Clinical Advances in the Preventive Treatment of Migraine

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Abstract- Evidence is emerging on the physiological processes underlying episodic migraine and the rationale for preventive treatment. Objectives for preventive treatment include limiting future pain and disability and potentially modulating the course of disease progression. Many factors influence medication choice for patients such as migraine type, patient preference, co-existing conditions, and medication side effects. In this paper, frequently prescribed treatment options for migraine prevention are reviewed. Most headache preventive medications treat other medical disorders and are found serendipitously to be beneficial in migraine or other headache disorders. A new treatment option is topiramate, with proven safety and efficacy across the largest controlled migraine prevention trials conducted to date. New clinical information is enhancing patient care and enabling clinicians to ease the burden of migraine worldwide.

Key Words: Headache, Migraine, Pain, Prophylaxis, Prophylactic, Treatment, Therapy, Pharmacological, Drug

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INTRODUCTION

Burden of migraine worldwide

Migraine prevalence is historically considered lower in Asian populations than reported elsewhere in the world[1]. Only with the International Headache Society (IHS) published criteria for migraine diagnosis[2] did epidemiological studies offer consistent definitions and inclusion criteria across migraine studies. More recent epidemiological studies of headache in Asia using IHS criteria report migraine prevalence between 8.4% to 12.7%, with gender-specific migraine prevalence from 11.3% to 14.4% in women and 3.6% to 6.7% in men[3,4]. These data emphasize that migraine is a significant disease in Asia with overall prevalence rates comparable to, or slightly lower than those reported from other parts of the world.[5,6]

Despite the high prevalence of migraine headaches in Asia and around the world, both clinical and societal barriers limit effective headache management. One of the major barriers to providing effective treatment is the notion that migraine is still unaccepted as a medical illness among many physicians and patients. Migraine is often dismissed or receives limited medical attention since it is not life threatening. Approximately half of migraine sufferers never seek medical attention, and of those who do, only 29% report satisfaction with the acute treatments usually available to them[7]. For 71%,

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dissatisfaction results from the fact that headaches return after treatment. Fortunately, new clinical information and treatment options are available to enhance clinical practice and improve patient care.

The second edition of The International Classification of Headache Disorders (ICHD-II) was published in January 2004[8], and reflects an updated understanding of many headache disorders and the identification of new disorders. Clinicians treating headache patients should become familiar with the revised criteria. Evidence-based guidelines for preventive treatment of headache were developed several years ago by the United States Headache Consortium[9,10] and can be accessed by clinicians worldwide via the American Academy of Neurology website: (http://www.aan.com/professionals/practice/pdfs/gl0090.pdf). The guidelines provide valuable insights into the goals of migraine prevention, though based on publication date do not include information on more recently completed clinical trials. Overall the goals of migraine prevention are to: (1) decrease the frequency, severity and duration of migraine headaches; (2) enhance treatment response to acute medications; and (3) improve the quality of life of migraineurs.

The guidelines also assist in the identification of appropriate candidates for migraine prevention. The number of migraine attacks per month is the most commonly used factor in determining whether migraine preventive treatment should be initiated. Migraine preventive therapy is generally indicated in patients experiencing 2 or more migraines per month[9] with decreased functional capacity. The absolute number of migraine attacks per month, however, is debated by clinicians. Equally as important to migraine frequency is the degree of impairment individual patients experience with recurring migraines. For patients experiencing considerable disability, preventive treatment should be considered regardless of actual frequency of attacks[9]. Patients with contraindications to acute treatment, those in whom acute treatments no longer produce relief and patients who experience side effects to acute therapy are also candidates for preventive therapy[9,10]. Other factors to consider are listed in Table 1.

Table 1. *Consider prevention if any of the criteria are met:* [9,10]

1. Migraine significantly interferes with patients' daily routine, despite acute treatment
2. Frequency of attacks (>2 per month) with risk of acute medication overuse
3. Acute medications ineffective, contraindicated, troublesome side effects or overused
4. Patient preference
5. Presence of uncommon migraine conditions
* Hemiplegic migraine
* Basilar-type migraine
* Migraine with prolonged aura
* Migrainous infarction

Recent observations suggest that interictal changes in baseline neurologic function (psychological changes, nonspecific headache pain) may occur between migraine episodes[11]. These observations support a clinical strategy of early migraine diagnosis and preventive treatment together with acute management of migraine pain. Physicians should review treatment expectations with patients to ensure they realize that even with preventive therapy, headaches may still occur and require treatment. Both acute and preventive medications are necessary for adequate migraine management, and patients should be educated to understand the differences between their medications and when to use them appropriately.

NEUROCIRCUITRY, CUTANEOUS ALLODYNIA AND MIGRAINE

Trigeminovascular pathways play a pivotal role in migraine and associated symptoms[12]. One hypothesis is that the throbbing pain of migraine is mediated primarily through peripheral and to a lesser extent through central sensitization[13]. Most migraine patients (79%) exhibit cutaneous allodynia (elevated skin sensitivity) both prior to and during migraine attacks[14-17]. The following sequence likely occurs along the trigeminovascular pain pathway to mediate cutaneous allodynia. Meningeal blood vessels are heavily innervated by nociceptive sensory afferents of the trigeminal nerve and upon dysfunctional activation these first-order sensory fibers transmit signals to second-order neurons in the dorsal horn resulting in neuronal hypersensitivity. The sensitized path-

ways carry impulses centrally to thalamic nuclei and other brain structures important in pain perception. Consequently, the peripheral nociceptors stimulate a sequential cascade of second-order, and then third order neurons that signal central sensitization and mediate cutaneous allodynia first ipsilaterally on the head then arm[14]. Such a signaling sequence in peripheral and central neurons supports the notion that a migraine preventive drug with neuromodulatory action may alter the firing patterns of nociceptive afferents and may "silence" trigeminovascular pathways before the development of central sensitization. This in turn, may short circuit the development of migraine attacks.

In addition, the cortical event of spreading depression may play a role in migraine with and without aura. Spreading depression is defined as a wave of neuronal hyperexcitability across the cortex followed by suppression[18]. The wave of neuronal suppression moves across the cortex in animal models at a rate of roughly 3 to 5 mm per minute[19], and the visual aura of migraine can expand at a comparable rate. The prevailing view is that cortical spreading depression links mechanistically to cortical hyperexcitability and central sensitization phenomena in migraine[20,21]. Since migraine pathophysiology is intimately linked to neuronal activity, it follows that effective migraine preventives should modulate neuronal signaling and hence sensitization.

PHARMACOLOGICAL TREATMENTS FOR MIGRAINE PREVENTION

Treatment selection in migraine prevention depends on a variety of factors, including the presence of comorbidities, sensitivities, and contraindications to specific medications. In Taiwan, the following medications are currently available for migraine prevention: amitriptyline, propranolol, metoprolol, nadolol, atenolol, flunarizine, topiramate, valproic acid and verapamil. The general principle that applies to many drugs also applies to migraine preventives: one should initiate at a low starting dose and gradually titrate to achieve the desired therapeutic effect. It is important to allow sufficient time (up to 3 months) for response before concluding that a medication is ineffective. If an agent is discontinued, it should be tapered off appropriately rather than stopped abruptly.

Critiquing which migraine preventive agents are consistently efficacious is challenging within the existing migraine prevention literature since the methodological quality of most clinical studies is unsatisfactory. Study designs and primary endpoints differed among the older studies. Other shortcomings include insufficient enrollment and short treatment duration (Table 2). The situation is changing, however, and the quality of the evidence is improving. Several years ago clinical trial guidelines were drafted "to improve the quality of controlled trials in migraine" in order to assess adequately medication safety and efficacy[22]. Thus, the following queries should be kept in mind when reading older and more recent migraine prevention literature: (1) Were sufficient numbers of patients studied? (2) Were study subjects and clinicians blinded to treatment assignment ? (3) Were appropriate inclusion/exclusion criteria clearly provided ? (4) Was treatment allocation random ? (5) Were the outcome measures appropriate? (e.g. headache frequency or index, 50% responder rates), (6) Was patient attrition minimal in the study ? (7) Was the follow-up duration adequate ? (e.g. at least 6 months for preventive trial) (8) Were appropriate statistical analyses with "intention-to-treat" cohorts (ITT) and statistical power calculations conducted ?

Table 2. *Migraine prevention: treatment options. Evaluating migraine clinical trials.*

Trial evaluation criteria	Year of publication	Study size	Treatment period
		Cited trial (N)*	# of Weeks
Amitriptyline[78]	1979	162	12 weeks
Divalproex sodium[51]	1997	176	12 weeks
Flunarizine[75]	1986	58	12 weeks
Propranolol[67]	1989	55	12 weeks
Topiramate[32]	2004	575	26 weeks
Verapamil[72]	1989	< 24	12 weeks

* Largest reported or typically cited double-blind, placebo-controlled trial.

Commonly prescribed migraine preventive medications

Effective migraine preventive medications may work through a variety of cellular and molecular mechanisms, though it is currently unknown which mechanisms are specifically required in producing a decrease in headache frequency[23]. Thus, medication choice is based on clinical effectiveness, safety and tolerability, a patient's co-existing medical disorders and treatment preferences.

A. Topiramate

Several pilot studies[24-29] and more recently published large controlled trials[30-32] demonstrate topiramate's efficacy in migraine prevention. Topiramate has multiple mechanisms of action that may contribute to its antimigraine properties, as well as its potential therapeutic effects in other CNS disorders. At the cellular level, topiramate inhibits voltage-gated sodium channels and suppresses action potentials associated with sustained repetitive cell firing[33]. Topiramate inhibits high voltage-activated (L-type) calcium channels[34] and facilitates neuronal potassium conductance[35]. In addition, topiramate augments the inhibitory chloride ion influx in neurons mediated by γ-aminobutyric acid (GABA)[36] and antagonizes the (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) AMPA/kainate subtype of glutamate receptors[37,38]. It has no effect on the N-methyl-D-aspartate (NMDA) receptor subtype, and is also a weak inhibitor of type II and IV isozymes of carbonic anhydrase[39]. Individually or synergistically, these cellular actions likely contribute to topiramate's broad therapeutic profile in headache. In an animal model of migraine, topiramate modulates neuronal activity in trigeminovascular pathways[40].

Two 26-week, randomized, double-blind, placebo-controlled studies, with identical study designs, were conducted at 101 North American headache centers[30,1]. Patients aged 12-65 years of age were enrolled with at least a 6-month history of episodic migraine with or without aura (International Headache Society criteria) and 3 to 12 migraines per month. Of 970 patients randomized, 937 comprised an intent-to-treat population across both clinical studies. Statistically significant reductions in migraine frequency occurred within the first month of topiramate treatment, and were sustained for the duration of the trials. Mean monthly migraine frequency decreased significantly for patients receiving topiramate 100 mg/day (-2.1, $p < 0.05$) and topiramate 200 mg/day (-2.4, $p < 0.001$). The responder rates for those subjects exhibiting 50% or greater reduction in migraine frequency were 49-54% (100-mg dose), and 47-52% (200-mg dose) versus placebo (23%; $p < 0.001$). Migraine days and "rescue" medication use were significantly lower for the topiramate-treated groups. Commonly reported side effects with topiramate were paresthesia, fatigue, loss of appetite, nausea and diarrhea (> 10% of subjects).

Weight decrease in overweight or obese individuals is a known attribute of topiramate therapy[41-44]. In the migraine studies, roughly 20% of patients experienced weight loss on topiramate 100-mg and 200-mg. Weight loss with topiramate therapy contrasts with weight gain on nearly all other migraine preventives. This side effect is desirable for patients struggling with iatrogenic weight gain on other migraine medications. To date, the molecular mechanisms of weight decrease with topiramate are unknown, though being addressed in laboratory studies[45,46].

A large placebo-controlled, dose-ranging trial was conducted with topiramate worldwide, with propranolol as an active control[32]. Five hundred and seventy-five subjects were enrolled from 61 centers in 13 countries. Main findings showed topiramate100-mg was superior to placebo and similar to propranolol as measured by reduction in monthly migraine frequency, overall 50% responder rate, reduction in monthly migraine days, and reduction in the rate of daily rescue medication use. No unexpected safety risks emerged.

Together, these findings demonstrate that topiramate at a target dose of 100-mg daily is effective in migraine prevention. Topiramate should be started at low doses, generally 15-25 mg once at bedtime, and increased slowly over several weeks to a target dose of 100 mg daily, usually given in divided doses. Paresthesias are common in migraine patients taking topiramate (40-50% of

patients) that generally appear and resolve during drug titration, and some patients may experience mild symptoms of CNS-slowing or word finding difficulties. A dose-dependent decrease in ethinyl estradiol exposure occurs with topiramate ≥ 200-mg daily, though these higher dosages are typically not used for migraine prevention. Topiramate has been associated with very rare cases of secondary angle closure glaucoma[47] that is reversible upon drug discontinuation. Kidney stones[48], metabolic acidosis and oligohydrosis are also listed as rare events in the topiramate prescribing information.

B. Divalproex sodium

Divalproex and its related compounds, sodium valproate and valproic acid (VAL) modulate GABAergic mechanisms and are thought to increase GABA turnover in the brain and influence signaling at glutamate receptors[49]. These actions may limit the development of neurogenic inflammation and sensitization. A broad literature details the efficacy of VAL as a migraine preventive[50-55].

Doses of VAL should start at 125-mg or 250-mg once or twice a day, and be titrated up to 1000-1500-mg daily in divided doses. Although VAL does not affect estrogen levels it can cause elevations of androgens[56]. Women taking VAL are at increased risk of polycystic ovary syndrome[57,58]. Weight gain and hair loss are also reported in the headache population[59]. Valproate is associated with neural tube defects[60] and extreme caution should be exercised in prescribing valproate to any woman with migraine who is of childbearing potential. In general, VAL should not be considered a first-line medication in this population. Valproate can cause rare idiosyncratic reactions such as pancreatitis or hepatitis. Rarely, thrombocytopenia, pancytopenia and bleeding disorders can occur with valproate. Baseline blood tests (liver chemistry and complete blood count) are suggested but laboratory monitoring of blood levels is not indicated, as valproate serum levels do not correlate with headache control[52].

C. Gabapentin

The mechanisms of action of gabapentin are unknown and may involve interaction with voltage-gated calcium channels[61,62]. Despite its efficacy in neuropathic pain syndromes[63,64], gabapentin is only modestly effective in preventing migraines[65]. Doses of 1800-2400 mg per day and higher may be necessary for migraine prevention. Gabapentin is typically well tolerated with drowsiness and dizziness the most common complaints.

D. Propranolol

Beta-blockers are a commonly prescribed class of migraine medication. Their exact mechanism of action in migraine is unknown. Propranolol may reduce headache frequency by 50% for most uncomplicated cases[66,67]. Beta-blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, and pindolol) are not effective migraine preventive agents[68]. As propranolol, timolol, atenolol, nadolol, and metoprolol are thought to be equally effective, selection among them depends upon adverse effects, ease of administration, and cost. Propranolol has high lipid solubility and may lead to neurological side effects such as depression, sleep disturbances (nightmares), and lethargy[69]. Many physicians do not use beta blockers for those patients with prolonged aura and basilar-type migraines because of concerns over cerebral ischemia[70], though this may be necessary only when a clear stroke risk other than migraine is present.

Propranolol is typically initiated at a dose of 20-mg po bid and titrated to 40-mg bid. The dose can be gradually increased to 160-mg and as high as 360 mg/day. Because of side effects, few patients are able to tolerate higher dosage levels. Propranolol has a long-acting preparation (up to 160 mg/day), permitting once-a-day dosing following initial titration with short acting propranolol.

E. Calcium channel antagonists

Calcium-channel antagonists are frequently used for migraine prevention, in spite of contradictory evidence regarding their efficacy[10]. Verapamil is the calcium channel antagonist most frequently used for headache prevention in the United States, however it does not have strong data supporting its efficacy in migraine[71,72]. The

calcium channel antagonist flunarizine, is widely used as a migraine preventive in Europe and elsewhere in the world[73-75]. In certain clinical studies, flunarizine appears comparable to propranolol, metoprolol, pizotifen, and methysergide[74]. The mechanism of action of flunarizine in migraine prophylaxis is largely unexplained and may relate to its anti-dopaminergic effects. Its side effects include somnolence, weight gain, and, in rare cases, depressive mood and extrapyramidal motor disorders.

F. Amitriptyline

In general, antidepressants modulate serotonin activity in the nervous system. Amitriptyline's anti-headache effect might result from modulation of both the serotonergic and noradrenergic systems. It is the most studied antidepressant drug in migraine, though has unsatisfactory controlled efficacy data in episodic migraine[76-80]. Decades of anecdotal use in clinical practice supports its use in migraine and its effects appear independent of antidepressant actions[77]. Amitriptyline is best started at 10 or 12.5-mg (1/2 of a 25-mg tablet) given in the evening and titrated up as tolerated to not more than 100-mg daily. Amitriptyline is usually well-tolerated in the small doses required to treat headaches. Initial drowsiness decreases with time and is dose-related. Dry mouth and weight gain are common side effects and may not be well tolerated.

Serotonergic agents: Methysergide 2-mg tid can be an effective antimigraine medication when other agents have failed[81]. It is a semi-synthetic ergot alkaloid which has an antagonistic action at the 5-HT2 receptor and the ability to block neurogenic inflammation. Retroperitoneal and retropleural fibrosis have been associated with long-term methysergide use. Other serotonin antagonists include cyproheptadine, pizotifen and lisuride. These agents lack systematic data on their use in migraine prevention[82].

G. Miscellaneous migraine preventive agents

A variety of other compounds have been used in migraine prevention: riboflavin[83], magnesium[84-86], botulinum toxin[87], feverfew[86,88]. Results for these compounds are not replicated across robust clinical studies. These agents may be used in isolation, but in general do not yet see widespread use in migraine prevention.

Which preventive therapy should be chosen for which patient (Fig.)?

Most headache preventive medications are designed to treat other medical disorders and serendipitously were found to be beneficial in migraine or other headache disorders. For instance, topiramate was initially developed as a seizure medication[89-91], and is prescribed for a variety of other neurologic and psychiatric disorders[92-96] and obesity[41,44]. Drugs used for other conditions that have beneficial effects on headache frequency are an opportunistic situation for most patients. Co-morbid or co-existing illnesses can be deciding factors in selecting migraine preventive medications. For example, a patient with both depression and migraine may find both conditions improve with the use of antidepressant therapy. Topiramate may be a suitable option in those patients in whom weight is an issue, and alternatively propranolol for patients with migraine and hypertension. In the same manner, co-existing conditions can also limit the use of certain drugs. A patient with asthma should not be prescribed beta-blockers for migraine prevention because safer alternatives exist. Consequently, medications considered "first-line" treatment for migraine prevention have different thresholds of acceptance for patients (Table 3). Some common side effects are unacceptable

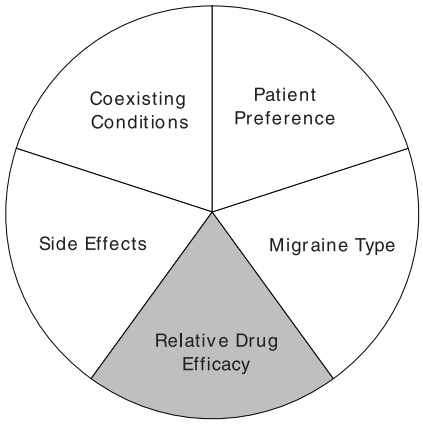

Figure. Principles of migraine prevention. Clinical factors influencing medication choice.

Table 3. *Safety and tolerability with migraine prophylaxis medications: Which preventive therapy for which patient?*

Adverse effect	Medications
Teratogenesis	VPA-associated neural tube defects
Weight gain	VPA, GBP, beta blockers, antidepressants, flunarizine
Weight loss	TPM
Fatigue	TCAs, beta blockers, TPM, GBP, VPA
Nightmares	Beta blockers,
Cognitive slowing	VPA, TPM
Hair loss	VPA
Sexual dysfunction	Beta blockers, TCAs
Orthostatic hypotension	Beta blockers, TCAs,
Constipation	CCA, TCAs

TCAs: tricyclic antidepressants; CCAs: calcium-channel antagonists; VPA: valproate; GBP: gabapentin; TPM: topiramate.

weight gain or teratogenic potential. Unfortunately, weight gain occurs commonly with many of the typically used preventive agents. A recent study highlighted the importance of this problem[97]. The weight of patients begun on 5 migraine treatments was monitored over 9 months. Patients on fluoxetine gained an average of 5 pounds, those on nortriptyline and divalproex gained on average 3 pounds. Patients on riboflavin did not, on average, gain or lose weight. Topiramate use was associated with an average 10 pound weight loss. It is important to recognize that medications can contribute to weight gain either directly, by increasing appetite or decreasing activity levels[98,99], or indirectly, as in cases where an increase in body weight may reflect improvement of migraine and consequent return of appetite. For this reason, regular aerobic exercise should be encouraged for all headache patients, not just those taking a pharmacological agent that may contribute to weight gain. The serious health consequences of weight gain[100], underscore the importance of avoiding medications that cause weight gain when efficacious alternatives exist. In addition, factors associated with the onset of chronic daily headache include both headache frequency and obesity[101,102]. Hence, overweight and obesity are emerging as modifiable variables contributing to migraine transformation to chronic daily headache.

CAN MIGRAINE PREVENTION ALTER THE COURSE OF HEADACHE PROGRESSION ?

Disease modification is a concept applied to interventions that may preserve wellness and functional capacity for longer periods of time. For example, this concept has been evaluated in multiple sclerosis treatment trials using beta-interferon[103]. This concept is of considerable interest in migraine and other disorders of the nervous system[104]. Many patients with migraine have a fairly stable course to their disorder that is reasonably managed by current therapies, whereas others experience deterioration and worsening of symptoms and consequent disorder progression to a more debilitating, chronic form. These patients lose their typical pattern of acute recurring attacks separated by pain-free intervals and progresses to a pattern of chronic daily headache. Studies of chronic daily headache in Taiwan[105] report prevalence rates (3.2% to 3.9%) similar to those of Western countries (3.0% to 4.7%)[106,107]. In addition to headache pain, disability from chronic migraine results in failure to participate in daily life (e.g. work and family) and consequent development of behavioral and psychopathology. Selected risk factors for the development of chronic daily headache are listed in Table 4.

Not only do changes in the headache frequency punctuate the transformation of migraine from episodic to chronic, now imaging techniques are revealing structural evidence (e.g. biomarkers) of putative damage to the nervous system in migraine. Ongoing headache attacks or aura can result in iron accumulation in the periaqueductal gray perhaps disrupting pain signaling[108,109]. In addition, the pathogenesis of migraine may

Table 4. *Selected risk factors for development of chronic daily headache:* [101,102]

* Frequency of migraine attacks (> 1 attack/week)
* Acute medication overuse
* Duration of disease
* Obesity, snoring
* Stressful life events

disrupt cortical tissue resulting in white matter lesions[110,111]. For patients with no history of stroke or transient ischemic attack, migraine patients exhibit a higher prevalence of cerebellar infarct than controls[111]. Adjusted odds ratios for posterior lesions varied by migraine subtype and attack frequency. Interestingly, the highest risk for tissue damage occurs in patients with a "high" migraine frequency (1 attack or more per month). To date, it is unknown whether migraine preventive therapies possess any capacity to "protect" brain tissue from sub-clinical disruption, however, generating hypotheses in this realm is provocative.

CNS damage and consequent functional disability from repeated migraine attacks may occur in several ways. Kindling models have been implicated in the pathophysiology of other neurologic and psychiatric disorders[112,113] and a similar process may underlie migraine since the physiology of neuronal kindling and central sensitization share similar mechanistic features. If sensitization is dependent upon migraine frequency, and consequent structural and functional alterations to pain signaling pathways, then it follows that therapeutically altering migraine frequency and severity should alter disease progression. Limited evidence suggests that some patients experience lasting benefits from migraine preventive treatments even after medication cessation[114]. In 64 patients, successful migraine prophylaxis was discontinued to assess enduring effects on headache reduction. Long-lasting reductions of migraine frequency were experience by 25% of patients, while three quarters experienced relapse[114]. Hence, there may be a critical period during which the nervous system possesses sufficient plasticity for "disease modification". Patients who had frequent (> 15 headache days) but not daily migraine attacks exhibited greater improvement with migraine prophylaxis than patients with daily headache[115].

CONCLUSIONS

Data from controlled clinical trials to date support the use of topiramate, some beta-blockers, and valproic acid/divalproex sodium as first-line agents for migraine prevention. Other agents have not undergone sufficient study for firm conclusions to be drawn. In addition to headache frequency, many factors influence medication choice for patients such as: migraine type, patient preference, co-existing conditions, and medication side effects. Clinical trials of migraine preventive agents have not assessed reduced migraine frequency on disease progression. There are obvious challenges in assessing disease-modifying effects of migraine preventives, namely the length of clinical trials required and the notion that prophylaxis is not a cure. Future research addressing such issues in longer term clinical trials and migraine natural history studies, together with the use of migraine biomarkers, will be required. In the meantime, new therapeutic options are emerging and improving patient care.

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