# Pharmacologic prevention of migraine

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See a related review article at www.cmaj.ca/lookup/doi/10.1503/cmaj.211969 and a first-person account of trying to access migraine treatment at www.cmaj.ca/lookup/doi/10.1503/cmaj.221783

In this second in a series of 2 reviews focusing on the management of migraine, we discuss pharmacologic treatments that health care practitioners may prescribe to help reduce the frequency, severity, duration and disability of patients' migraine attacks and optimize their use of medications for acute headache treatment. Our first article[1] discussed diagnosis and acute treatment; herein, we focus on migraine prevention, an important part of management for which evidence is accumulating. The 2021 American Headache Society consensus guideline recommends that preventive pharmacologic therapy should be considered for patients with 4 or more migraine headache days per month or those with 2 or more migraine headache days per month that are associated with substantial disability despite use of acute medication.[2] Preventive treatment should also be considered for patients with atypical aura (hemiplegic migraine, migraine with brain stem aura) and migraine with associated complications (e.g., persistent aura, migrainous infarction [stroke], migraine aura–triggered seizure, status migrainosus), even if the frequency of attacks is low.[2] We draw on original research, reviews and clinical practice guidelines (Box 1).

### Key points

- Oral medications traditionally used for the prevention of migraine and known to be effective include anti-epileptic, β-blocker, antihypertensive and antidepressant drugs.
- OnabotulinumtoxinA (Botox) injection is indicated for prevention in patients with chronic migraine, as it has very few drug interactions or systemic or long-term adverse effects; however, it must be administered by a trained provider.
- The newer calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) specifically target migraine pathophysiology and are effective and safe treatment options particularly for patients who have contraindications to or have previously not responded to other therapies.
- Lifestyle changes, behavioural therapies and certain supplements can augment migraine prevention.

## What is the general approach to migraine prevention?

The goal of preventive treatment for migraine is to reduce the frequency, severity, duration and disability of attacks, and improve response to and minimize use of acute medications. Although many patients benefit from lifestyle modifications — including attention to sleep hygiene, exercise and diet, maintaining a headache diary, and using techniques to manage stress and increase their coping ability — we discuss only pharmacologic prevention and the use of nonpharmacological supplements in this article. Other, more formal, nonpharmacologic measures have been shown to help with prevention of migraine and are guideline recommended; these include cognitive behavioural therapy, biofeedback and relaxation training. Mindfulness-based therapies have also been studied and found to be promising (Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.221607/tab-related-content).

When choosing a preventive treatment, a medication with a high level of efficacy should be considered first. However, treatment choice is influenced by patient comorbidities, individual preferences, medication adverse effects and drug coverage. Medications should be started at a low dose and titrated slowly until the minimum effective or maximum tolerated dose is reached. An 8- to 12-week trial at a therapeutic dose is reasonable to determine efficacy. If a medication is ineffective, clinicians should consider a medication from a different drug class. Tapering the dose, and possibly stopping the medication, can be considered after an adequate treatment response has been maintained for 6–12 months.[3]

Patient involvement is crucial to a successful preventive treatment plan, which requires long-term commitment and careful adherence to treatment, as well as communication with their

### Box 1: Evidence used in this review

We conducted a targeted search of Google Scholar and PubMed to identify original research, review articles and clinical practice guidelines published through November of 2021, using search terms that included, but were not limited to, "migraine acute treatment," "migraine preventive treatment," "migraine CGRP monoclonal antibodies," "migraine 5-HT1F," "migraine behavioural treatments," and "migraine neuromodulation." We also consulted the most recent guidelines from the Canadian Headache Society and the American Headache Society, and the *International Classification of Headache Disorders, 3rd edition*.

health care provider, which can be facilitated by the use of a headache diary to monitor response to treatment. Providers should explain that the goal of preventive treatment is not to "cure" migraine, but to reduce attack frequency, duration and severity.

## What are the classic pharmacologic options for migraine prevention?

### Oral medications

Oral medications include anti-epileptic, β-blocker, antihypertensive and antidepressant drugs. Many of the medications have moderate-to-high potential for drug interactions and adverse effects that may preclude their use in some patients or result in poor tolerability and low adherence rates (estimated to be 26%–29% at 6 mo and 17%–20% at 12 mo).[4,5] Nevertheless, they are relatively inexpensive and most are covered by public and private insurance providers; thus, they remain first-line treatment for migraine prevention. The most recent Canadian Headache Society guideline on migraine prophylaxis was published in 2012; its recommendations are summarized in Table 1.[6] Recent randomized controlled trials (RCTs) support the efficacy of candesartan and memantine,[7,8] which will likely be added in the next iteration of the guideline.

### OnabotulinumtoxinA injection

Since 2011, onabotulinumtoxinA (Botox) injection has been approved in Canada for prevention in patients with chronic, not episodic, migraine. The standard treatment follows the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol, which consists of 155–195 units injected at 31–39 sites across the head and neck every 12 weeks by a trained physician. In a pooled analysis of RCTs, treatment with onabotulinumtoxinA resulted in a greater reduction in mean monthly headache days compared with placebo at 24 weeks (–8.4 d v. –6.6 d, $p < 0.001$, 95% confidence interval [CI] –2.52 to –1.13).[9] Furthermore, reduction in headache days by 50% or more was reported by 47.1% of patients treated with onabotulinumtoxinA compared with 35.1% of patients in the placebo group ($p < 0.001$),[9] and was associated with reduced attack severity and medication overuse, as well as improved quality of life.[9] OnabotulinumtoxinA has shown few drug interactions or systemic or long-term adverse effects. The most common adverse effects, including neck pain and ptosis, are mostly reversible.[9] Recent retrospective studies considering pregnant people who received onabotulinumtoxinA injection (a population not eligible for inclusion in RCTs) suggest no increased risk to the fetus compared with the general pregnant population.[10–12]

**Table 1: Medications traditionally used for migraine prevention[6]**

| | | | Canadian Headache Society | |
|---|---|---|---|---|
| Drug | Drug class | Target daily dose | Levels of evidence* | Strength of recommendation† |
| Topiramate | Anti-epileptic | 100 mg | High | Strong |
| Propranolol | β-blocker | 80–160 mg | High | Strong |
| Metoprolol | β-blocker | 100–200 mg | High | Strong |
| Amitriptyline | Antidepressant | 10–100 mg | High | Strong |
| Nadolol | β-blocker | 80–160 mg | Moderate | Strong |
| Candesartan | Angiotensin receptor blocker | 16 mg | Moderate | Strong |
| Gabapentin‡ | Antidepressant | 1200–3600 mg | Moderate | Strong |
| Divalproex sodium | Anti-epileptic | 500–1500 mg | High | Weak |
| Flunarizine | Calcium channel blocker | 10 mg | High | Weak |
| Pizotifen | Serotonin antagonist | 1.5–4.0 mg | High | Weak |
| Venlafaxine | Antidepressant | 150 mg | Low | Weak |
| Lisinopril | Angiotensin-converting enzyme inhibitor | 20 mg | Low | Weak |
| Verapamil | Calcium channel blocker | 120–480 mg | Low | Weak |
| OnabotulinumtoxinA (chronic migraine only) | Neurotoxin | 155–195 units | Not applicable | Not applicable |

Note: GRADE = Grading of Recommendations, Assessment, Development and Evaluation.
Adapted with permission from Pringsheim T, Davenport WJ, Mackie G, et al.; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012;39(Suppl 2):S1-59.
*Levels of evidence using the GRADE system: high = the guideline authors are confident that the true effect lies close to the estimate given by the evidence available; moderate = the guideline authors are moderately confident in the effect estimate, but there is a possibility it is substantially different; low = the confidence in the effect estimate is limited. The true effect may be substantially different; very low = the guideline authors have little confidence in the effect estimate.
†Recommendation categories using the GRADE system: strong = benefits clearly outweigh risks and burdens for most patients; weak = the balance between benefits and risks is narrow and there is uncertainty about when it should be used.
‡Considering available data from unpublished negative trials, the efficacy of gabapentin for migraine prevention has been somewhat discredited since the Canadian Headache Society guideline was published.

The greatest barriers to receiving onabotulinumtoxinA are cost and access to a trained administrator. Coverage is available through private insurers and some government drug plans in Canada (Alberta, Ontario and Quebec), but this covers only the cost of the drug, not the administration fee. To qualify for coverage, a patient must have a diagnosis of chronic migraine and have previously failed, been intolerant of, or have a contraindication to at least 2–3 oral preventives from different oral drug classes.

## What are the newer treatments for migraine prevention?

Calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) have recently revolutionized migraine prevention. Four CGRP mAbs, administered subcutaneously or intravenously every month or every 3 months, have been approved in Canada for the prevention of episodic and chronic migraine: erenumab,[13] fremanezumab,[14] galcanezumab[15] and eptinezumab[16] (Table 2). These have several advantages over other medications, including a more convenient dosing schedule, a migraine-specific mechanism of action and more favourable efficacy, safety and tolerability profiles than classic options.[18]

The safety and efficacy of each CGRP mAbs has been evaluated in double-blind RCTs for prevention of both episodic (Appendix 1, Appendix Table 1) and chronic (Appendix 1, Appendix Table 2) migraine. Because the study designs adhered to the Guidelines of the International Headache Society for controlled trials of preventive treatments of chronic migraine in adults, patient demographics and outcome measures were similar. Study participants were adults aged 18–65 years (mean age 40–42 yr, 83%–88% female and 70%–94% white) and had a diagnosis of migraine with or without aura (Appendix 1, Appendix Tables 3 and 4). The primary efficacy outcome was the change from baseline in monthly migraine days, typically measured after a 12-week blinded treatment period. Secondary outcomes included the 50% responder rate (i.e., the proportion of patients achieving at least a 50% reduction from baseline in monthly migraine days), as well as a number of patient-reported outcomes such as migraine-related disability (Migraine Disability Assessment [MIDAS]), functional impairment (Headache Impact Test [HIT-6], Migraine Physical Function Impact Diary [MPFID]) and quality of life (Migraine-Specific Quality of Life [MSQ]).

All 4 CGRP mAbs were more effective than placebo in decreasing the frequency of primary and secondary outcomes for the prevention of episodic (Appendix 1, Appendix Table 1) and chronic (Appendix 1, Appendix Table 2) migraine. Erenumab, galcanezumab and fremanezumab showed a statistically significant treatment effect within 4 weeks of the start of treatment;[19–25] eptinezumab in as soon as 1 day.[26,27] Patient-reported outcome measures were significantly improved with all 4 CGRP mAbs compared with placebo.[19–25] Open-label extension trials showed that efficacy was maintained with all drugs through a minimum of 1 year of treatment.[28–32]

Because the trials described above largely excluded patients who had not responded to treatment with more than 2 drugs, additional double-blind RCTs were conducted to specifically assess efficacy in this patient population.[33–35] The trial for erenumab (LIBERTY; *n* = 246) included patients with episodic migraine who had failed treatments with 2–4 preventive drugs and excluded patients with medication overuse, and the trials for galcanezumab (CONQUER; *n* = 462) and fremanezumab (FOCUS; *n* = 838) included patients with both episodic and chronic migraine who had failed treatment with 2–4 preventive drugs and those with medication overuse (about 50% of study participants) (Appendix 1, Appendix Tables 5 and 6). Compared with placebo, within 1 month, all 3 drugs showed statistically significant reductions in monthly migraine days and use of migraine-specific acute medications, and an increase in the proportion of patients achieving a 50% or higher response rate. Patients on CGRP mAbs had improvement in patient-reported measures of disability, functional impairment and migraine-related quality of life.[33–35] These studies provide strong evidence that the CGRP mAbs are efficacious in patients with migraine who have not responded well to other traditional medications.

**Table 2: New pharmacologic treatments for migraine prevention[13–17]**

| Drug | Indication | Dosing | Discontinuation rate,* % | Injection-site reactions,* % | Constipation,* % | Incidence of ADA,*[17] % |
|---|---|---|---|---|---|---|
| Erenumab[13] | Episodic and chronic migraine | SC injection; 70 mg or 140 mg monthly | 1.3 | 4.5–5.6 | 1.3–3.2 | 2.0–8.0 |
| Galcanezumab[14] | Episodic and chronic migraine | SC injection; 240 mg loading dose, then 120 mg monthly | 1.8 | 10.6–30.3 | 0.7–1.8 | 3.0–12.0 |
| Fremanezumab[15] | Episodic and chronic migraine | SC injection; 225 mg monthly or 675 mg quarterly | 1.7 | 43.0–45.0 | < 1.0 | 0.3–2.0 |
| Eptinezumab[16] | Episodic and chronic migraine | IV infusion; 100 mg or 300 mg quarterly | 1.9 | < 2.0 (infusion-site reactions) | 0.7–1.2 | 16.0–18.0 |

Note: ADA = antidrug antibodies, IV = intravenous, SC = subcutaneous.
*Direct comparisons cannot be made between any of the presented data.

The 4 CGRP mAbs are highly specific to either the CGRP ligands or receptors, do not cross the blood–brain barrier and do not undergo hepatic metabolism or renal clearance, which decreases their potential for adverse effects and drug interactions. They are cleared by the reticuloendothelial system.[18] In the RCTs, all 4 CGRP mAbs showed good safety and tolerability profiles. Severe adverse events were rare and not increased compared with placebo,[19–25] discontinuation rates owing to adverse effects were low (1.3%–1.9%), and injection-site reactions were the most common adverse event.[13–16]

In the postmarketing period, new-onset or worsening hypertension and severe constipation were reported with erenumab, resulting in a new United States Food and Drug Administration label warning.[13] Mild hypertension can occur within 1 week of treatment initiation, and constipation can occur early or late in treatment.[13] Thus, erenumab should be used in caution in patients with a history of hypertension or constipation and all patients treated with erenumab should have periodic blood pressure measurement and should be asked about symptoms of constipation in follow-up.

Immunogenicity and formation of antidrug antibodies have been observed but do not appear to affect safety or efficacy.[17] Calcitonin gene-related peptides play a role in implantation, trophoblast proliferation and invasion, and fetal organogenesis.[36] Therefore, CGRP mAbs should be avoided in people who are pregnant or breastfeeding and should be stopped at least 6 months before planned conception (the half-life is about 1 mo for the CGRP mAbs, and it takes about 5.5 half-lives before the drug is completely cleared from the system). The 4 CGRP mAbs should be used with caution in the cohorts of patients who were excluded from the clinical trials, including patients younger than 18 years or age 65 years and older; patients with substantial hepatic or renal impairment; and patients with a history of substantial cardiovascular or cerebrovascular disease, vascular ischemia or thrombotic events. Longer postmarketing data are needed to characterize drug-specific versus class-specific adverse effects, identify patient factors that may increase the likelihood of developing certain adverse effects, monitor for new harms and determine long-term safety.

Our previous article on treatment of acute migraine discussed use of gepants and mentioned that this drug class may also be used for prevention.[1] Currently, rimegepant and atogepant are approved in the US for prevention of episodic migraine. Health Canada recently approved atogepant for the preventive treatment of episodic migraine in adults. Rimegepant is not available in Canada yet.

## How do CGRP mAbs compare with other drugs used for migraine prevention?

A 2021 meta-analysis indirectly compared the safety and efficacy of the CGRP mAbs with topiramate, which is considered one of the most effective drugs to prevent migraine attacks.[37] The study included data from 13 double-blind RCTs assessing erenumab (3 RCTs), galcanezumab (2 RCTs), fremanezumab (2 RCTs), eptinezumab (1 RCT) and topiramate (5 RCTs) for the prevention of episodic migraine in adults.[37] The efficacy of the CGRP mAbs was comparable to topiramate both for the reduction of mean monthly migraine days (–1.55 d v. –1.11 d, $p = 0.15$) and acute medication days (–1.26 d v. –0.78 d, $p = 0.10$),[37] but topiramate was associated with a higher risk for cognitive-related (risk ratio [RR] 2.21 v. 1.12, $p = 0.03$) and sensory- or pain-related (RR 8.01 v. 0.99, $p < 0.001$) adverse events.[37]

In 2022, a trial (Head-to-Head Study of Erenumab Against Topiramate in Patients with Episodic and Chronic Migraine [HER-MES]) comparing erenumab and topiramate for the prevention of migraine was published.[38] The HER-MES study was a 24-week, randomized, double-blind, placebo-controlled trial conducted in adults ($n = 777$); most patients had episodic migraine (89%) and had not received previous preventive treatment (59%).[38] Participants (mean age 41 yr, 86% female, 99% white) were randomized to treatment with erenumab (70 mg or 140 mg monthly) or topiramate (50–100 mg daily).[38] The primary outcome was the proportion of patients who stopped each drug owing to an adverse event, and the secondary outcome was the proportion of patients who achieved 50% or higher reduction from baseline in monthly migraine days during the last 12 weeks of the study.[38] After 24 weeks, the proportion of patients in the topiramate group who stopped treatment owing to adverse events was almost 4 times higher than in the erenumab group (38.9% v. 10.6%, odds ratio [OR] 0.19, 95% CI 0.13–0.27, $p < 0.001$).[38] Likely as a consequence of the high discontinuation rate, only 31.2% of patients in the topiramate group achieved a 50% or higher reduction in monthly migraine days compared with 55.4% in the erenumab group (OR 2.76, 95% CI 2.06–3.71, $p < 0.001$).[38] Thus, the superior tolerability of erenumab may lead to improved efficacy. Other CGRP mAbs have not yet been the subject of published head-to-head trials.

## How can use of CGRP mAbs be incorporated into clinical practice in Canada?

Currently, CGRP mAbs are substantially more expensive than orally administered treatments for the prevention of migraine.[39] Guidelines from the American Headache Society suggest that treatment with a CGRP mAb is indicated in adults who have a diagnosis of migraine and if they have previously failed to tolerate or had an inadequate response to 2 or more traditional migraine preventive treatments.[2,3] Treatment can be considered successful if the patient experiences a 50% or more reduction in mean monthly migraine days or meaningful clinical improvement (≥ 5-point reduction in MIDAS, HIT-6 or MPFID).[2,3]

Until recently, no Canadian provincial drug plans provided coverage for CGRP mAbs, but fremanezumab now receives public formulary coverage in Ontario, British Columbia, Nova Scotia, New Brunswick, Newfoundland and Labrador, Alberta, Saskatchewan and Quebec, as well as through Veterans Affairs Canada and the Non-Insured Health Benefits Program. The Canadian Agency for Drugs and Technologies in Health has recommended that galcanezumab be reimbursed with conditions by Canada's publicly funded drug plans.[40] The other CGRP mAbs are not currently reimbursed. Both public and private insurers require patients to meet qualifying clinical criteria, typically that a patient has failed treatment with 2–3 oral preventives from

**Table 3: Vitamins and herbal supplements for migraine prevention[6]**

| Compound | Daily dose | Canadian Headache Society: Level of evidence* | Canadian Headache Society: Strength of recommendation† |
|---|---|---|---|
| Magnesium citrate | 600 mg (300 mg twice daily) | Low | Strong |
| Riboflavin | 400 mg (200 mg twice daily) | Low | Strong |
| Coenzyme Q10 | 300 mg (100 mg 3 times daily) | Low | Strong |
| Butterbur‡ | 150 mg (75 mg twice daily) | Moderate | Strong |

Note: GRADE = Grading of Recommendations, Assessment, Development and Evaluation. Adapted with permission from Pringsheim T, Davenport WJ, Mackie G, et al.; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012;39(Suppl 2):S1-59.
*Levels of evidence using the GRADE system: high = the guideline authors are confident that the true effect lies close to the estimate given by the evidence available; moderate = the guideline authors are moderately confident in the effect estimate, but there is a possibility it is substantially different; low = the confidence in the effect estimate is limited. The true effect may be substantially different; very low = the guideline authors have little confidence in the effect estimate.
†Recommendation categories using the GRADE system: strong = benefits clearly outweigh the risks for most patients; weak = the balance between benefits and risks is narrow and there is uncertainty about when it should be used.
‡Only commercially prepared products in which plant carcinogens and hepatotoxic alkaloids have been removed and that have been standardized to contain a minimum of 15% petasins are recommended. Patients should be cautioned against consuming the plant in any other form.

different drug classes. Concurrent use of onabotulinumtoxinA with any of the new CGRP mAbs is not presently covered despite evidence supporting safety and potential additive efficacy of combined treatment.[41–43] The cost to patients for CGRP mAbs who do not have coverage is more than $600 per month.[39]

## Can nonpharmacologic supplements augment the prevention of migraine?

Vitamin and herbal supplements can be used as an adjunct to optimize migraine prevention or as first-line preventive treatment in patients who are hesitant to try prescription medications owing to fear of adverse effects, lack of drug coverage or preference for a more "natural" approach. However, only a few RCTs have assessed their efficacy.[44] Butterbur (2 RCTs), magnesium citrate (4 RCTs), coenzyme Q10 (2 RCTs) and riboflavin (1 RCT) have the most available data; all 4 have been shown to be superior to placebo in reducing migraine frequency and may also reduce migraine duration and severity. Despite relatively low levels of evidence, butterbur, magnesium citrate, riboflavin and coenzyme Q10 are strongly recommended by the Canadian Headache Society as they are well tolerated, inexpensive and easily accessible (Table 3).[44] The Canadian Headache Society cautions clinicians about the risk of hepatotoxicity associated with many formulations of butterbur and advises that only commercially prepared products from which hepatotoxic pyrrolizidine alkaloids have been removed should be used.[45]

**Box 2: Unanswered questions**

- How does the efficacy and safety of onabotulinumtoxinA compare with calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs)?
- What is the efficacy and safety of the concurrent use of gepants and CGRP mAbs with other drugs (e.g., CGRP mAbs and onabotulinumtoxin A; CGRP mAbs and gepants; triptans and gepants)?
- How safe are gepants and CGRP mAbs in specific populations such as older adults, patients with autoimmune diseases and those with moderate-to-high cardiovascular risk factors?
- What is the safety of CGRP mAbs when used for longer than 5 years?

## Conclusion

In this and our related review, we have discussed evidence for both acute and preventive treatment for migraine. Primary care practitioners may consider referral to a neurologist or headache specialist if a patient has features that are concerning for secondary headache, has treatment-refractory migraine, does not respond to 2 or more oral preventive medications, or if the patient is complex (e.g., concern with drug–drug interactions, pregnancy, comorbid neurologic disorders such as stroke, patients who have contraindications to classic migraine treatments and patients who may benefit from onabotulinumtoxinA and nerve blocks). In Box 2, we identify some unanswered questions pertaining to the new treatments in migraine. An approach to the overall treatment of people with migraine is included in our earlier review.[1]

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