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ACUTE AND PROPHYLACTIC TREATMENT OF MIGRAINE: 2023 UPDATE

Introduction

Migraine is a chronic neurological disorder that causes significant disability in patients and has a substantial economic impact in Canada. Effective treatment for migraine will improve our patients' quality of life; additionally, it will reduce the economic burden generated by healthcare visits and employee absenteeism.

The novel treatments in migraine target calcitonin gene-related peptide (CGRP), a neuropeptide which plays a role in the initiation of a migraine attack.[1] Although our current understanding of migraine pathophysiology is incomplete, it is believed to involve the trigeminal nerve and its connections with the cerebral vasculature with nociceptive signals activated through a variety of neuropeptides including CGRP, substance P and nitric oxide.[1]

As a result of an improved understanding of migraine pathophysiology, the past several years have seen the advent of a variety of new therapeutic options in both the acute and prophylactic management of migraine. Although these agents represent additional options in the clinician's arsenal, they have, in addition, introduced challenges in determining their cost-effectiveness. In this review, we provide an update on new acute and prophylactic migraine therapies and how they integrate into current practice from a primary care perspective.

Non-Pharmacological Management

Despite the availability of novel medications, non-pharmacological approaches continue to play a role in migraine management. Patients should be counselled on lifestyle measures they can adopt to help mitigate attacks. This includes adequate sleep hygiene with regular sleep patterns such as sleeping and waking at the same time each day. Regular exercise can also be recommended as a reduced level of activity is associated with more frequent migraines.[2] Obesity has a known association with poor migraine control, including increased frequency and severity which further supports regular low-level physical activity.[2] Finally, supplementation with Vitamin B, CoQ10, magnesium and Vitamin D may confer additional benefit.[3]

Acute Migraine: Therapeutic Approaches

The objective of therapy for acute migraine is to provide a prompt reduction in pain and associated symptoms without recurrence, with minimal need for repeat dosing and minimal or no side effects.[3] All patients with a diagnosis of migraine should be counselled on acute and abortive treatments.[4]

Despite the introduction of new migraine medications, first-line therapies have not changed. For patients with mild-to-moderate attacks, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, and caffeinated analgesic combinations (i.e. acetaminophen and caffeine combination) are recommended.[4,5] The use of triptans with NSAIDs (such as sumatriptan plus naproxen) can be more effective than monotherapy for some patients.[6] For attacks that are more severe (moderate-to-severe), migraine-specific abortive therapies including triptans and small molecule CGRP receptor antagonists (gepants) can be effective **(Figure 1).**[4,7]

Approximately 30% of patients provided a prescription for triptans may have a poor response.[7] Newer therapies such as gepants offer a targeted mechanistic abortive and prophylactic treatment of migraine.[8] Ubrogepant was approved by Health Canada for the acute treatment of migraine in 2022 and rimegepant is pending approval. Considerable evidence has demonstrated that gepants represent efficacious and well-tolerated therapy for acute migraine.[5,9,10] Ubrogepant can be administered at a dose of 50 mg to 100 mg as a single dose with a repeat dose that may be administered if recurrent symptoms persist after two hours (up to a maximum dose of 200 mg/day). Rimegepant can be administered as a single oral 75 mg dose. Both of these agents have been demonstrated to work in patients who have previously failed with or been intolerant to triptans.[11] Both ubrogepant and rimegepant are metabolized by CYP3A4. Drug interactions with agents that are strong CYP3A4 inhibitors (ketoconazole and verapamil) and CYP3A4 inducers (phenytoin) have been observed.[11] Side effects associated with the gepants have been minimal; these include nausea, somnolence and dry month.[12]

Use of prophylactic medications in migraine

The objectives of prophylactic migraine therapy are to reduce the frequency, duration and severity of attacks; improve the response to therapy; reduce the likelihood of escalation to acute migraine; reduce overall disability; and improve function.[4] Patients with both episodic and chronic migraine can benefit from prophylactic medications. Indications to begin prophylactic therapy include both long-lasting migraine headaches that impact the patient's quality of life, and frequent migraines. Prophylactic therapy should be considered if attacks (even if infrequent) interfere with a patient's daily routine, regardless of abortive treatment, and in patients who experience frequent attacks as defined by four or more moderate headaches per month.[5] In addition, patients who experience significant adverse effects with acute treatments can be considered for the administration of a prophylactic agent.[4]

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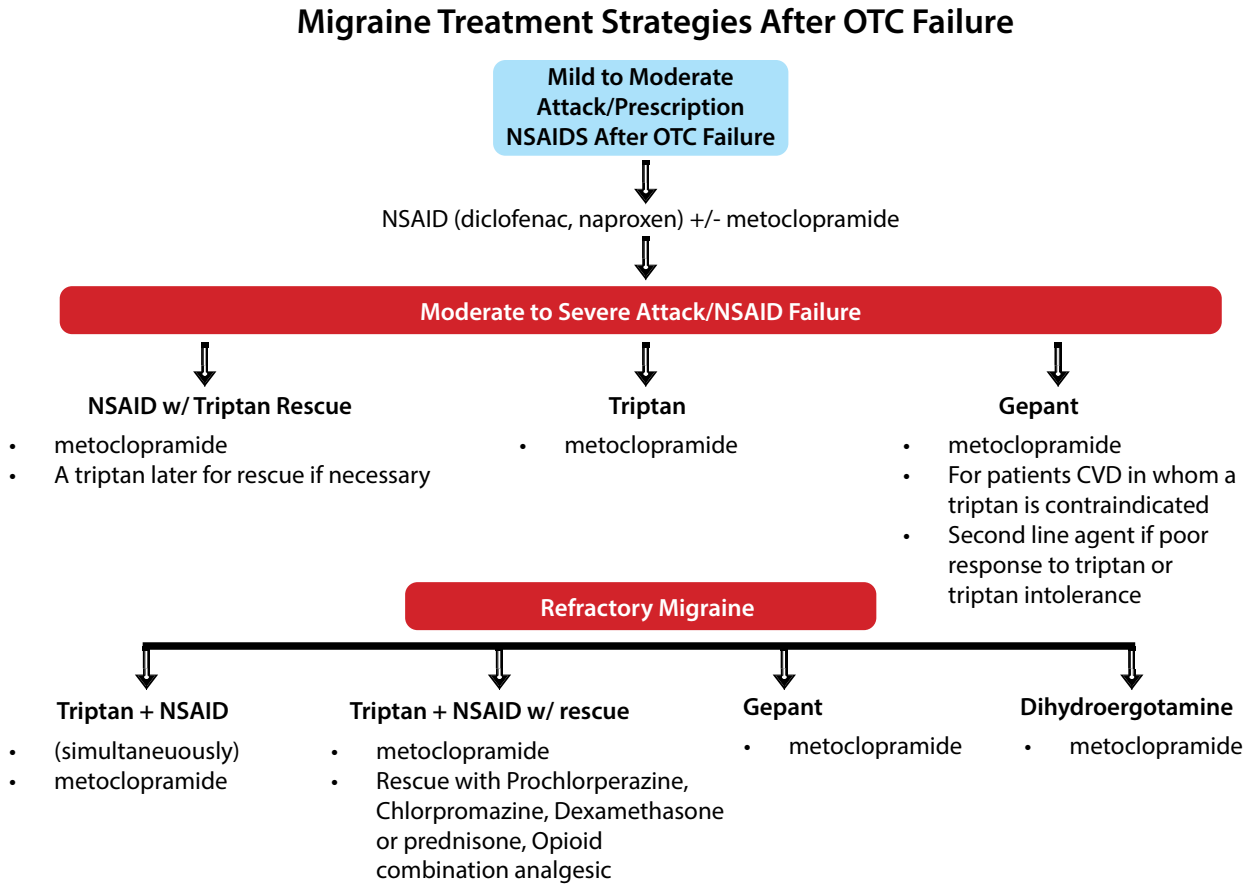

Figure 1: Acute Migraine Treatment Strategies. Adapted from Worthington et al, 2013.[5]

First-line prophylactic therapy is initiated with the traditional oral migraine agents. These should be initiated at low doses and titrated gradually until the desired outcome or maximum medication dosage is achieved. The treating clinician should ensure an adequate trial of the prophylactic medication, typically defined as treatment for a minimum of 12 weeks. If the desired response is not achieved at an adequate dose following 12 weeks, switching to a different prophylactic medication can be considered. Several lines of prophylactic migraine medications are available including antihypertensives (i.e., metoprolol, propranolol, candesartan); antiepileptic agents (i.e., topiramate, valproate); and antidepressants (amitriptyline, venlafaxine)[3,4] **(Figure 2)**. Key patient characteristics should be considered in selecting prophylactic agents, including comorbidities, pregnancy and the potential for pregnancy. In addition, botulinum toxin injections can also be effective prophylaxis for chronic migraine and used in place of or concurrently with other pharmacological agents. Ultimately, patient preference should be strongly considered.

The past several years have seen the introduction of new injectable migraine medications that can be used prophylactically **(Figure 2)**. The CGRP monoclonal antibodies mAbs have shown favourable efficacy in migraine management through targeting of the CGRP ligand or CGRP receptor, and have been shown to be safe in episodic and chronic migraine. They are quite safely tolerated in most patients but significant cardiac history or peripheral vascular disease are relative contraindications. Generally, the evidence from clinical trials suggests an approximately 50% reduction in mean headache days per month for patients treated with these agents.[12] The lack of a need for gradual dose titration, relative quick onset of therapeutic action, a more favourable side effect profile, and favourable tolerability are all advantages of the new CGRP monoclonal antibody treatments. The most reported side effect is injection site reaction (swelling, pain, redness) with subcutaneous administration.[4] Other reported side effects are constipation, upper airway symptoms, sinusitis, and flu-like symptoms. Hypertension has been reported with the CGRP receptor mAbs. Rare cases of Reynaud's phenomenon exacerbations have been reported in the literature in association with CGRP monoclonal treatments.[13]

The gepants are not only effective in aborting migraines; there is now clinical evidence for their use in migraine prophylaxis.[14] Atogepant has been approved by Health Canada for migraine prophylaxis with a recommended dose of 10 mg, 30 mg or 60 mg/day. It is expected that Health Canada approval will be sought for rimegepant for migraine prophylaxis as it has already received FDA approval for this indication. Both atogepant and rimegepant have been shown to be safe and well tolerated even up to a year of use; primary side effects

Drugs with strong recommendations	Quality of evidence
Topiramate	High
Propanolol	High
Metoprolol	High
Amitriptyline	High
Nadolol	Moderate
Gabapentin	Moderate
Candesartan	Moderate
Butterbur	Moderate
Riboflavin	Low
Coenzyme Q10	Low
Magnesium citrate	Low

Drugs with weak recommendations	Quality of evidence
Divalproex	High
Flunarizine	High
Pizotifen	High
Venlafaxine	Low
Verapamil	Low
Lisinopril	Low

New agents not yet included in Canadian guidelines

- Onabotulinum toxin type A (since 2010) is for chronic migraine only, so not in the guidelines for episodic migraine
- Calcitonin Gene Related Peptide (CGRP) antibodies arrived in Canada in 2018
- Atogepant recieved Health Canada approval 2022

Figure 2: Canadian Guidelines: Prophylactic Options Recommended for Use in Episodic Migraine. Adapted from Pringsheim T et al.[3]

include nausea, fatigue and constipation.[14]

As with traditional oral prophylactic migraine medications, clinicians need to monitor and measure patient response to the new CGRP-targeted drugs with similar metrics including days with migraine and headache, migraine-related disability and functional impairment. A 50% or greater reduction in mean headache days per month is a marker of therapeutic benefit.

The primary anticipated barriers for patient access to the gepants and CGRP mAbs are cost and insurance coverage. Currently, the majority of insurance companies and provincial pharmaceutical formularies require a patient to have failed two traditional oral prophylactic medications from two different therapeutic classes before being eligible for a CGRP mAb trial or gepant.

Recommendations for Incorporation of Novel Migraine Therapies into Primary Practice

The Canadian guidelines on the novel migraine therapies have not yet been updated. Based on the current data available for the treatment of acute migraine, the gepants are a good first-line option following NSAID failure in patients with cardiovascular disease (CVD) who cannot use a triptan. The efficacy of gepants is similar to that of triptans, with a superior side effect profile; however, gepants are more expensive. In patients without extended healthcare coverage, gepants can be considered for second-line therapy following triptan failure or intolerance. As clinicians' experience with gepants continues, we may find the superior side effects profile of this medication justifies use as first-line therapy. In migraine prophylaxis, both the CGRP mAbs and the gepants have demonstrated favourable efficacy and side effects profiles. Based on their costs and limitation of access by insurance companies and provincial formularies, we recommend a trial of two traditional oral medications prior to the initiation of these novel therapies.

Conclusion

Migraine is a significant contributor to patient disability and burden of disease globally, including in Canada. Over the past several years, numerous therapies have become available in Canada for both the acute and prophylactic treatment of migraine, including the gepant class of medications, as well as the CGRP mAbs, which are injectable prophylactic agents. Their relative ease of use and favourable side effects profile position them as an excellent option in the treatment of migraine. Potential patient barriers to these medications include cost and health insurance coverage.

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Financial Disclosures

None to report.

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