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Current Status of Antiepileptic Drugs as Preventive Migraine Therapy

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Abstract

Background Antiepileptic drugs (AEDs) are an important class of agents used in the treatment of migraine, a neurological disorder that imparts significant socioeconomic burden. It is important for neurologists to understand the rationale for AEDs in migraine-preventive treatment, as well as each agent's efficacy and tolerability profile, in order to best determine clinical care.
Purpose of this review This article specifically provides the following: (1) a review of the mechanism of action, efficacy, and tolerability of topiramate and divalproex sodium/sodium valproate, the most widely used AEDs for migraine prevention, (2) a discussion on emerging evidence regarding the efficacy of zonisamide and levetiracetam, and (3) comments on gabapentin, pregabalin, carbamazepine, oxcarbazepine, and lamotrigine, AEDs which have insufficient evidence for use in migraine prevention.
Recent findings The potential role for new extended-release formulations of topiramate in migraine prevention is discussed.
Summary There is substantial evidence supporting the use of AEDs in migraine prevention. Specific agents should be chosen based on their efficacy and tolerability profiles. Further studies are needed to determine the efficacy of the newer AEDs, zonisamide and levetiracetam, in migraine prevention and to clarify the role of gabapentinoids in headache management.

Introduction

Migraine is a neurologic disorder that causes significant global disability and socioeconomic burden [1•, 2]. It is associated with substantial healthcare costs, reduced work productivity, and social limitations [3–5]. Patients with a chronic or disabling migraine are offered pharmacological preventive options to reduce the frequency of migraine exacerbations and improve the efficacy of medications used to stop exacerbations [1•, 6••]. However, less than half of the patients choose to use preventive therapy [1•, 7]. Factors such as poor medication efficacy and tolerability and incomplete understanding of available options and benefits play a role in inadequate use of preventative therapy [7]. This review on the use of antiepileptic drugs (AEDs) for migraine-preventive treatment in adults discusses the most widely used preventive AEDs, topiramate and divalproex sodium/sodium valproate. We also discuss zonisamide and levetiracetam, AEDs that may be on the horizon of migraine-preventive care, and comment on gabapentin, pregabalin, carbamazepine, oxcarbazepine, and lamotrigine, which have insufficient evidence for use in migraine prevention. It is important to understand the efficacy and tolerability of each agent in selecting migraine-preventive therapy (see Fig. 1).

Mechanisms of AEDs in migraine prevention

Migraine is a neurological disorder characterized by recurring attacks of head pain, accompanied by symptoms such as photophobia, phonophobia, nausea, or vomiting. Cortical spreading depression (CSD) is thought to be integral in the pathophysiology of migraine. CSD is a wave of brief neuronal excitation followed by neuronal inhibition that propagates slowly across the cortex [8•, 9]. In its wake, CSD results in the extracellular release of potassium ions, hydrogen ions, and glutamate, which activate meningeal nociceptors. This induces an antidromic axonal reflex that causes sensory trigeminovascular axons innervating the pia and dura to release vasoactive neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), leading to neurogenic inflammation [8•, 10]. With repeated or continued activation, trigeminovascular neurons eventually develop sensitization, or an amplified responsiveness and a reduced response threshold to stimuli [8•]. The general role of AEDs in migraine prevention lies in their potential to block CSD and prevent central sensitization [9, 11]. Generally, AEDs act by stabilizing neuronal membranes through their effect on voltage and receptor-gated ion channels and reducing the release of vasoactive neuropeptides [9].

Topiramate and divalproex sodium/sodium valproate are the only two FDA-approved AEDs for migraine prevention and are substantiated by high-quality evidence. A 2013 Cochrane review did not show a benefit toward reduced headache frequency from carisbamate, clonazepam, lamotrigine, oxcarbazepine, pregabalin, or vigabatrin [12•, 13].

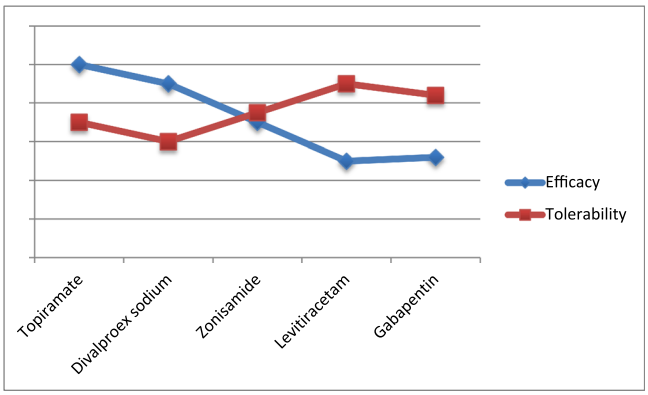

Fig. 1. Comparative efficacy vs. tolerability of select AEDs used in migraine prevention.

While the review also did not show a benefit in using zonisamide, levetiracetam, and gabapentin, these medications may still have a role in migraine prevention.

FDA-approved AEDs for migraine prevention

Topiramate

History

Topiramate (TPM) (Topamax®) was first synthesized in 1979 as an intermediate product in a study of fructose-1,6-diphosphate and its inhibition of gluconeogenesis to treat diabetes [14, 15•, 16••]. Researchers noticed that while TPM did not have a hypoglycemic effect, it has a structural resemblance to carbonic anhydrase inhibitors, which propelled its serendipitous discovery as an anticonvulsant and eventually as a preventive treatment for migraine [14]. Chemically, TPM is derived from the naturally occurring monosaccharide D-fructose and has a weakly acidic sulfamate group [14]. It readily enters the central nervous system (CNS) [14]. It is unique in those oxygen atoms, which contribute to hydrogen bond formation, account for nearly 40% of its mass [14, 15•].

Mechanism of action

TPM has variable activity on four protein complexes that are regulated by protein kinase phosphorylation: voltage-gated sodium channels, high-voltage-gated calcium channels, $GABA_A$ receptors, and AMPA/kainate receptors [14, 16••]. TPM's variable activity is likely due to its need to attach to protein complexes in the dephosphorylated state [14]. In the dephosphorylated state, TPM's unique structure, with its high number of oxygen atoms, allows it to form hydrogen bonds with protein complexes [14]. On binding, TPM then has a positive or negative allosteric modulatory effect on the channels [14, 17]. Furthermore, bound TPM prevents further phosphorylation of these channels, allowing it to have an increased, albeit delayed, modulatory effect over time [14].

Unlike other AEDs used in migraine prevention, TPM negatively modulates AMPA/kainate receptors, which indirectly inhibits the activity of the N-methyl-D-aspartic acid (NMDA) receptor, a glutamate receptor found on nerve cells [15•, 16••]. Glutamate is neuro-excitatory and is a major neurotransmitter involved in CSD [18]. Therefore, this inhibitory action of TPM is its most significant in both its anticonvulsant and antimigraine properties [15•, 16••].

TPM also negatively modulates voltage-gated sodium channels and high-voltage-gated calcium channels, although the extent of these roles in TPM's overall clinical pharmacology is not yet clear [15•]. Negative modulation of voltage-gated sodium channels prevents the propagation of the action potential. This in turn stabilizes neuronal membranes, which leads to a decrease in neuropeptide release and decreased neuronal hyperexcitability [9, 14, 15•, 16••]. Negative modulation of high-voltage-gated calcium channels prevents sustained membrane depolarization,

leading to increased membrane stability [9, 14, 15•, 16••, 19]. It also reduces the release of neuropeptides and neurotransmitters, such as CGRP and glutamate from trigeminovascular nerve terminals [20, 21].

The relationship of TPM with $GABA_A$ receptors is complex [15•, 22]. GABA is an inhibitory neurotransmitter distributed widely in the CNS. $GABA_A$ receptors in pyramidal neurons of the hippocampus mediate normal inhibitory postsynaptic potentials as well as depolarizing potentials. It is thought that TPM, by preventing protein phosphorylation, causes a shift in the equilibrium potential and partially inhibits depolarizing potentials [15•].

TPM also selectively but not specifically inhibits isoenzymes II and IV of carbonic anhydrase [15•]. While the relevance of carbonic anhydrase inhibition in migraine prevention is not known, it can lead to decreased neuronal excitation and increase inhibitory responses [14, 16••]. TPM's role in carbonic anhydrase inhibition may also lead to its ability to activate a hyperpolarizing potassium conductance [23].

By targeting multiple protein complexes, TPM has been shown to inhibit CSD [16••, 24–27]. This multimodal impact is also likely the reason TPM is more efficacious than other AEDs [16••].

Efficacy

The efficacy of TPM in treating both episodic and chronic migraine has been widely studied [6••, 16••, 28, 29••, 30–36, 37••, 38••, 39–41]. TPM, given in doses ranging from 100 to 200 mg/day, is effective in migraine prevention, although studies have suggested that doses of 200 mg/day are no more effective and have more side effects than 100 mg/day in patients without intractable migraine [16••, 28, 34, 36]. TPM is more effective than placebo in lowering 28-day migraine frequency [16••], with the onset of action typically occurring with the first month of starting the medication [11, 38••]. Studies have also shown that TPM is more effective than lamotrigine, propranolol, and sodium valproate in migraine prevention [34–36, 42]. Patients using TPM for migraine prevention have significantly improved mean functional disability scores than those using amitriptyline, while a combination of amitriptyline and TPM may produce an overall improved efficacy than either one alone [40, 41]. TPM is classified as having level A, established, evidence for use in preventing episodic migraine and is one of the most widely prescribed medications for migraine prevention [6••, 16••].

Tolerability

As with other CNS-active drugs, TPM can have dose-dependent cognitive side effects, including fatigue, somnolence, and mood changes including suicidal ideation, dizziness, word-finding problems, slowed thinking/mental processing, and concentration/attention and memory difficulty [15•, 16••, 43]. TPM's inhibitory effect on carbonic anhydrase may contribute to paresthesias, which can be alleviated with potassium supplementation [16••]. Other adverse effects from this action include an increased risk for renal calculi, metabolic acidosis, hypokalemia, and taste disturbances [16••]. Similarly to other sulfonamide medications, TPM

may lead to an increased, albeit rare, risk of ophthalmic side effects; these include acute angle closure glaucoma and visual problems without an increased intraocular pressure [16••]. Other adverse effects include decreased appetite and weight loss, which can be considered beneficial to obese patients [16••, 43]. Interestingly, neurocognitive symptoms and paresthesias are more prominent in patients with migraine than those with epilepsy, suggesting an underlying disorder-dependent vulnerability [44]. Additionally, migraine itself may result in an increased risk of renal calculi, independent of topiramate use [45]. Overall, side effects are mild to moderate, and occur primarily in the titration phase to target dose, and subsequently subside [38••, 43]. Women of childbearing potential should be cautioned regarding teratogenicity [16••].

New formulations

Immediate-release TPM is typically dosed twice a day. Although the half-life of immediate-release topiramate is about 24 h at doses of 100–200 mg/day [15•], with daily dosing, peak TPM concentrations are higher and trough concentrations are at least 30% lower compared with twice-daily administration [46]. New extended-release formulations (Trokendi XR®, Qudexy®), slow drug absorption and deliver more constant plasma concentrations. With less daily fluctuation in drug concentrations, extended-release formulations can mitigate side effects associated with peak concentrations. Daily dosing schedules can maximize medication adherence [47].

Long-term use

For those who respond to TPM in the first 1–2 months, TPM should be continued for at least 6 months prior to an attempted medication taper or discontinuation [48, 49]. Even the use of TPM for migraine prevention for only 6 months can result in a sustained benefit for some patients [49]. If a patient's migraine worsens after an attempted taper, then TPM should be re-introduced and a taper should be reattempted after another period of 6 months [48, 49]. Notably, worsening of migraine after the initial taper may be indicative of a refractory disease that would again worsen after the second taper [16••, 48]. A 6-month double-blinded study followed by an 8-month open-label extension study showed that TPM has long-term safety, tolerability, and benefit in improving migraine frequency compared with placebo [37, 50]. There has not been evidence of tachyphylaxis with TPM, although tolerability to its side effects does improve over time suggesting a change in the body's response to the medication [38, 43].

Divalproex sodium/sodium valproate

History

The anticonvulsant properties of valproic acid were discovered serendipitously in 1962 when researchers were testing valproic acid (VPA) as a liquid lipophilic carrier to dissolve water-insoluble compounds for clinical use [51]. The researchers found that VPA alone carried anticonvulsant properties. It quickly

became widely used to treat epilepsy, generally in the form of sodium valproate (Depakene® syrup). Divalproex sodium (Depakote®) is an enteric-coated, equimolar combination of valproic acid and sodium valproate. In this discussion, all forms will be referred to as VPA unless otherwise specified. Chemically, VPA is known as 2-propylpentanoic acid and is a simple branched-chain fatty acid. VPA readily crosses into the CNS; sodium valproate reaches the CNS within minutes of administration [52••].

Mechanism of action

The mechanism of VPA in migraine prevention is not completely understood [52••]. VPA increases neuro-inhibitory GABA activity by inhibiting the GABA-degrading enzymes aminotransferase and succinic semialdehyde, and by potentiating GABA's postsynaptic effects [52••, 53]. Active metabolites (such as 2-en-valproic acid) accumulate, which, over time, reach concentrations high enough to activate glutamic acid decarboxylase, a GABA-synthesizing enzyme [52••, 53]. This leads to a further eventual increase in GABA activity and contributes to the development of VPA's benefit over time. VPA also inhibits NMDA-evoked neuroexcitatory signals [53]. These actions on GABA and NMDA activity may play a role in blocking CSD [26, 27]. In addition, VPA attenuates plasma extravasation of vasoactive neuropeptides, thus decreasing neurogenic inflammation [52••, 53]. At high doses, VPA has also been shown to increase extracellular serotonin and dopamine and their active metabolites [53].

Efficacy

VPA has an established efficacy as a prophylactic treatment of migraine with study results favoring the doses ranging from 500 to 1000 mg/day [42, 54–59]. A pooled analysis suggests that a >50% reduction in headache frequency is twice as likely to occur in patients taking divalproex sodium as compared with those in placebo and three times as likely to occur in patients taking sodium valproate [60]. Compared with other migraine-preventive agents, studies have also shown that VPA is at least as equally effective as propranolol and is equally or slightly less effective as TPM in migraine prevention [42, 58, 59]. Sodium valproate formulations are generally rapidly absorbed, with peak serum concentrations occurring in 1–4 h [52••]. Divalproex sodium is an exception, with its absorption delayed by 2–4 h [52••].

Tolerability

In trials for migraine prevention, the most clinically significant symptoms included fatigue, dizziness, nausea, tremor, and weight gain [54–58, 60]. With the possible exception of nausea, VPA does not appear to cause unexpected adverse events when used for migraine prevention [60]. However, patients should still be monitored for more serious but rare adverse effects, including pancreatitis and liver failure [52••]. Women of childbearing potential should be cautioned regarding teratogenicity [52••].

Long-term use

In an open-label multicenter study of VPA for migraine prevention with a 3-year follow-up, migraine rates decreased each year on the dose, suggesting no development of tachyphylaxis and sustained benefit over time [61••]

AEDs of emerging importance in migraine prevention

Zonisamide

History

Zonisamide (Zonegran®) is a second-generation sulfonamide anticonvulsant that was introduced in 1972.

Mechanism of action

Zonisamide has several mechanisms of action that are similar to topiramate, including blocking voltage-gated sodium channels, modulating GABA-ergic and glutamatergic neurotransmission, and acting as a weak carbonic anhydrase inhibitor. Zonisamide also uniquely reduces the activity of the low-voltage-gated T-type calcium receptors, which are found in the trigeminal ganglion and trigeminal nucleus caudalis and play a role in mediating CGRP release [62].

Efficacy

In small-scale studies, zonisamide use results in an increased number of headache-free days and decreased migraine severity as compared with placebo, suggesting a role for its use in migraine prevention [63, 64]. More recently, a 3-month double-blind randomized clinical controlled trial of 80 patients compared the efficacy of zonisamide (titrated from 50 to 200 mg/day) with topiramate (titrated from 25 to 100 mg/day) [65]. This trial showed equal improvement in migraine frequency and no significant differences between the two groups [65]. These results suggest that zonisamide could be as effective as topiramate in migraine prevention [65]. Clinically, zonisamide may be considered as an alternative for those who cannot tolerate topiramate [64–66]. However, large-scale studies are still needed to establish conclusive evidence of its use in migraine prevention.

Tolerability

While there is a concern of the Stevens-Johnson syndrome or toxic epidermal necrolysis with rapid dose titration, zonisamide at slowly titrated and stable doses is well tolerated. In patients taking zonisamide at doses between 200 and 500 mg/day for more than 24 months, common adverse effects included decreased appetite and weight, memory impairment, and decreased hemoglobin level [67]. Women of childbearing age should be cautioned regarding teratogenicity. No evidence of tachyphylaxis was reported.

Levetiracetam

History

Several small-sample studies have suggested that levetiracetam (Keppra®; LEV) may be safe and effective to use as migraine prevention [68–72].

Mechanism of action

LEV has a unique mechanism of action as compared with other AEDs. LEV targets hyperexcitable neurons actively releasing neurotransmitters. It does this by binding to a synaptic vesicle protein, specifically SV2A, as it is being recycled just following neurotransmitter release [73]. By binding to the vesicle protein, LEV blocks further release of the neurotransmitter resulting in reduced neuronal hyperexcitability. LEV also blocks high-voltage-gated N-type calcium channels; N-type calcium channels have shown to play a major role in generating KCl-induced CSD [74].

Efficacy

There is conflicting evidence regarding the use of oral LEV for migraine prevention [12, 69, 75]. A 2011 placebo-controlled, crossover trial of 96 patients found 3000 mg of LEV failed to produce a statistically significant reduction in migraine frequency [75]. However, researchers did show a trend toward decreased head pain frequency, pain severity, and disability in patients taking LEV [75]. A 2013 prospective randomized placebo-controlled study of 52 patients showed LEV at 1000 mg daily resulted in a significantly lower headache rate as compared with placebo [69]. However, this trial had notable limitations, including high dropout rates and more patients in the treatment arm than in the placebo arm [69]. A 2008 placebo-controlled, double-blind parallel group study of 69 patients randomized to levetiracetam 1000 mg/day, TPM 100 mg/day, or placebo, showed that patients were nearly 13 times as likely to experience a ≥ 50% reduction in headache frequency with LEV as compared with placebo [12, 76]. There was a small but significant difference favoring the efficacy of TPM [12, 76]. Similarly, a 2014 prospective, randomized, placebo-controlled study of 85 patients randomized to levetiracetam 500 mg/day, valproate 500 mg/day, or placebo, showed that patients experienced a more than 50% decrease in headache frequency in the LEV group compared with the placebo group, with no statistical difference in improvement between LEV and VPA [70]. Conflicting evidence and small-scale trials underscore the need for large-scale studies to establish evidence for LEV's use in migraine prevention.

Tolerability

LEV is very well tolerated. Common adverse effects include dizziness, somnolence, and mood changes including irritability, hostility, and hyperactivity [12, 69, 75].

Long-term use

A 2-year prospective study of patients using LEV and TPM for seizure prevention indicated that LEV had high long-term tolerability with a more favorable side effect profile than TPM [77].

Other AEDs with insufficient evidence for use in migraine prevention

Gabapentin and pregabalin

History

Gabapentin (Neurontin®; GBP) is a gamma-aminobutyric acid derivative that was introduced in the 1990s as an AED and has subsequently been used for the treatment of neuropathic pain and migraine prevention.

Mechanism of action

GBP's most well-established mechanism of action is blockage of voltage-gated calcium-channel receptors, which reduces transduction of membrane potential changes [78]. It can also block vasoactive neuropeptide release and inhibit neuro-excitatory glutamate [78]. Through these roles, GBP eventually reduces excitatory amino acid content in the cerebrospinal fluid (CSF) and inhibits activation of protein kinase C, a pain signal transduction molecule that functions to regulate neuropathic pain [79]. Mouse models show that GBP reduces neuronal excitability in the spinal nucleus of the trigeminal nerve and inhibits the formation of central sensitization during migraine [79]. Furthermore, a single dose of IV GBP at doses of 100 or 200 mg/kg has been shown to increase the electrical threshold for CSD and diminish recurrent CSDs, although repeated or long-term use of GBP has not been tested [80].

Efficacy

Despite the molecular evidence of GBP's potential use in migraine prevention, clinical evidence has suggested that GBP is not beneficial in migraine prevention. A randomized, double-blind, placebo-controlled, phase II study showed no statistically significant difference gabapentin (1800 mg/day and 2400 mg/day doses) and placebo [81••].

A pooled analysis of high-quality clinical trials also failed to show that GBP produces a significant benefit in migraine prevention [13]. Patients had a ≤ 50% likelihood of their headache frequency being reduced with gabapentin as compared with placebo [13]. Increased doses of GBP (2000 mg/day compared with 1200 mg/day) did not result in any statistical difference [13]. However, due to concerns regarding intention-treat analysis and primary outcomes measured, the pooled analysis did not include a study that provides evidence for the use of GBP in migraine prevention. This 12-week, double-blinded, placebo-controlled trial of 143 patients showed that GBP titrated to doses of 2400 mg PO daily resulted in a statistically significant increase in the number of patients with a 50% reduction migraine frequency over 4 weeks when compared with placebo (46.4% vs. 16.1%)

[82]. The bottom line is that the evidence is insufficient regarding the efficacy of GBP in migraine prevention, and it is not indicated as primary therapy [6••, 78]. As large-scale trials are likely not feasible for this generic medication, small trials or trials of new formulation extended-release gabapentin may continue to help answer this question of GBP's role in headache management [78].

Tolerability

GBP is generally well tolerated. Its main side effects include dizziness, fatigue, nausea, and somnolence, which occur primarily during the dose titration period [81••]. Given a potential for misuse, GBP should be used with caution in those with history of substance abuse [83].

More trials are also needed to assess the efficacy of pregabalin (Lyrica®), a structurally similar gabapentinoid with linear pharmacokinetics. A recent 2018 randomized, double-blinded study comparing the efficacy of pregabalin with valproate sodium for migraine prevention suggested that both medications were equally effective in migraine prevention after the first month [84]. This study suggests a potential for pregabalin use in migraine prevention; although larger scale, placebo-controlled trials should be conducted to confirm this benefit.

Lamotrigine

Lamotrigine (Lamictal®), is a potent Na+ channel blocker that has been used to treat aura associated with migraine and other headache disorders [11, 85]. Consistent with its benefit on aura, lamotrigine has shown to have a significant suppressive effect on CSD [86]. However, studies have failed to demonstrate the efficacy of lamotrigine as compared with placebo for the prevention of migraine without aura [6••, 12, 35, 85]. This may be because medications with multiple molecular targets, rather than one highly selective target, are more effective in multifactorial disorders like migraine [16••]. Moreover, lamotrigine is associated with several adverse effects, most notably rash [85].

Carbamazepine and oxcarbazepine

Carbamazepine (Tegretol®) binds to and inhibits voltage-gated sodium channels, and may also contribute to an increase in extracellular serotonin [87]. Data for its efficacy is based on one 8-week study of 48 patients done in 1970 [88]. It is not commonly used for migraine prevention, as these results have not been reproduced. Furthermore, oxcarbazepine (Trileptal®), a structural derivative of carbamazepine with reduced hepatic metabolism, is likely ineffective for migraine prophylactic treatment [6••]. A study on the efficacy of oxcarbazepine (1200 mg/day) vs. placebo did not show any difference in migraine frequency [89••].

Teratogenicity of AEDs

In general, given limited and low-quality evidence regarding long-term outcomes of in utero exposure, women of childbearing potential being prescribed any anticonvulsant medication should be counseled about teratogenicity [90]. Teratogenic effects resulting in abnormal tissue development are most likely to occur 18–56 days after fertilization, during embryogenesis [90]. VPA and TPM have been associated with major congenital abnormalities. VPA exposure

increases the risk of hypospadias and congenital craniofacial, cardiac, neural tube, and skeletal limb abnormalities [91]. VPA use during pregnancy has been linked to lower child IQ [92]. TPM use during pregnancy also increases the risk of major congenital malformations, including risk of fetal loss, prenatal growth retardation, and craniofacial malformations [91, 93] Gabapentin exposure has been linked to the development of congenital cardiac malformations and hypospadias; however, evidence has not shown that it leads to a statistically significant increased risk of major congenital malformations [91, 93]. In a Cochrane review, zonisamide and LEV were also not associated with a statistically significant increased risk of major congenital malformations; however, there is limited data available regarding the outcomes of in utero exposure to these newer generation AEDs [91].

Conclusion

Given their ability to block CSD and prevent central sensitization, AEDs can be effective in migraine-preventive therapy. In general, given its good tolerability and robust evidence, topiramate is the first choice among AEDs for migraine prevention. Newer extended-release topiramate formulations may mitigate side effects associated with peak concentrations of immediate-release formulations. Valproic acid and its derivatives should also be considered, as their use is substantiated by high-quality evidence. We recommend starting at low doses with slow titration to determine an individualized benefit-to-side effect profile for each patient. Women of childbearing potential should be counseled regarding teratogenicity. Further studies are needed to delineate the roles of newer AEDs, zonisamide and levetiracetam, in migraine prevention. Finally, although gabapentinoids do not have high-quality clinical evidence to support their use as primary preventive therapy, their potential to suppress CSD and neurogenic inflammation may substantiate further trials reassessing their role in headache management.

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Compliance with Ethical Standards

Conflict of Interest

Stephen D. Silberstein reports personal fees from Alder Biopharmaceuticals, grants and personal fees from Allergan, grants and personal fees from Amgen, grants and personal fees from Avanir Pharmaceuticals Inc., personal fees from eNeura, non-financial support from Curelator, Inc., grants and personal fees from electroCore Medical, LLC, grants and personal fees from Dr. Reddy's Laboratories, personal fees from Medscape, LLC, grants and personal fees from Teva Pharmaceuticals, grants and personal fees from Supernus Pharmaceuticals, Inc., grants and personal fees from Eli Lilly and Company, personal fees from Theranica, non-financial support from Trigemina, Inc., outside the submitted work. Simy Parikh declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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