Preventive Agents for Migraine: Focus on the Antiepileptic Drugs

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Abstract: Migraine is among the 10 most disabling disorders worldwide. It is characterized by episodes of moderate or severe headaches with various degree of disability, resulting in a considerable health burden upon the sufferers and their family. The objective of this article is to review the use of prophylaxis with antiepileptic drugs. Particular focus is given to their mechanism of action, metabolism, pharmacokinetics, safety profile, efficacy and to provide a summary of the most relevant clinical studies and patient preference.

Keywords: antiepileptic drugs, migraine, prophylaxis

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Introduction

Migraine is a chronic neurological disorder affecting about 12% of the population with an estimated prevalence of 18.2% in women and 6.5% in men.[1,2] Its etiology also seems to have a hereditary component.[3] Over 70% of migraine sufferers have a family history of migraine.[4] Migraine varies with age and tends to occur most commonly in the second and third decades of life.[5]

This common and occasionally severe disabling disorder is usually characterized by recurrent headaches frequently unilateral, lasting between 4 and 72 hours, typically aggravated by routine physical activity and often accompanied by a variety of gastrointestinal, neurologic and autonomic symptoms including loss of appetite, nausea, vomiting, photophobia, phonophobia and osmophobia.[5,6] Approximately one third of migrainous patients experience migraine attacks with aura, typically with visual symptoms (scintillating shapes, hallucinations, black spots) preceding or occurring with the attack, but other sensory or language disturbances may occur.[7] These transient focal neurological symptoms develop gradually over a period of at least 5 minutes and last less than 1 hour.[6] Migraine attacks are heterogeneous in regard to the symptomatology, frequency, severity, duration, disability and impact on quality of life, both between different patients and between separate attacks in the individual sufferer.[8] From the clinical and economic perspectives, there is a great demand for rapidly acting, effective, safe and abortive headache agents.

Migraine pathophysiology is particularly complex and poorly understood. Migraine attacks are believed to be caused by activation of the trigeminal nerve and trigeminovascular system, leading to the release of several neurotransmitters (calcitonin gene-related peptide, substance P) that affect vasomotor tone, causing neurogenic inflammation of intracranial and extracranial cerebral vessels.[9] The aura is thought to be caused by cortical spreading depression, a slowly propagating wave of intense neuronal and glial depolarization progressing over the cortex and followed by a period of inactivity.[10]

The most common external triggers for migraine attacks are, in decreasing frequency, stress (80%), hormonal fluctuations in women (65%), skipping meals (57%), changes in weather (53%), lack of sleep (50%), perfumes or odors (44%), neck pain (38%), certain foods (27%) and physical activity (22%).[11]

In addition to environmental triggers, several genetic factors contribute to migraine pathophysiology.[12] Family and twin studies have clearly demonstrated that both the rare and common forms of migraine have significant genetic basis. However, approaches to understand this genetic basis have had varying degrees of success.[13] Recent genetic findings have revealed ion channel and transporter mutations as causative of migraine.[7]

Considerable insights into the pathogenesis of migraine have come from the investigation of the rare autosomal dominant subtype of migraine with aura, familial hemiplegic migraine. Three susceptibility genes (*CACNA1A*, *ATP1A2* and *SCNA1*), which encode either ion channels or ion transport proteins involved in regulating membrane potential, have so far been identified. It is likely that mutations in these genes reduced the threshold for cortical spreading depressions. However, these mutations are not found in typical migraine with aura, suggesting that other ion channels may be involved.[7]

Recently a mutation in the *KSNK18* gene, encoding the two-pore domain potassium channel, TRESK (TWIK-related spinal cord potassium channel), has been described in a large family with migraine with aura. This mutation disrupts the normal functioning of this potassium channel protein. TRESK modulates neuronal excitability, seems to be involved in pain pathways and is activated by volatile anesthetics, which have been shown to inhibit cortical spreading depression, a key mechanism in the generation of migraine aura. Moreover this channel, abundantly expressed in the trigeminal ganglia, controls the sensitivity of pain nerves. TRESK agonist could help decrease neuronal excitability and therefore reduce migraine frequency or severity. This is a possible new approach to the treatment of migraine.[4]

A wide range of medications have been used for the treatment of acute migraine headache. Dihydroergotamine has been used for several decades and produces good relief in 70%–80% of patients within 2 h of administration.[14] Triptans produce similar efficacy.[15] Despite their widespread use and availability, a significant proportion of patients with migraine are refractory to these agents and require opiate and analgesics for control of acute headache.[16] Moreover, the

presence of cardiovascular risk factors prohibits the use of triptans or ergotamines in many patients.[17] Recent studies suggest as well the risk of development of chronic daily headaches with the overuse of acute medication including triptans, ergots and other analgesics.[18]

The management of migraine can be divided into acute (abortive) and preventive treatment. Patients with frequent and severe headaches often require both approaches.[6]

Preventive therapy is important in reducing migraine morbidity. It should be considered in patients with attacks that are long, severe, frequent (two or more a month), or when there is a marked impact on daily functioning. In addition it may be used for those with adverse events to, or overuse of acute care medicines. The main goal of prophylaxis is the reduction in frequency, intensity and duration of migraine attacks as well as the prevention of chronicity. However, good prophylaxis will usually result in better response to acute treatment, with improved daily function and reduction in disability. The ultimate target is to improve the quality of life and patient's performance in daily activities and work productivity, and to reduce healthcare costs.

When choosing a prophylactic treatment, one should take into account its efficacy, tolerability and the existence of comorbid conditions.[6,19–21] Currently, the recommended first-line agents come from different pharmacological classes with primary indications that are usually approved for other medical conditions. They include the beta-adrenoceptor blocking drugs propranolol and metoprolol, the antidepressant amitriptyline, the calcium channel blocker flunarizine and most recently the neuromodulator drugs valproate and topiramate that are playing an increasingly important role. These agents are effective and well tolerated. Second line drugs have either been less effective in clinical trials or have only been tested in a small number of less well-designed trials and require further investigation. Table 1 lists preferred prophylactic

Table 1. Migraine preventive medications adapted from the US headache consortium and the quality standards subcommittee of the American Academy of Neurology.[22,23]

Group 1 (1st choice)	Group 2 (2nd choice)	Group 3 (3rd choice)
Medium to high efficacy good strength of evidence infrequent to frequent side effects Multiple randomized clinical trials	Lower efficacy than drugs listed in group 1 or limited strength of evidence mild to moderate side effects Few randomized trials	Clinically efficacious based on consensus and clinical experience but no scientific evidence of efficacy Absence of relevant controlled clinical trials
Beta-adrenoceptor blocking drugs	Beta-adrenoceptor blocking drugs	Analgesics
Metoprolol	Atenolol	Ibuprofen
Propranolol	Bisoprolol	Antidepressants (tricyclic)
Antidepressants (tricyclic)	Timolol	Doxepin
Amitriptyline	Analgesics	Imipramine
Calcium channel blocker	Acetylsalicylic acid	Nortriptyline
Flunarizine	Mefenamic acid	Protriptyline
Antiepileptic drugs	Naproxen	Antidepressants (MO inhibitors)
Valproate	Calcium channel blockers	Bupropion
Topiramate	Nimopidine	Mirtazapine
	Verapamil	Trazodone
	Antiepileptic drugs	Venlafaxine
	Gabapentin	Antidepressants (serotonine recapture inhibitors)
	Zonisamide	Fluvoxamine
	Antihypertensive	Paroxetine
	Candesartan	Sertraline
	Lisinopril	Calcium channel blocker
	Nutritional supplements	Diltiazem
	Butterbur root extract	Serotonin antagonist
	Magnesium	Cyproheptadine
	Vitamine B2	

agents according to their efficacy, strength of evidence and frequency of side effects.[22,23]

It is proposed that epilepsy and migraine share some of the same pathophysiological mechanisms (Table 2) including abnormal function of voltage-gated sodium and calcium channels and an imbalance between GABA-mediated inhibition and excitatory glutamate-mediated transmission.[24] Evidence suggests that epilepsy is a comorbid condition of migraine. It occurs more commonly in patients with migraine than in the general population, and the prevalence of migraine in epileptic patients is higher than in controls.[25] The use of antiepileptic drugs for migraine prevention is well known and the effectiveness of these medications has been demonstrated in several clinical trials. However, only a few antiepileptic drugs have been shown to be effective in migraine prophylaxis. Valproate and topiramate are effective and well tolerated in migraine prevention and are suitable first-line agents. Zonisamide may be an alternative to patients intolerant to topiramate. On the other hand, acetazolamide, lamotrigine, oxcarbazepine and vigabatrin are not effective. The efficacy of gabapentin in migraine prevention is variable; it is not considered to be a first line treatment and requires further evaluation.[8,23]

Mechanism of Action, Metabolism and Pharmacokinetic Profile

The antiepileptic drugs, also referred to as neuromodulators, appear to act in migraine by targeting multiple molecular sites in the brain (Figs. 1 and 2), altering neurotransmission through their effects on ion channels, neurotransmitter receptors, and neurotransmitter metabolism.[3,26] The interaction with these multiple sites decreases abnormal brain excitability and protects vulnerable neurons in conditions with a high-energy demand, such as neuronal hyperactivity as well as metabolic impairment.[27]

Valproate is available as valproic acid, divalproex sodium or both formulations, without differences in efficacy between the various forms. The mechanism, by which valproate (Fig. 3A) stops or prevents migraine is not clearly understood.[2] Valproate has been shown to have both central and peripheral mechanisms of action that may have relevance in the migraine cascade.[28] (1) It increases gamma-aminobutyric acid (GABA) levels in synaptosomes and in the brain, via activation of glutamic acid decarboxylase (GABA-synthetic enzyme) and via inhibition of GABA aminotransferase and succinate semialdehyde dehydrogenase (GABA-degradative enzymes).[29] (2) It inhibits the voltage-sensitive

Table 2. Migraine versus epilepsy: similarities and contrasts.

Migraine	Epilepsy
Common neurological disorders (greater prevalence for migraine) with episodic manifestations, characterized by recurrent attacks of nervous system dysfunction (hyperexcitability) with a return to baseline between attacks	
Migraine attack may precede, accompany or follow an epileptic attack	
Highly comorbid	
Similarities in the following symptoms: post-event lethargy, visual disturbances, paresthesia, vertigo	
Therapeutic options overlap (certain antiepileptic drugs effective in migraine prophylaxis)	
Recurrent attacks of pain and associated symptoms	Recurrent attacks of neurological symptoms, often progressing to altered or lost consciousness, and, at times, convulsive features
Prevalence of idiopathic forms more frequent	Less frequent
Female prevalence	Sex prevalence differences not marked
Low prevalence during childhood, peaks in adult age and decreases in old age	Incidence highest in extremes of life
Long attacks developing gradually (hours)	Brief and sudden attacks (minutes)
Not associated with reduced lifespan	Life-threatening

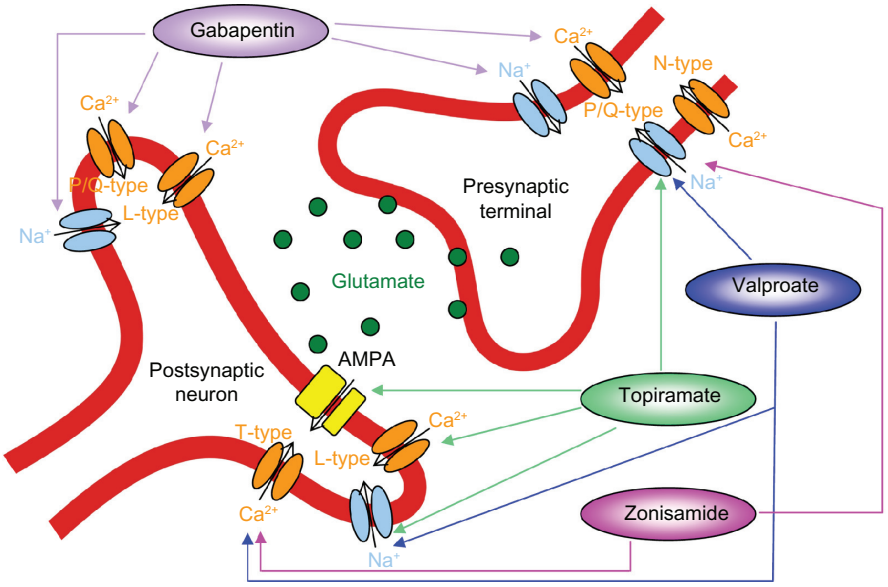

Figure 1. Pre- and postsynaptic sites of action of neuromodulators on excitatory glutamate-mediated transmission.
Note: The neuromodulators target multiple voltage-gated channels at both pre- and postsynaptic levels.

calcium channels (T-type).[2] (3) It interacts with central 5-HT system thereby reducing the effect of inflammation of serotoninergic neurons in the brainstem. (4) It reduces the central trigeminal nerve activation (by increasing GABA levels).[25] (5) Finally, valproate was shown to reduce experimental neurogenic inflammation in the peripheral trigeminal vascular system, an effect that is mediated through $GABA_A$ receptor agonism.[28] Valproate is effective for long-term migraine prophylaxis, and initial benefits are maintained for periods in excess of 3 years.[30] It is rapidly absorbed in the gastrointestinal tract and metabolized almost entirely by the liver. The relationship between dose and plasma concentration is not linear and its bioavailability depends on the formulation and dosing regimen.[31]

Topiramate is a sulfamate-substituted monosaccharide derived from the naturally occurring sugar D-fructose (Fig. 3B). Its antimigraine potential is based on several possible mechanisms of

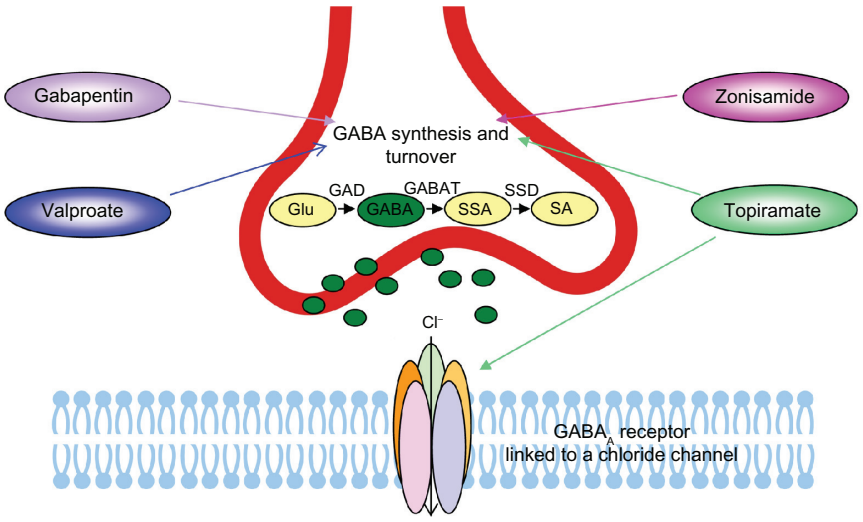

Figure 2. The effects of neuromodulators on inhibitory GABA-mediated transmission.
Notes: Gabapentine, valproate, topiramate and zonisamide influence GABA synthesis and turnover by acting at multiple and distinct biochemical steps. Moreover, topiramate also directly targets the $GABA_A$ receptor channel complex.
Abbreviations: GABAT, GABA transaminase; SSA, succinic semialdehyde; SSD, succinate semialdehyde dehydrogenase; SA, succinic acid.

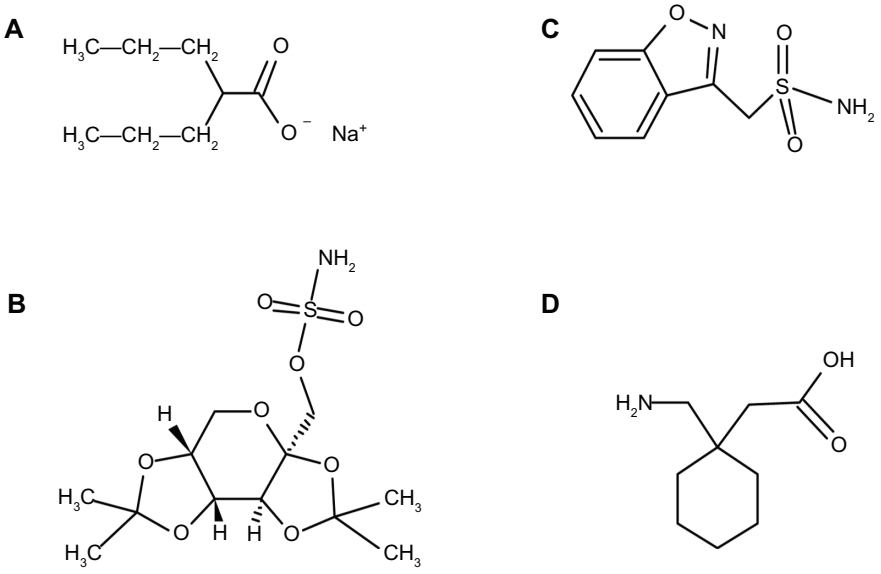

Figure 3. Neuromodulators molecular structure. (**A**) Valproate sodium: sodium 2-propylpentanoate.[31] (**B**) Topiramate: 2,3:4,5-Di-O-isopropylidene-b-D-fructopyranose sulfamate.[62] (**C**) Zonisamide: 1,2-benzisoxazole-3-methanesulfonamide.[36] (**D**) Gabapentin: 2-[(1-aminomethyl)cyclohe-xyl]acetic acid.[64]

action namely: (1) modifies the excitability of nerves by blocking voltage-sensitive sodium channels and L-type voltage-activated calcium channels.[27,28] (2) Inhibits carbonic anhydrase activity.[32] (3) Inhibits the excitatory glutamate pathway while enhancing the inhibitory effect of GABA.[30] The actual mechanism of action for its antimigraine activity is not known.[5] It is rapidly and almost completely absorbed from the gastrointestinal tract with t_{max} between 1 and 4 hours, has a high oral bioavailability (81% to 95%) while being virtually unaffected by food. It has a low level of binding to plasma proteins (about 10%–20%) and does not significantly inhibit or induce other drug metabolizing enzymes. It is not extensively metabolized (approximately 20% is metabolized in the liver) and readily enters the central nervous system (CNS). It shows linear steady-state pharmacokinetics and has a long half-life ranging from 19 to 25 hours.[31–33]

Zonisamide is a sulphonamide derivative (Fig. 3C), chemically and structurally different from other antiepileptic drugs. This new generation of antiepileptic drugs has been available in Japan for over 10 years and has only recently been introduced into the USA and Europe. It has some mechanisms of action very similar to those of topiramate including blockade of voltage-gated sodium channels, inhibition of carbonic anhydrase, inhibition of potassium-mediated release of glutamate, and enhancement of GABA release. Furthermore, it has a specific mechanism of action by reducing ion flow through T-type calcium channels.[19,33,34] It also reduces nitric oxide production and scavenges nitric oxide free radicals.[1] It is well tolerated and presents a favorable pharmacokinetic profile for clinical use. It is rapidly and completely absorbed from the gastrointestinal tract, with peak plasma concentrations occurring 2 to 4 hours following its administration. It has a long plasma elimination half-life (63 to 69 hours in healthy volunteers) allows reduced frequency of administration. Food tends to reduce the rate but not the extent of its absorption. Zonisamide does not induce its own metabolism and does not induce liver enzymes. Since it is metabolized by the cytochrome P450 3A4, other drugs inducing or inhibiting this enzyme may affect its plasma elimination.[35,36]

Gabapentin (Fig. 3D) is a structural analog of GABA. It enhances GABA-mediated inhibition and inhibits GABA metabolism. It binds with high affinity to two of the four known $\alpha_2\delta$ subunits ($\alpha_2\delta1$ and $\alpha_2\delta2$) of voltage-gated calcium channels, producing an inhibition of high-voltage-activated calcium currents and resulting in reduction of synaptic transmission.[37] It has a very attractive pharmacokinetic profile. It is not bound to plasma proteins, does not have significant drug-drug interactions, does not induce hepatic enzymes and is not metabolized. The oral bioavailability is 60% and the half-life is 6–8 h.[9,39]

Clinical Studies

The effectiveness of valproate in migraine prophylaxis was first reported in an open-label study,[38] with another open-label study demonstrating decreased severity and frequency of headaches in migrainous patients.[39] Its efficacy has been demonstrated in three randomized double-blind controlled studies.[42–44]

In the first trial, 107 patients were treated with valproate (n = 70) or placebo (n = 37) respectively, during a period of 3 months. Valproate was started at a dose of 250 mg/day and then titrated gradually to achieve a plasma concentration of approximately 70 to 120 mg/L. The number of participants with a 50% or greater reduction in headache frequency with valproate was significantly better (48%) than with placebo (14%).[40]

The efficacy and safety of valproate was evaluated in the second study during a 3 month period. A total of 176 patients were randomized into four groups: placebo (n = 44), valproate 500 mg/day (n = 45), 1000 mg/day (n = 43) and 1500 mg/day (n = 44). The initial dose for valproate-treated patients was 250 mg/day and was then increased by 250 mg every 4 days (every 8 days for the 500 mg group) until the assigned randomized dose was achieved. The monthly migraine frequency decreased significantly for the 500-mg/day group (from 4.5 to 2.8), the 1000-mg/day group (from 4.7 to 2.7) and the 1500-mg/day group (from 4.7 to 3.0) versus the placebo group (from 6.1 to 5.6). However the overall median reduction of 38% in the valproate 1000-mg/day group was not significantly greater than the overall 19% median reduction observed in the placebo group.[41]

In the third study 234 patients were treated during a period of 17 weeks with valproate (n = 119) or matching placebo (n = 115). The treatment was initiated at 500 mg once daily for 1 week, and the dose was then increased to 1000 mg during the second week. Mean migraine frequency decreased significantly for the valproate treated group (from 5.8 to 3.7) versus the placebo group (from 6.3 to 4.6).[42]

The efficacy of topiramate in migraine prevention was initially shown in small preliminary studies,[43,44] and thereafter established in three pivotal multicentre, randomized, double-blind, placebo-controlled trials.[45,47,48] The first was a multicentre 6-month trial performed in 49 locations in the USA. A total of 487 patients were randomized to four groups: placebo (n = 117), topiramate 50 mg/day (n = 125), 100 mg/day (n = 128) or 200 mg/day (n = 117). Topiramate was started at 25 mg/day and increased by 25 mg/week for 8 weeks until the maximum assigned dose given in divided doses in the morning and evening was reached. The mean monthly migraine frequency decreased significantly for the 100-mg/day group (from 6.4 ± 2.7 to 3.7 ± 3.3; $P < 0.001$) and the 200-mg/day group (from 6.6 ± 3.1 to 3.9 ± 3.4; $P < 0.001$) versus the placebo group (from 6.4 ± 2.6 to 5.3 ± 3.6), but not for the 50-mg/day group (from 5.8 ± 2.5 to 4.5 ± 3.1; $P = 0.12$). The improvements occurred within the first month of treatment. Topiramate-treated patients (50 mg/day: 35.9% ($P = 0.04$); 100 mg/day: 54% ($P < 0.001$); 200 mg/day: 52.3% ($P < 0.001$)) exhibited a 50% or more reduction in monthly migraine frequency (responder rate) than placebo-treated patients (22.6%).[45]

The second trial was conducted during a period of 26 weeks at 52 North American clinical centers. A total of 483 patients were randomized into four groups: placebo (n = 114), topiramate 50 mg/day (n = 116), 100 mg/day (n = 120) or 200 mg/day (n = 117). Mean monthly migraine frequency decreased significantly for patients receiving topiramate at 100 mg/day (from 5.8 ± 2.6 to 3.5 ± 3.5; $P = 0.008$) and at 200 mg/day (from 5.1 ± 2.0 to 3.0 ± 2.2; $P < 0.001$) versus the placebo group (from 5.6 ± 2.2 to 4.5 ± 2.9). Reduction in migraine frequency was observed during the first month of treatment. Topiramate-treated patients (50 mg/day: 39% ($P = 0.01$); 100 mg/day: 49% ($P < 0.001$); 200 mg/day: 47% ($P < 0.001$)) exhibited a significant reduction in monthly migraine frequency than placebo-treated patients (23%). Patients who received 200 mg/day tended to have more frequent adverse events.[46]

A third study took place in 88 neurology clinics throughout 21 countries in Europe and the Middle East. A total of 559 patients completed the 26-week open-label phase of the study and 514 of them who completed this phase continued to the 26-week randomized, double-blind, placebo-controlled phase of the trial. Patients were assigned to topiramate (n = 255) or placebo (n = 259). Although the number of migraine days increased and the quality of life was lower, sustained benefit was observed after discontinuation of topiramate. The mean increase in number of migraine days before and after topiramate

discontinuation was greater in the placebo group (1.19 days in 4 weeks, $P < 0.0001$) compared to the topiramate group (0.10 days, $P < 0.5756$). The results of this trial suggest that patients should be treated for 6 months with the option to continue to 12 months in some cases.[47]

These pivotal trials are supported by a fourth study performed in the Headache Centre in Rome, where 35 patients were assigned to topiramate and 37 patients to placebo. The frequency of migraine attacks was significantly reduced (from 5.26 to 2.60). Moreover we observed a significant reduction in the quantity of symptomatic drugs taken as compared to the placebo group (from 6.17 ± 1.80 to 2.57 ± 0.80) and a significant downward trend in the number of days of disability.[48]

In a combined analysis, topiramate showed a greater reduction in migraine frequency than placebo. Several large, randomized, placebo-controlled clinical trials have shown that topiramate administered at 100 mg daily significantly reduced the number of migraine headache days in patients with episodic migraine who experienced between three and 12 migraine episodes per month[48,49] and in patients with chronic migraine who experienced ≥15 headache days per month.[52,53] Furthermore, the number of participants with a 50% or greater reduction in headache frequency with topiramate was significantly better than with placebo.[49] In these clinical trials topiramate treatment was safe and generally well-tolerated.

A double-blind randomized clinical trial compared zonisamide efficacy to topiramate in migraine prophylaxis. A total of 80 patients were recruited and randomly allocated to zonisamide 200 mg/day and topiramate 100 mg/day. Zonisamide was gradually titrated up from 50 mg/day to 200 mg/day and topiramate from 25 mg/day to 100 mg/day. This study was conducted during a period of 3 months. Both drugs were associated with a significant decrease in frequency and severity of migraine along with a decrease in the need for acute medication in migraine attacks and migraine disability assessment score. No significant differences were observed between the 2 groups other than greater reduction in headache severity with Zonisamide. These results suggest that zonisamide is as effective as topiramate in migraine prophylaxis and therefore can be considered as an alternative treatment in patients with poor tolerance to topiramate. Larger studies are still needed before zonisamide can expect FDA approval.[1]

Two double-blind, randomized, placebo-controlled trials have shown that gabapentin reduces the frequency and intensity of migraine attacks.[50,51]

The first study was conducted during a period of 3 months, at seven participating centers. Ninety eight patients were assigned to gabapentin and 45 to matching placebo. During the 4-week titration phase, patients were started on 300-mg/day gabapentin, increasing to 900 mg/day in the first week, and thereafter had weekly increases to 2400 mg/day. Mean migraine frequency decreased significantly in the gabapentin treated group (from 4.2 to 2.7) versus the placebo-treated patients (from 4.1 to 3.5). The number of patients achieving at least 50% reduction in monthly headache frequency with gabapentin was significantly better than with placebo (46% versus 16%, $P < 0.01$).[51]

In the second study, gabapentin was used at a dosage of 1200 mg/day and compared with placebo. It was associated with a significant reduction in the frequency and intensity of migraine compared with placebo.[50]

Efficacy

The primary measure of efficacy is the change in frequency of migraine attacks per month (28 days) from the baseline frequency. Results are considered clinically relevant if a reduction of 50% or more in migraine frequency can be demonstrated.[46]

Preventive drugs must be used for periods of months. International guidelines suggest a minimum trial of 2 to 3 months of daily administration. Although there is no general agreement on the ideal duration of prophylaxis, recently published data suggest greater efficacy with longer treatment periods.[52]

Valproate has been demonstrated to be an efficacious and well-tolerated agent for the preventive treatment of migraine, chronic daily headache and cluster headache and has received the approval of the FDA.[28] The recommended oral starting dose is 250 mg taken at bedtime and is gradually increased, usually by 125–250 mg per week, to the desired dose of 750 mg per day in 2–3 divided doses.[53]

Topiramate has FDA approval for migraine prophylaxis.[54] At a dose of 100 mg per day, it is reported to be the most effective and well tolerated of all drugs

used for migraine prevention.[55] A dose of 200 mg per day is no more effective than the 100 mg per day and is not as well tolerated. In the responders, positive effects were usually seen within the first month, and improvement continued during the 6-month observation period.[43,49] The efficacy of topiramate was further increased with longer periods of prophylaxis. A group of migraine patients were treated for 8 months in an open-label extension phase after two large double-blind, placebo-controlled trials of 26 weeks duration. The mean number of attacks decreased from 3.4 ± 2.6 per month at the end of the double-blind treatment periods to 2.2 ± 2.4 per month after completion of the open-label extension phase with the active drug.[56]

Zonisamide acts slower than topiramate, requiring 3 months to reach a 2/3 reduction in frequency of migraine attacks. It has been shown to be effective and well tolerated for migraine prevention in patients refractory to topiramate.[34,57] A better control in headache severity was obtained with zonisamide in comparison to topiramate. These advantages can be explained by its specific mechanisms of action.[1]

Gabapentin is less effective than topiramate or valproate and is therefore considered as drug of second choice.[58] Efficacy has been shown with a daily dose of between 1200 and 1600 mg.[51]

Safety

Adverse effects leading to withdrawal of therapy are more likely to occur during the initial titration periods. It has been demonstrated that the drop-out rate is lower during long-term treatment extension phases than during initial treatment periods.[55] In order to avoid or minimize side effects and therefore reduce the risks of withdrawal from treatment, the daily dose should be increased slowly over a period of at least 4 weeks or more, until targeted clinical benefits are achieved or until adverse effects interfere. If no side effects emerge and the desired clinical response has not yet been achieved, the dose can be increased providing the ceiling dose for the drug. The majority of migraine prophylactic drugs can cause tiredness or dizziness, therefore it is better to give them in the evening.[19,58] It is important to always bear in mind contraindications to and the risk/benefit ratio of the drug for any patient.

The most common side effects of valproate are tiredness, drowsiness, dizziness, weight gain, tremor, hair loss, skin rash and nausea. Serious side-effects include pancreatitis, and rarely liver failure and thrombocytopenia. Its use during pregnancy is contraindicated due to teratogenicity (neural tube defects).[52] Long-term treatment with neuromodulators may alter the metabolism of sex hormones. Use of valproate in women appears to be associated with a frequent occurrence of reproductive endocrine disorders characterized by polycystic changes in the ovaries, high serum testosterone concentrations (hyperandrogenism) and menstrual disorders.[59,60] Younger women seem to be especially vulnerable to the effects of valproate on serum androgen levels and they are more likely to develop polycystic ovary syndrome. The age of patients should therefore be considered while prescribing this medication.[60] In males, it causes sexual dysfunction by decreasing follicle-stimulating hormone and luteinizing hormone.[61] The endocrine effects of the new generation of neuromodulators have not yet been widely studied.[59]

Topiramate is generally considered to be safe and well tolerated in migraine prophylaxis. In clinical trials, topiramate has been associated with a range of adverse events. Paresthesia is the most frequent of these, reported by half of patients.[62] Adverse events are usually mild or moderate in severity; they are transient and decrease substantially over time. Cognitive adverse events, including tiredness, psychomotor slowing, drowsiness, language difficulties, and difficulties with memory and concentration, arise in about 22% of patients treated with 100 mg per day of topiramate compared with 10% in those given placebo. These usually decrease in the second month of treatment and do not typically require discontinuation of the drug. Unlike most other migraine-prevention drugs, topiramate is more likely to be associated with weight loss (two of three patients) than with weight gain. Serious adverse events leading to treatment discontinuation were infrequent in clinical trials (2%). The risk of renal calculi is increased especially in patients with an underlying predisposition. The risk of secondary angle closure glaucoma is rare.[43] Despite being efficacious, some patients will not tolerate the adverse effects and hence will need an alternative.[1]

Zonisamide is a well tolerated antiepileptic drug with a generous safety profile.[63] It has as similar mechanism of action to topiramate, and similar, but lower incidence of side effects.[57]

Gabapentin most commonly causes dizziness, tremor, somnolence, nausea and ataxia. However, they are generally transient and only of mild or moderate severity.[20,64]

Patient Preference

A preventive management plan represents an important part of the migraine therapy. The choice of drug should take into account comorbidities, and patient preferences in addition to the overt risk/benefit ratio of the medication.[65] Sometimes infrequent migraine attacks might be enough to impair quality of life such that the patient feels that commencing prophylaxis is warranted. Hence, the decision to start regular prevention is a tailored, individual one that must take patient preference into account. A discussion between practitioner and patient about indications, and treatment goals is crucial. Physicians should understand patient treatment preferences, and help select the drug most suited to their needs.[66] It is axiomatic that the patient should understand the reasons for starting preventive treatment and feel comfortable with the drug chosen. This increases the likelihood of adherence to the long-term preventive treatment plan.[3]

The factors influencing patient preference are likely to involve the following parameters: effectiveness, duration of relief, attack recurrence, ease of use, required doses, side-events, time to go back to normal functioning.[67]

The patient should be aware of the timing and extent of clinical benefit. Many preventive medications take a minimum of 3 or 4 weeks for a therapeutic response at a particular dose, and maximum clinical effect might take another 2 to 3 months, during which time compliance is most important. The inefficacy of one drug does not necessarily mean that all migraine prophylactic drugs are ineffective. Different drugs may have to be tried before one is identified as being really helpful in prophylaxis. It is also very useful to explain the potential side effects of these drugs in order to engage the patient in decision-making process and ensure compliance. The patients should be assured that the medications do not induce tolerance or addiction.[19,58,68]

Unlike patient preference for acute migraine treatment, patient preference for prophylaxis has not been well studied. In one study evaluating patient preference for migraine prophylaxis, patients were asked to rate the following aspects of headache prevention: efficacy, speed of onset, out-of-pocket expenses, adverse events, formulation of therapy, the type of treatment and frequency of dosing. These variables have to be considered when tailoring patient's treatment plan. Each patient also evaluated 12 different clinical scenarios, each containing a simulation of 2 hypothetical headache preventive treatments, wherein patients could choose product A, product B, or neither. Patients were informed of each product's efficacy data (50%, 75%, or 100% of headache elimination), adverse events profile (weight gain, concentration difficulty, and/or fatigue), and dosing frequency. Patients were more likely to choose treatments with higher efficacy rates, fewer adverse events and less frequent dosing schedule. They also preferred treatment options with higher efficacy rates even if increased adverse events occurred or more frequent dosing was necessary.[66]

Place in Therapy

Several matters are central to choice of drugs in patients with migraine. The selection a migraine prevention agent should be made on the basis of its efficacy, cost, potential adverse events, impact on quality of life, headache profile, patient preference, previous efficacious or unsuccessful treatments and any coexisting disorders.[54]

The European Federation of Neurological Society (EFNS) guidelines aim to give evidence-based recommendations for the drug treatment of migraine attacks and prophylaxis. The level 'A' recommendation corresponds to drugs of first choice with efficacy and safety well established in clinical trials. Level 'B' drugs are second line, with evidence of efficacy but are either less effective or have more side effects than level 'A'. Level C drugs are third line, with only probable efficacy. Based on these guidelines, valproate in a dose of at least 600 mg and topiramate in a dose between 25 and 100 mg are the two recommended first line agents for the prophylactic treatment of migraine with an A level of evidence. Gabapentin in a dose between 1200 and 1600 mg with a grade C is a drug of third choice. The EFNS guidelines were last published in 2009 and zonisamide was not included.[69]

Conclusions

Migraine has a major socioeconomic impact, causing a considerable burden to the patients, their families

and the society. It deeply affects the wellbeing and general functioning, not only during the acute attack, but also in terms of work performance, family and social relationships, and school achievement.[70]

The major goals of migraine prophylaxis are improving patients' quality of life by reducing migraine frequency, severity, duration and disability. The results of the different randomized controlled clinical trials have proven that migraine prophylaxis with anticonvulsants such as valproate and topiramate is generally a safe and effective way of reducing the attack frequency and thus the burden of migraine. Despite their good efficacy, some patients discontinued the prophylaxis with these agents because of clinically significant adverse events. With its low rate of side events and better tolerance than valproate or topiramate, zonisamide could play a more important role in the future. Furthermore its long half-life permits once-daily dosing, may enable better patient compliance.[57]

Antimigraine prophylaxis is still relatively underused. Only 15%–20% of all patients that fulfill the criteria for migraine prophylaxis treatment receive the appropriate treatment.[71] The side-effects, compliance, and cost of prolonged treatment are important limiting factors. Physicians should therefore be aware that treatment strategies for migraine prophylaxis require patient understanding and acceptance. Patient preference plays a key role in migraine prevention.

All the drugs currently used in migraine prophylaxis have been discovered serendipitously without consideration of migraine pathophysiology. The next generation of prophylactic drugs will be developed on the basis of the recent understanding of migraine pathophysiology. The identification of new anti-migraine drug targets will hopefully lead to more effective and specific treatments with fewer side events.

New medicines are currently being developed for migraine prevention. Cortical spreading depression inhibition and calcitonin gene-related peptide antagonists such as talcagepant, seem promising, but need further investigation. Drugs such as melatonin, vitamin E and botulinum toxins seem to have only marginal or no effect.[72]

Migraine is a polygenic multifactorial disorder that is most likely influenced by multiple genes and environmental triggers.[13] The emerging genetic findings will have implications for better understanding of migraine pathogenesis. They will hopefully lead to the development of new effective drugs with a better design and fewer side effects, and change the future of migraine therapy. The TRESK channel represents an interesting target for the development of migraine specific treatment and needs therefore to be further explored. Upregulation of this channel's activity could be of great benefit for migraine sufferers, either as in acute treatment or long-term prophylactic.[4]

Author Contributions

Conceived and designed the review: RS, KB. Analysed the data: RS, KB. Wrote the first draft of the manuscript: RS, KB. Contributed to the writing of the manuscript: RS, KB. Agree with manuscript results and conclusions: RS, KB. Jointly developed the structure and arguments for the paper: RS, KB. Made critical revisions and approved final version: RS, KB. All authors reviewed and approved of the final manuscript.

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References

1. Mohammadianinejad SE, et al. Zonisamide versus topiramate in migraine prophylaxis: a double-blind randomized clinical trial. *Clin Neuropharmacol*. 2011.
2. Vikelis M, Rapoport AM. Role of antiepileptic drugs as preventive agents for migraine. *CNS Drugs*. 2009;24(1):21–33.
3. Fenstermacher N, Levin M, Ward T. Pharmacological prevention of migraine. *BMJ*. 2011;342:d583.

4. Lafreniere RG, Rouleau GA. Migraine: Role of the TRESK two-pore potassium channel. *Int J Biochem Cell Biol*. 2011;43(11):1533–6.
5. Naegel S, Obermann M. Topiramate in the prevention and treatment of migraine: efficacy, safety and patient preference. *Neuropsychiatr Dis Treat*. 2010;6:17–28.
6. Silberstein SD. Preventive migraine treatment. *Neurol Clin*. 2009;27(2): 429–43.
7. Lafreniere RG, et al. A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. *Nat Med*. 2010;16(10): 1157–60.
8. Dowson AJ. Treatment Options fo Acute Migraine. *European Neurological Disease*. 2006:28–32.
9. Solomon GD. The pharmacology of medications used in treating headache. *Semin Pediatr Neurol*. 1995;2(2):165–77.
10. Anttila V, et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. *Nat Genet*. 2010;42(10): 869–73.
11. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27(5):394–402.
12. Piane M, et al. Genetics of migraine and pharmacogenomics: some considerations. *J Headache Pain*. 2007;8(6):334–9.
13. Maher BH, Griffiths LR. Identification of molecular genetic factors that influence migraine. *Mol Genet Genomics*. 2011;285(6):433–46.
14. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. *Headache*. 1986;26(4):168–71.
15. Cady RK, et al. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*. 1991;265(21):2831–5.
16. Klapper JA, Stanton JS. Ketorolac versus DHE and metoclopramide in the treatment of migraine headaches. *Headache*. 1991;31(8):523–4.
17. Kelly KM. Cardiac arrest following use of sumatriptan. *Neurology*. 1995;45(6):1211–3.
18. Limmroth V, et al. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology*. 2002;59(7): 1011–4.
19. Rapoport AM, Bigal ME. Migraine preventive therapy: current and emerging treatment options. *Neurol Sci*. 2005;26 Suppl 2:S111–20.
20. D'Amico D. Antiepileptic drugs in the prophylaxis of migraine, chronic headache forms and cluster headache: a review of their efficacy and tolerability. *Neurol Sci*. 2007;28 Suppl 2:S188–97.
21. Shukla R, Sinh M. Migraine: prophylactic treatment. *J Assoc Physicians India*. 2010;58 Suppl:26–9.
22. Ramadan N, et al. Evidence-based guidedlines for migraine headache in the primary care setting: pharmacological management fro prevention of migraine. *Neurology*. 2000.
23. Dodick DW, Silberstein SD. Migraine prevention. *Pract Neurol*. 2007;7(6): 383–93.
24. Pietrobon D. Migraine: new molecular mechanisms. *Neuroscientist*. 2005;11(4):373–86.
25. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol*. 2006;5(2): 148–57.
26. Krymchantowski AV, Jevoux CC. Topiramate vs. divalproex sodium in the preventive treatment of migraine: a prospective "real-world" study. *Headache*. 2011;51(4):554–8.
27. Calabresi P, Centonze D, Bernardi G. Cellular factors controlling neuronal vulnerability in the brain: a lesson from the striatum. *Neurology*. 2000;55(9):1249–55.
28. Shahien R, Saleh SA, Bowirrat A. Intravenous sodium valproate aborts migraine headaches rapidly. *Acta Neurol Scand*. 2010;123(4):257–65.
29. Cutrer FM, Limmroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. *Cephalalgia*. 1997;17(2):93–100.
30. Silberstein SD, Collins SD. Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study. Long-term Safety of Depakote in Headache Prophylaxis Study Group. *Headache*. 1999;39(9):633–43.
31. Valproate. Drugs.com (FDA):1–25.
32. Shank RP, et al. Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase. *Epilepsy Res*. 2005;63(2–3):103–12.
33. Kito M, Maehara M, Watanabe K. Mechanisms of T-type calcium channel blockade by zonisamide. *Seizure*. 1996;5(2):115–9.
34. Bermejo PE, Dorado R. Zonisamide for migraine prophylaxis in patients refractory to topiramate. *Clin Neuropharmacol*. 2009;32(2):103–6.
35. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure*. 2004;13 Suppl 1:S5–9; discussion S10.
36. Kothare SV, Kaleyias J. Zonisamide: review of pharmacology, clinical efficacy, tolerability, and safety. *Expert Opin Drug Metab Toxicol*. 2008;4(4): 493–506.
37. Silberstein SD. Preventive treatment of migraine. *Trends Pharmacol Sci*. 2006;27(8):410–5.
38. Sorensen KV. Valproate: a new drug in migraine prophylaxis. *Acta Neurol Scand*. 1988;78(4):346–8.
39. Mathew NT. Valproate in the prophylaxis of migraine. *Cephalalgia*. 1992;12(2):67.
40. Mathew NT, et al. Migraine prophylaxis with divalproex. *Arch Neurol*. 1995;52(3):281–6.
41. Klapper J. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia*. 1997;17(2):103–8.
42. Freitag FG, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology*. 2002;58(11):1652–9.
43. Adelman J, et al. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. *Pain Med*. 2008;9(2):175–85.
44. Storey JR, et al. Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache*. 2001;41(10):968–75.
45. Silberstein SD, et al. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol*. 2004;61(4):490–5.
46. Brandes JL, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA*. 2004;291(8):965–73.
47. Diener HC, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2007;6(12):1054–62.
48. Mei D, et al. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. *Neurol Sci*. 2004;25(5):245–50.
49. Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia*. 2008;28(6):585–97.
50. Di Trapani G, et al. Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. *Clin Ter*. 2000;151(3): 145–8.
51. Mathew NT, et al. Efficacy of gabapentin in migraine prophylaxis. *Headache*. 2001;41(2):119–28.
52. D'Amico D, Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. *Neuropsychiatr Dis Treat*. 2008;4(6):1155–67.
53. Garza I, Swanson JW. Prophylaxis of migraine. *Neuropsychiatr Dis Treat*. 2006;2(3):281–91.
54. Minton GC, et al. Topiramate: Safety and Efficacy of its Use in the Prevention and Treatment of Migraine. *Journal of Central Nervous System Disease*. 2011 (2733-JCNSD-Topiramate:-Safety-and-Efficacy-of-its-Use-in-the-Prevention-and-Treat.pdf):155.
55. Malessa R, et al. Prevention of episodic migraine with topiramate: a prospective 24-week, open-label, flexible-dose clinical trial with optional 24 weeks follow-up in a community setting. *Curr Med Res Opin*. 2010;26(5): 1119–29.
56. Rapoport A, et al. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. *Headache*. 2006;46(7):1151–60.
57. Villani V, et al. Zonisamide for migraine prophylaxis in topiramate-intolerant patients: an observational study. *Headache*. 2011;51(2):287–91.
58. Evers S, Treatment of migraine with prophylactic drugs. *Expert Opin Pharmacother*. 2008;9(15):2565–73.
59. Isojarvi JI, Tauboll E, Herzog AG. Effect of antiepileptic drugs on reproductive endocrine function in individuals with epilepsy. *CNS Drugs*. 2005;19(3):207–23.
60. Verrotti A, et al. Antiepileptic drugs, sex hormones, and PCOS. *Epilepsia*. 2011;52(2):199–211.
61. Leskiewicz M, Budziszewska B, Lason W. Endocrine effects of antiepileptic drugs. *Przegl Lek*. 2008;65(11):795–8.

62. Edvinsson L, Linde M. New drugs in migraine treatment and prophylaxis: telcagepant and topiramate. *Lancet*. 2009;376(9741):645–55.
63. Baulac M. Introduction to zonisamide. *Epilepsy Res*. 2006;68 Suppl 2: S3–9.
64. Beydoun A, Uthman BM, Sackellares JC. Gabapentin: pharmacokinetics, efficacy, and safety. *Clin Neuropharmacol*. 1995;18(6):469–81.
65. Loj J, Solomon GD. Migraine prophylaxis: who, why, and how. *Cleve Clin J Med*. 2006;73(9):793–4, 797, 800–1. passim.
66. Peres MF, et al. Patients' preference for migraine preventive therapy. *Headache*. 2007;47(4):540–5.
67. Patrick DL, et al. Measuring satisfaction with migraine treatment: expectations, importance, outcomes, and global ratings. *Clin Ther*. 2003;25(11): 2920–35.
68. Evans RW, Linde M. Expert opinion: adherence to prophylactic migraine medication. *Headache*. 2009;49(7):1054–8.
69. Evers S, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol*. 2009;16(9):968–81.
70. Wessman M, et al. Migraine: a complex genetic disorder. *Lancet Neurol*. 2007;6(6):521–32.
71. Diener HC. Topiramate in Migraine Prevention. *European Neurological Disease*. 2006;(2):24–6.
72. Bekkelund SI, Alstadhaug KB. Migraine prophylactic drugs—something new under the sun? *Expert Opin Investig Drugs*. 2011;20(9):1201–10.