Clinical pearls for management of migraines

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Migraines are common in patients in Canada, with a prevalence of around 10%.[1] Women are 2 to 3 times more likely than men to have migraines[2] and prevalence peaks in middle life.[3] Evidence suggests that migraines are undertreated in many patients; for example, less than 10% of Canadians with migraines use a triptan[4] and only around 30% of patients who might benefit from medications for migraine prophylaxis receive them.[5]

This article discusses 10 evidence-based clinical pearls for migraine management that may change your practice. These pearls were selected following one-on-one and group education visits on this topic provided by the RxFiles Academic Detailing Program of the University of Saskatchewan to family physicians in the province in 2022.

Ten clinical pearls for managing migraines

Long-acting triptans are also slow-acting triptans. In Canada, 5 fast-onset triptans are available: almotriptan, eletriptan, rizatriptan, sumatriptan, and zolmitriptan. The oral formulations of these triptans have an onset time of 30 to 60 minutes.[6] Two long-acting triptans are also available: frovatriptan and naratriptan. Frovatriptan has an onset time of 2 hours and a half-life of approximately 25 hours.[6] Naratriptan has an onset time of 1 to 3 hours and a half-life of approximately 6 hours.[6]

Waiting more than an hour for a long-acting triptan to take effect is unacceptable to many patients. When treating patients with migraines, treatment success is more likely the sooner the inflammatory cascade can be interrupted. For this reason, naratriptan and frovatriptan may be inferior to fast-acting triptans for the average patient.[7] A potential role for naratriptan or frovatriptan is for patients with difficulty tolerating fast-acting triptans—a slower onset typically means less nausea and other adverse effects. Due to having longer half-lives, frovatriptan and naratriptan also have evidence for twice-daily dosing in the prevention of menstrual migraine (eg, start taking the medication 2 days before menstruation and continue for approximately 6 days).[8]

Taking nonsteroidal anti-inflammatory drugs (NSAIDs) on an empty stomach may increase effectiveness in patients with migraines. Nonsteroidal anti-inflammatory drugs are effective for treatment of acute migraine in around 40% to 50% of patients.[9,10] For many clinicians, "Take your NSAID with food" is standard advice given to patients with chronic pain to reduce stomach upset. However, food delays the onset of NSAIDs—for example, ibuprofen onset time is around 30 minutes on an empty stomach versus 60 minutes with food.[11] In a patient with migraine this can reduce the efficacy of the NSAID.

Prokinetic agents can boost the efficacy of analgesic medications. Prokinetic agents, such as 10 mg of oral domperidone or metoclopramide, can help with the nausea commonly associated with migraines. Evidence suggests that prokinetics may also boost the efficacy of other analgesic medications when administered simultaneously, perhaps by enhancing the absorption of the analgesic. For example, a trial showed that a combination of 1000 mg of acetaminophen and 10 mg of metoclopramide had similar efficacy to 100 mg of oral sumatriptan.[12]

The most efficacious triptan is subcutaneous sumatriptan. Triptans typically have a response rate of around 50% to 60%. Subcutaneous sumatriptan, injected at a dose of 6 mg at the first sign of migraine pain, has a response rate of up to 80%.[13] This is thought to be due to its faster onset than oral options and reliable absorption. As a result, it is a useful option for patients who do not respond to oral triptans. Subcutaneous sumatriptan is delivered by an autoinjector device for ease of patient use. Body sensations (such as pressure, tingling, heaviness, or tightness) and injection site reactions are common.[14] Cost may also be a barrier (a single dose costs around $35).[15]

The risk of serotonin syndrome when combining a triptan and a selective serotonin reuptake inhibitor (SSRI) is low. As highlighted in a 2018 *Canadian Family Physician* article,[16] triptans are unlikely to cause serotonin syndrome. Even when a triptan is combined with an SSRI, the risk of serotonin syndrome may be less than 0.03%.[17] When initiating a triptan in a patient already taking an SSRI, monitor the patient for symptoms of serotonin syndrome such as agitation, delirium, fever, or tachycardia. Conversely, combining a triptan with a monoamine oxidase inhibitor (eg, moclobemide) is an absolute contraindication due to the risk of serotonin syndrome.

Oral calcitonin gene-related peptide (CGRP) receptor blockers (gepants) can be useful when triptans are contraindicated. Calcitonin gene-related peptide is an inflammatory mediator. Gepants are a new class of small molecules that block the CGRP receptor and interrupt the migraine pain cascade. Two gepants are currently approved in Canada: atogepant for migraine prophylaxis and ubrogepant for acute migraines. In the United States, other gepants (rimegepant and zavegepant) have been approved for acute migraines, migraine prophylaxis, or both.

Gepants have some advantages for patients with acute migraines. Unlike triptans, they appear safe for patients with cardiovascular disease.[18] They also have

little to no risk of causing medication overuse headache (which is unsurprising since some are approved for migraine prophylaxis). Disadvantages include a likely lower chance of efficacy than triptans (although data from head-to-head trials are lacking) and cost—a single dose of ubrogepant costs around $20.[15]

Ensure a trial of 8 to 12 weeks at target dose before evaluating the effectiveness of prophylactic medications. There are more than 30 medications and herbal products from various classes that may help with migraine prophylaxis. Some medications are approved only for treating migraines (eg, CGRP antagonists) while some medications are approved for other conditions and used off-label for migraines (eg, metoprolol).

Evidence suggests that the efficacy of most medications for migraine prophylaxis is related to dose and duration of treatment.[19] Titrating doses to target (**Table 1**)[20] and ensuring an adequate trial of 8 to 12 weeks at the target dose before assessing efficacy give the best chance of success. Guidelines suggest a realistic goal of therapy for migraine prophylaxis is a reduction in headache severity or frequency of 50%.[17] One of the best ways to evaluate efficacy is by encouraging patients to use headache diaries, which are freely available from Migraine Canada at **https://migrainecanada.org/diaries**.

Candesartan is effective for migraine prophylaxis. Recent migraine guidance has highlighted the role of select angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in migraine prophylaxis.[5,21] To date, the best-studied agent in this class is candesartan. Data from 2 randomized controlled trials suggest that around 40% of patients taking 16 mg per day of candesartan will have a clinically significant reduction in their number of headache days per month.[22,23]

Table 1. Target doses for selected migraine prophylaxis medications

MEDICATION	DOSE
Propranolol	80-160 mg/day
Metoprolol	100-200 mg/day
Amitriptyline	50-75 mg/day
Nortriptyline	50-75 mg/day
Topiramate	100 mg/day
Candesartan	16 mg/day
Venlafaxine	150 mg/day
Verapamil	240 mg/day
Magnesium	500-600 mg/day
Riboflavin	400 mg/day
Fremanezumab	225 mg/month
Atogepant	10-60 mg/day

Data from Regier et al.[20]

Candesartan for migraine prophylaxis has several advantages. It is typically well tolerated, although it does require monitoring of electrolyte levels, serum creatinine level, and hypotensive symptoms. It is an excellent option for patients who have additional comorbidities such as hypertension, cardiovascular disease, or chronic kidney disease. It is generally inexpensive. However, it may not be as effective as other first-line options such as amitriptyline or metoprolol (although data from head-to-head trials are sparse).

Starting prophylactic medication can help resolve medication overuse headaches. Medication overuse headache accounts for up to 50% of headaches in patients with chronic migraine (ie, 15 or more headache days per month).[24,25] Medication overuse headache is typically associated with using acetaminophen or NSAIDs on more than 14 days per month, using a triptan or opioid on more than 9 days per month, or taking combinations of medications for more than 9 days per month (eg, combination acetaminophen and codeine).[22]

A recent trial examined 3 strategies for resolving medication overuse headache: stopping the offending medication, adding prophylaxis therapy, or both. All 3 approaches were similarly effective, reducing the mean number of days with headaches by 8.5, 10, and 12 days per month, respectively.[26] For patients experiencing medication overuse headache, consider shared decision making to determine which management strategy might work best for them. A medication overuse headache patient booklet for guiding this conversation is available from RxFiles at **https://www.rxfiles.ca/migraine**.

Injectable CGRP antagonists have evidence for treatment-resistant migraine prophylaxis. Injectable CGRP antagonists are biologic antibodies that bind to either CGRP or the CGRP receptor; this new class of migraine therapy arrived on the Canadian market in 2018. Agents such as eptinezumab, erenumab, fremanezumab, and galcanezumab provide effective migraine prophylaxis in approximately 40% of patients with migraine.[18]

Injectable CGRP antagonists are effective for migraine prophylaxis in patients for whom other therapies have failed[27]; most drug plans in Canada provide coverage for these agents after adequate trials of at least 2 oral options. Other advantages include no known drug interactions; dosing is required only every 1 to 3 months (depending on the agent); and there is potential for a rapid onset of action of a few days (although an adequate trial of 3 to 6 months is still encouraged).[28] However, cardiovascular safety is uncertain (postmarketing reports have flagged a risk of developing hypertension)[29] and injection site reactions are common. Medications from this class are expensive, costing approximately $600 per month.[15]

Conclusion

One theme of this article is that when a migraine therapy fails, there is often a solution. The following is a summary of examples of what to try when a therapy does not work:

- When acute treatments fail, try faster-onset options. This may include adding a prokinetic agent to speed up analgesic absorption, switching to a faster-onset triptan or NSAID, ensuring an NSAID is taken on an empty stomach, or using subcutaneous sumatriptan.
- Combining medications for acute migraines can increase efficacy, but monitor the patient closely for medication overuse headache (eg, maximum of 9 medication days per month).
- With so many unique classes of medications available for migraine prophylaxis, few patients have truly "tried everything." Further, before deeming a prophylactic medication ineffective, ensure the patient has done an adequate trial (at a target dose) for an adequate duration (8 to 12 weeks) with consistent documentation (ie, using a headache diary).
- Recent trial evidence (eg, for candesartan and CGRP antagonists) provides new approaches in those for whom traditional therapies have failed.

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