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Expert Opinions

Long-Term Use and Safety of Migraine Preventive Medications

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Migraine preventive medications are used to reduce the frequency, severity, and disability of migraine attacks. Once migraine preventive therapy is initiated, the question of how long to maintain this therapy arises. This article will explore the literature pertaining to the long-term use of migraine preventive medications, including length of treatment and safety with long-term exposure.

Key words: migraine, headache, preventive therapy, beta blockers, anticonvulsants, antidepressants

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INTRODUCTION

Migraine can be a highly disabling pain condition that influences the daily activities of those affected. The 1-year prevalence of migraine has been reported to be 11.7%, and it is ranked among the top 10 causes of disability worldwide.[1,2] Migraine is often viewed as an episodic disorder; subsequently, the treatment of migraine commonly focuses on acute therapies for headache attacks. However, preventive medications are often used to reduce the frequency, severity, and disability of migraine attacks. Despite the availability of multiple evidence-based guidelines providing recommendations on migraine preventive treatment options,[3–5] research suggests that approximately 40% of migraine sufferers would benefit from preventive therapies, while only 13% receive them.[1] The decision to start preventive treatment is multifactorial, based on assessment of patient preference, frequency of migraine attacks, impairment of quality of life, severity of accompanying symptoms, including aura, and failure of acute drug treatment. The decision to stop preventive treatment is also multifactorial and based on many of the same considerations as the decision to initiate the treatment in the first place. This article will explore the literature pertaining to the long-term use of migraine preventive medications, including length of treatment and long-term safety. This article will not review all potential adverse effects associated with migraine preventive therapies but rather some of the more serious adverse effects and those that may arise with long-term use.

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CASE HISTORY

A 38-year-old woman has a 15 year history of chronic migraine for which she has been taking topiramate 100 mg daily for the last 8 years. She lost 12 pounds initially, which she has kept off, and has some mild cognitive side effects. Her headaches

decreased from almost daily, of mild to severe intensity, to about once a week, rapidly relieved by a triptan. Whenever she has been taken off the topiramate, the headaches have increased in frequency.

QUESTIONS

How often do migraineurs require preventive medication long-term? What is the long-term safety of preventive medications?

EXPERT COMMENTARY

How Often Do Migraineurs Require Preventive Medication Long-Term?.—Once initiated, the minimum recommended duration of preventive treatment for migraine is 3–6 months.[6] However, the literature suggests that many patients require preventive treatment beyond 3–6 months to maintain a reduced migraine attack frequency.[7–12] Also, long duration of preventive treatment (11.0 ± 7.0 months vs 5.8 ± 7.4 months) has been found to be protective against increasing frequency of migraine attacks ($P = 0.009$).[7] This finding has also been supported by Silva-Neto et al, who prospectively evaluated the duration of migraine prophylaxis (combination of atenolol 25–50 mg/day, nortriptyline 10–20 mg/day, and flunarazine 2.5–4 mg/day) after patients became pain-free for more than 90 days.[8] Patients were randomized to either continue prophylaxis for 12 or 24 months and subsequently followed for $\geq$3 years after the period of prophylaxis. They found that 76.0% of those on continued prophylaxis for 24 months vs 44.0% on continued prophylaxis for 12 months remained pain-free during the follow-up 3 years without prophylaxis.[8]

Wober et al examined the long-term use of flunarazine, propranolol, and metoprolol for migraine prophylaxis for at least 18 months up to 78 months with a particular focus on the duration of therapeutic success after withdrawal and potential for success of prophylactic re-initation.[9] They found that 25% of patients had a long lasting reduction of migraine frequency by at least 50% after discontinuation, while the remaining 75% had an initial benefit for an average of 6 months but decreased efficacy thereafter (mean time to worsening: flunarazine 7.2 months, beta-blockers 4.4 months). Of note, the second and further prophylaxis attempts were not as effective as the first if the same treatment was administered again. A high-frequency of attacks at baseline, history of analgesic abuse, and higher number of previously ineffective preventive treatments were risk factors that predicted relapse after the discontinuation of prophylaxis.[9] Physicians may consider prolonged courses of preventive medications in patients with the above risk factors, especially since future attempts at prophylaxis may not be as successful.

Diener et al evaluated the effects of discontinuation of topiramate after a treatment period of 6 months, and found that there was sustained benefit since the number of migraine days did not return to pre-treatment values.[10] However, patients that continued topiramate beyond 6 months compared with placebo had less number of migraine days, lower number of days on acute medication, and stable quality of life as assessed by the MIDAS, a well-validated disability measure in migraine.[10] Pascual et al evaluated the long-term use of topiramate in patients with migraine who experienced more than 3 attacks per month.[11] In 50% of patients, headaches worsened after withdrawal of topiramate at 6 months and required re-initiation of treatment. Topiramate withdrawal was again attempted at 1 year and 95% of the patients worsened, suggesting that most patients whose headaches worsen after withdrawal at 6 months will require preventive treatment for longer than 1 year.[11]

Bhoi et al followed patients on either sodium divalproate 500–750 mg or amitriptyline 25–50 mg and attempted withdrawal of medication at 6 months, 9 months, and 1 year.[12] They found remission rates of 43.6% at 6 months, 39.1% at 9 months, and 36.4% at 1 year, suggesting that the majority of migraine patients need long-term preventive treatment. Notably they found that patients who responded at 3 months of treatment ($P = .02$) are more likely to have long-term remission.[12]

Several studies have demonstrated that repeated onabotulinumtoxinA injections over time may have a cumulative prophylactic effect.[13,14] However, there is some question as to what interval of

onabotulinumtoxinA injections is required to maintain that benefit and if injections are required at all once patients have reached a headache remission state. Cernuda-Morollon et al explored the effect of lengthening intervals between onabotulinumtoxinA injections in the treatment of chronic migraine.[15] Patients were injected every 3 months for the first four injections but then the fifth injection was delayed to 4 months to explore the need for further injections. Among the patients who responded during the first four injections, 45.4% worsened with extension of the injection interval to 4 months suggesting that they required injections every 3 months for effective migraine prevention, 39.8% were able to extend their injections to 4 month intervals, 1.9% were able to extend to 6 month intervals, and 3.7% required no further injections.[15] Furthermore, their study showed that chronic migraine patients maintained a sustained response to onabotulinumtoxinA for years. Secondary failure, after having responded to the first year of treatment, was seen most commonly in the second year of treatment as none of the 20 patients treated for more than 3 years lost their response to onabotulinumtoxinA later.[15]

Rothrock et al injected 256 consecutive chronic migraineurs (mean age 44.7 years) with onabotulinumtoxinA.[16] One hundred and twenty-five (49%) had a greater than 50% reduction in headache days/month at some point during the course of therapy. Eighty of these responders (64%) had fewer than 5 headache days per month and MIDAS scores of less than 5 for 2 consecutive 12 week inter-treatment periods and injections were stopped. During a mean follow-up period of 14.4 months (range 6–23 months), 2 (2.5%) relapsed to chronic migraine, and 64 (82.5%) continued to require no preventive treatment.[16]

Despite different patient populations (episodic or chronic migraine) and different preventive treatment options, the studies regarding long-term use of preventive migraine therapies suggest that the majority of patients placed on a migraine preventive treatment will experience worsening of migraine with withdrawal of treatment within 6–12 months of initiation with the exception of the recent onabotulinumtoxinA study. [16] This is important to note as preventive medication withdrawal is worth attempting in efforts to reduce polypharmacy. However, a large subset of patient will experience headache recurrence and will require more extended duration of migraine prophylaxis. A high frequency of migraine attacks, history of analgesic abuse, and high number of previously ineffective preventive treatment options may be risk factors for relapse after the discontinuation of prophylaxis. The absence of these clinical features could be used to predict which patients may tolerate discontinuation. Further research is needed to elucidate more clearly how long and for whom long-term migraine prophylaxis is required.

What Is the Long-Term Safety of Migraine Preventive Medications?.—Rates of medication persistence, which is defined as the amount of time a patient remains on a prescribed medication, for migraine prophylaxis are reported at 41%–88% at 2 months, 19%–79% at 6 months, and 7%–55% at 12 months.[17] Adverse events are the most common reason for discontinuation. In the following section, we will discuss the long-term safety of medications with level A or B evidence for migraine prevention based on the AAN Guidelines for the prevention of episodic migraine and also the long-term safety of Onabotulinumtoxin A injections, which is the only FDA-approved treatment for chronic migraine.

Anticonvulsants.—Valproate products and topiramate have been on the market since 1967 and 1994, respectively, for use as anticonvulsants.[18] In 2000, divalproex sodium was FDA-approved for use as a migraine preventive treatment in adults. Topiramate was FDA-approved in 2004 for adult migraine prevention and in 2014 for adolescent migraine prevention.

TOPIRAMATE.—Topiramate has level A evidence to support its use for migraine prevention.[3] Greater persistence among patients on topiramate has been found compared with other prophylactic drugs.[19] However, topiramate can be associated with a variety of adverse effects, including: skin (oligohydrosis), bone health (osteoporosis, osteopenia), body weight (weight loss), renal and

electrolytes (renal stones, metabolic acidosis), visual (acute closed-angle glaucoma), neurological (cognitive impairment), psychiatric (mood changes), and pregnancy and postnatal development (teratogenicity).[18] Topiramate has a pregnancy category D designation by the FDA and thus is contraindicated in pregnancy.[20]

Lainez et al described the time course of adverse events that led to discontinuation of topiramate during three pivotal trials.[21] Adverse events led to discontinuation in 24.9% of patients receiving 100 mg/day of topiramate; these included paresthesias, cognitive symptoms, fatigue, insomnia, nausea, loss of appetite, anxiety, and dizziness.[21] Most of these adverse events occurred during the titration period. If a patient had not experienced these adverse events within the first 1–2 months of initiating topiramate, they were unlikely to occur later; but were likely to persist if they had occurred initially.

Weight loss is a well-documented adverse event with topiramate. Two 26-week trials reported weight loss as an adverse event in 9.5%–11.5% of patients (50 mg/d: −2.2% to 2.4% ± 4.39%–4.4%; 100 mg/d: −3.3% to 3.8% ± 4.1%–4.19%; and 200 mg/d: −3.9% to 4.6% ± 4.65%–5.1%).[22–24] Topiramate-induced weight loss may not be perceived as an adverse event by some patients as improved weight satisfaction has been found with topiramate compared with amitriptyline.[25] In an open-label study of patients aged ≤19 years treated with topiramate (mean dose, 84 mg/d), 65.9% of patients receiving topiramate had weight loss that was not reported as an adverse event: after a mean of 203 days of topiramate treatment, children and adolescents had a net weight loss of greater than 1 kg and weight decreases of 0.9, 2.7, and 3.0 kg were recorded at mean visits of 89, 203, and 319 days, respectively, after the start of treatment.[26] This is similar to the incidence of weight loss in adults, suggesting that some degree of weight loss occurs in as many as two-thirds of patients who use topiramate for migraine prevention.[22]

Increased degree of osteopenia, as reflected by bone mineral content and density measurements of the lumbar spine, has been associated with duration of topiramate therapy for migraine prevention independent of dose.[27] These findings suggest that even young patients with greater than 6 month exposure to topiramate, are at risk of significant bone loss. Currently, there are insufficient data to make firm recommendations on management of patients taking topiramate with respect to bone health but general measures include optimizing physical activity, maintaining a balanced diet, smoking cessation, moderation of alcohol and caffeine and taking 1000–1500 mg of calcium and 400 IU vitamin D daily.[28] If patients have known osteoporosis/osteopenia or risk factors for its development (prolonged topiramate therapy, reduced ambulation, concomitant steroid therapy) than specific measures to investigate and treat osteoporosis/osteopenia should be considered as outlined in a recent manuscript by Ali et al.[28]

One study in epileptic patients looked at the long-term safety of topiramate over 5.3 years (doses 200–600 mg) and found an incidence of kidney stones not requiring surgery of 1.5%.[29] Other studies have reported prevalence of symptomatic kidney stones to be 2.1%–10.7% and asymptomatic kidney stones in 20% of topiramate users.[30,31] Studies that looked at the association between duration of therapy and development of kidney stones have been mixed. Shorovon et al found no relationship between stone formation and duration while Kaplon et al found an inverse relationship between duration and urinary citrate levels, which increase the risk of stone formation.[29,32] There are no published trials on treatments to reduce the risk of topiramate associated kidney stones. General recommendations for stone prevention include adequate hydration and low-sodium diet for all patients on topiramate. Potassium citrate therapy may be considered in patients who develop metabolic acidosis or a stone and the benefits of continuing the medication outweigh the risks.[33] However, prospective trials of potassium citrate therapy for patients on topiramate are required to be able to provide more firm recommendations on this topic.[33]

VALPROATE PRODUCTS.—There is level A evidence to support the use of divalproex sodium

and sodium valproate as migraine preventive treatments.[3] Unfortunately, these medications are associated with a long list of clinically important adverse effects. These include effects on: skin and cosmetic (alopecia, hirsutism, acne), reproductive health (sperm abnormalities, infertility in women, polycystic ovary syndrome), bone health (osteoporosis, osteopenia), body weight (weight gain), lipids and atherosclerosis (acceleration of atherosclerosis, hyperlipidemia, metabolic syndrome), gastrointestinal (pancreatitis, hepatic failure, non-alcoholic fatty liver), hematological (leucopenia, thrombocytopenia, pseudolymphoma), neurological (essential tremor, parkinsonism), pregnancy and postnatal development (teratogenicity, impaired cognition in children exposed in utero).[18] Hepatic failure resulting in fatalities has occurred in patients receiving valproate.[34] These incidents usually have occurred during the first 6 months of treatment. Risk for hepatic failure is highest in patients with prior history of hepatic disease, on multiple anticonvulsants, children (particularly under the age of 2 years), those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease.[34] Although many of these risk factors do not pertain to the standard migraine population, they are important to recognize nonetheless. Safety monitoring for valproate products includes liver enzymes (at baseline and frequently during therapy especially during the first 6 months), CBC with platelets (baseline and periodic intervals), PT/PTT (especially prior to surgery), and serum ammonia (with symptoms of lethargy, mental status change).[34] Discontinuation of valproate products results in reversal of many of these adverse effects, except those associated with teratogenicity and postnatal development, which are permanent. Valproate products have a pregnancy category × designation by the FDA and thus are contraindicated in pregnancy.[34] To our knowledge, there are no studies looking at bone health in migraineurs on valproate products like there in patients on topiramate. Studies in epileptic patients using long-term valproate product therapy have demonstrated conflicting results but generally appear to suggest a risk for lower bone mineral density measurements, even in young patients.[28,35] Therefore, recommendations regarding bone health management with long-term valproate product use are similar to those for topiramate.[28]

Silberstein et al evaluated the safety of long-term use of divalproex sodium in migraine prophylaxis, with over 1080 days of treatment.[36] The most frequently reported adverse events were nausea, infection, alopecia, tremor, asthenia, dyspepsia, and somnolence. Nausea, vomiting, dizziness, dyspepsia, somnolence, asthenia, alopecia, and diarrhea showed reduced prevalence beyond 180 days of treatment; while tremor, weight gain, and pain remained relatively constant over time.[36] Weight gain was reported in 19% of patients and 4% had weight gain of 10.9 kg or more.[36] Freitag et al examined divalproex in the long-term treatment of chronic daily headache, including patients with transformed migraine.[37] Mean treatment duration was 13.2 months, with a range from 3 to 71 months. Adverse events occurred in approximately 35% of patients and none were severe. Weight gain was reported in 7.1% of patients (mean 2.9 lbs), with no correlation being found between weight gain and duration of treatment.[37]

Antidepressants.—AMITRIPTYLINE.— Amitriptyline is a commonly used migraine preventive treatment with level B evidence per the AAN guidelines for episodic migraine.[3] It is commonly used in patients who have comorbid tension-type headache, insomnia, or depression. The most commonly reported adverse effects are fatigue (16.9%), somnolence (11.9%), and other anticholinergic symptoms such as dry mouth or dry eye (35.5%).[25] A 26 week comparative trial of amitriptyline and topiramate found a mean weight change of +2.4 kg from baseline with amitriptyline; 64.6% of amitriptyline-treated subjects gained ≥1% of body weight, and 28.5% gained ≥5% of body weight.[25] A post-hoc analysis of this study found that patients who gained ≥5% of their baseline weight, which consisted mainly of patients on amitriptyline (87%), compared with patients who lost ≥5% of their body weight, mainly those receiving topiramate (91.0%), had greater increase in c-reactive protein, glycosylated

hemoglobin, total cholesterol, and triglycerides.[38] Furthermore, they also had significant elevations in mean diastolic blood pressure and mean change in heart rate from baseline to final visit.[38] Caution is required for its use in patients with angle-closure glaucoma, urinary retention, and prostatic hypertrophy.[39] Also amitriptyline has a pregnancy category C designation by the FDA.[40]

Tricyclic antidepressants have been associated with heart block, ventricular arrhythmias, and sudden death. Risk of cardiovascular adverse effects, including orthostatic hypotension, atrioventricular conduction delay, reduced heart rate variability, tachycardia, syncope, and lengthening of the QT interval, increases with higher dosages and in patients with concurrent cardiovascular disease.[41] Before initiating amitriptyline, physicians should carefully assess risk factors for adverse cardiac effects, such as symptoms suggestive of heart disease (syncope, palpitations, dyspnea on exertion, shortness of breath, or chest pain), pre-existing cardiovascular disease or history of drug overdose, age over 65 years, family history of cardiac dysrhythmias, cardiac conduction disturbances or sudden cardiac death, female sex, electrolyte abnormalities, or the simultaneous administration of other drugs that delay repolarization or interfere with drug metabolism.[42] Screening EKG should be performed before initiating amitriptyline therapy as well as 1–2 weeks after initiation and after increases in doses $\geq$50% or at any time if patients report symptoms suggestive of cardiac toxicity (eg, unexplained syncope, shortness of breath, dizziness, palpitations, or chest pain).[43] Tricyclic antidepressants should be tapered over two to four weeks as abrupt discontinuation can cause agitation, anxiety, chills, diaphoresis, headache, insomnia, irritability, malaise, myalgia, and nausea and rarely may cause akathisia, cardiac arrhythmia, and parkinsonism.[44]

VENLAFAXINE.—There is level B evidence to support the use of venlafaxine for migraine prevention.[3] Typical adverse effects of venlafaxine are nausea, vomiting, constipation, sedation or dry mouth. To our knowledge there are no studies in migraine patients assessing adverse effects of long-term use. A 2-year study looking at side effects of antidepressants among patients enrolled in the Netherlands Study of Depression and Anxiety found that venlafaxine showed more profuse sweating (OR = 1.79; P = .007).[45] Venlafaxine has a pregnancy category C designation by the FDA.[46] Venlafaxine should be prescribed with caution in patients with cardiac disease as conduction abnormalities have been reported in a small number of patients and blood pressure increases can occur. Blood pressure should be checked at baseline, and every 2–6 months in patients receiving venlafaxine at high doses (>300 mg/d).[47] Weight loss of about 0.5 kg has been reported in a pooled analysis of short-term treatment with venlafaxine (4–12 weeks).[48] However, mean weight gain of about 7 kg was found in a retrospective study of 49 patients treated for an average of 18 months.[49] In addition, venlafaxine should be tapered slowly when treatment is being discontinued because of withdrawal symptoms, such as anxiety, dizziness, headache, insomnia, nausea, and weakness.[50]

Beta-Blockers.—PROPRANOLOL. Propranolol has level A evidence to support its use as a migraine preventive treatment and is commonly considered for patients with concomitant hypertension.[3] However, compared with other antihypertensive drugs for primary treatment of hypertension, beta-blockers may be associated with inferior protection against stroke risk, particularly in patients over age 60 years.[51,52] In addition, beta-blockers are associated with impaired glucose tolerance and an increased risk of new onset diabetes.[53] Diamond et al studied the long-term use (8–16 months) of propranolol for treatment of migraine and found that 5.7% of patients prematurely terminated the study due to adverse effects.[54] Compared with placebo, dizziness, visual disturbance, diarrhea, epigastric distress, weakness/fatigue, malaise/lethargy, insomnia, chest pain/heaviness, weight gain, and significant nausea were more common with propranolol.[54] Weight gain has been reported after 6 months of therapy in 8% of patients taking propranolol (mean increase 6 kg).[55] Propranolol has a pregnancy category C designation by the FDA.[56] Abrupt discontinuation of propranolol can occasionally result in a rebound increase in blood pressure with symptoms and signs of sympathetic overactivity. Therefore, weaning propranolol is recommended.[57]

ONABOTULINUMTOXINA.— OnabotulinumtoxinA is the only FDA-approved treatment for chronic migraine based on the PREEMPT trials.[58] The long-term use of onabotulinumtoxinA injections has been evaluated by a few studies; however, each looked at slightly different headache populations and used varied injection paradigms, including chronic migraine (up to 8.5 years of treatment at doses between 100 and 200 U),[15] and chronic migraine with medication overuse headache (2 years of treatment at doses of 155–195 U).[13,14] Overall these studies found no severe treatment-related adverse events.[13–15] Those observed were mild to moderate and not a reason to interrupt onabotulinumtoxinA injections. Total reported adverse events ranged from 14.4% (over first year) to 20.3% (over 2 years) and included dysphagia (0.8%), injection-site pain (3.3%–3.5%), neck pain (3.8%–4.5%), musculoskeletal weakness (3.8%–4.9%), eyelid ptosis (2.9%–5.3%), and headache (3.7%–4.9%).[13–15] These events lasted from less than a week to a maximum of 2 months. Neck pain and musculoskeletal weakness were more likely to occur during the first 3 cycles of injections.[14] For cases of ptosis or neck pain, the Cernuda-Morollon et al group either reduced to half or totally avoided affected muscles to successfully address these issues.[15] Among eight patients treated for more than 5 years, two showed local muscle atrophy in the frontotemporal region but neither patient expressed any complaints regarding this.[15] OnabotulinumtoxinA has a pregnancy category C designation by the FDA.[59] Immunogenicity manifested as toxin neutralizing antibody formation has been reported as an uncommon occurrence with chronic use of onabotulinumtoxinA in therapeutic indications besides migraine (cervical dystonia 1.28%, glabellar lines 0.28%, overactive bladder 0%, post-stroke spasticity 0.32%, and primary axillary hyperhidrosis 0.46%).[60] Toxin neutralizing antibodies do not appear to be a significant concern in patients being administered onabotulinumtoxin A for prevention of chronic migraine either. Among 496 analyzable samples collected during phase 2 studies of onabotulinumtoxinA for migraine prevention, none were positive for toxin neutralizing antibodies and one patient had inconsistent results; based on these findings, analysis of toxin neutralizing antibodies were not required for the PREEMPT trials.[58]

CONCLUSION

The literature suggests that the majority of migraine patients requiring preventive treatment will require long-term prophylaxis (ie, for >6–12 months). As such, physicians have to be vigilant to monitor and address the potential adverse effects that may occur with long-term exposure to these medications.

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