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Original Article

Updated Canadian Headache Society Migraine Prevention Guideline with Systematic Review and Meta-analysis

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ABSTRACT: ***Objective:*** We have updated the migraine prevention guideline of the Canadian Headache Society from 2012, as there are new therapies available, and additionally, we have provided guidelines for the prevention of chronic migraine, which was not addressed in the previous iteration. ***Methods:*** We undertook a systematic review to identify new studies since the last guideline. For studies identified, we performed data extraction and subsequent meta-analyses where possible. We composed a summary of the evidence found and undertook a modified Delphi recommendation process. We provide recommendations for treatments identified and additionally expert guidance on the use of the treatments available in important clinical situations. ***Results:*** We identified 61 studies that were included in this evidence update and identified 16 therapies we focused on. The anti-calcitonin gene-related peptide (CGRP) agents were approved by Health Canada between 2018 and 2024 and provide additional options for episodic and chronic migraine prevention. We also summarize evidence for the use of propranolol, topiramate and onabotulinumtoxinA in addition to anti-CGRP agents as treatments for chronic migraine. We have downgraded topiramate to a weak recommendation for use and gabapentin to a weak recommendation against its use in episodic migraine. We have weakly recommended the use of memantine, levetiracetam, enalapril and melatonin in episodic migraine. ***Conclusion:*** Based on the evidence synthesis, we provide updated recommendations for the prevention of episodic and chronic migraine utilizing treatments available in Canada. We additionally provided expert guidance on their use in clinical situations.

RÉSUMÉ : Mise à jour des lignes directrices de la Société canadienne des céphalées portant sur la prévention de la migraine, revue systématique et méta-analyse. ***Objectif :*** Nous avons mis à jour les lignes directrices portant sur la prévention de la migraine de la Société canadienne des céphalées de 2012 dans la mesure où de nouvelles thérapies sont désormais disponibles. Nous avons également fourni des lignes directrices pour la prévention de la migraine chronique, ce qui n'avait pas été abordée dans l'itération précédente. ***Méthodes :*** Nous avons entrepris une revue systématique afin d'identifier les nouvelles études réalisées depuis la dernière itération. Pour ces nouvelles études, nous avons procédé à l'extraction de données et à des méta-analyses ultérieures lorsque cela était possible. Nous avons aussi rédigé un résumé des preuves trouvées et entrepris un processus modifié de recommandation à l'aide de la méthode Delphi. Nous avons ainsi fourni des recommandations pour les traitements identifiés ainsi que des conseils d'experts au sujet de l'utilisation des traitements disponibles dans le cadre de situations cliniques significatives. ***Résultats :*** Nous avons identifié 61 études qui ont été incluses dans cette mise à jour des preuves. Nous avons en outre identifié 16 thérapies sur lesquelles nous nous sommes concentrés. Les médicaments anti-CGRP ont été approuvés par Santé Canada entre 2018 et 2024 et offrent des options supplémentaires pour la prévention des migraines épisodiques et chroniques. En plus des médicaments anti-CGRP, nous avons également résumé les preuves de l'utilisation du propranolol, du topiramate et de l'onabotulinumtoxinA comme traitements de la migraine chronique. Dans le cas de la migraine épisodique, nous avons rétrogradé le topiramate à une recommandation faible pour son utilisation et la gabapentine à une recommandation faible contre son utilisation. Enfin, nous avons faiblement recommandé l'utilisation de la mémantine, du levétiracétam, de l'énalapril et de la mélatonine en cas de migraine épisodique. ***Conclusion :*** Sur la base de la synthèse des preuves disponibles, nous avons fourni des recommandations actualisées en ce qui

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regarde la prévention de la migraine épisodique et chronique, et ce, en recourant aux traitements disponibles au Canada. Nous avons également fourni des conseils d'experts portant sur leur utilisation dans le cadre de situations cliniques significatives.

Keywords: Migraine; headache; migraine research; guideline

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Introduction

Rationale

Migraine is common, with a worldwide prevalence ranging between 8% and 18%.[3–7] Migraine impacts a person's quality of life not only during the attack but also inter-ictally.[8–14] Migraine is ranked 2nd among all health disorders in terms of years lived with disability by the Global Burden of Disease.[15] Migraine also results in significant direct and indirect costs to society.[14,16]

The Canadian Headache Society (CHS) Guideline for Migraine Prophylaxis was published in 2012.[17] The primary objective of this guideline was to assist the practitioner in choosing an appropriate prophylactic medication for an individual with episodic migraine, based on current evidence in the medical literature and expert consensus.

Since that time, there have been multiple new randomized controlled trials (RCTs) with new agents including onabotulinumtoxinA, the anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs), oral CGRP antagonists (gepants) and other oral therapies. Therefore, the decision was made to update the CHS migraine prophylaxis guidelines for episodic and chronic migraine.

This guideline is divided into two parts. Part 1 consists of evidence-based recommendations.

Part 2 comprises treatment strategies based on expert opinion.

Part 1: Evidence-Based Recommendations

Objectives

The systematic review and pairwise meta-analysis had the objective of synthesizing new randomized clinical trials and further characterizing the preventive treatment response of both old and new migraine preventive therapies in adults.

All available data of relevance to clinicians was summarized, and expert guidance on utilization of therapies for migraine prophylaxis was provided through a consensus process. This guidance is intended for Canadian neurologists and primary care providers to have an approach for managing migraine prevention guided by a systematic synthesis and interpretation of the literature available in 2023.

Methods

Population, intervention, comparator, outcome, study design question

RCTs were identified that involved adults with episodic and chronic migraine, where a treatment was evaluated against a placebo or an accepted intervention.

We aimed to answer the following questions:

1. Have newer therapies identified since the last guidelines shown efficacy and safety in the prevention of episodic and chronic migraine when compared to placebo or active comparators?
2. Is there new evidence, likely to change our previous recommendations, regarding the efficacy and safety of previously identified therapies in the preventive treatment of episodic migraine?

Eligibility criteria

The population included adults ≥18 years of age who met the International Headache Society criteria for episodic or chronic migraine. The criteria could be current or previous versions of International Classification of Headache Disorders (ICHD) criteria; specifically, we allowed ICHD-2, ICHD3 beta and ICHD3.[18–20]

The studies evaluated were prospective, randomized, double-blind, controlled trials (RCT), comparing a treatment to a placebo or to an active control. The active control had to be a medication known to be effective in migraine as evidenced by inclusion in previous guidelines. Both randomized parallel group and cross-over designs were allowed. This guideline is restricted to pharmacologic interventions. Notably, we did not review behavioral interventions and neuro-modulation devices, which also have an evidence base for use in migraine.[21] This could be the subject of a future guideline.

The panel reviewed any new data on interventions reviewed in the previous guideline. Additionally, new pre-defined interventions included onabotulinumtoxinA, anti-CGRP mAbs and oral CGRP antagonists, gepants. If our review identified an intervention not previously defined, it was brought to the Steering Committee for consideration. The following additional interventions were therefore included: memantine, levetiracetam, enalapril and melatonin.

Outcomes

Efficacy outcomes included a reduction in monthly migraine days and a 50% reduction in mean migraine days per month. Where migraine days were not reported, a reduction in headache days was used as a surrogate outcome.

Safety outcomes included percentage of patients reporting adverse events (AEs), serious AEs and withdrawal due to AEs.

Information sources and strategy

A systematic search strategy was developed by an experienced information specialist in consultation with the review team. A second experienced research librarian peer-reviewed the MEDLINE search prior to execution using the PRESS checklist.[22] Using the multifile option and deduplication tool available on the Ovid platform, Ovid MEDLINE® ALL, Embase and Cochrane CENTRAL were searched. The search strategy employed a combination of controlled vocabulary (e.g., "migraine," "calcitonin gene-related peptide") and related key words (e.g., migraine, migraine prevention, anti-CGRP mAbs, erenumab). For additional information on the search and gray literature sources, please see Appendix 1. Articles found outside the main search were identified

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Table 1. Level of evidence in GRADE

Level of evidence	Definition
High	We are confident that the true effect lies close to the estimate given the evidence available
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different
Very low	We have little confidence in the effect estimate

in the Preferred Peporting Items for Systematic Review and Meta-analyses (PRISMA) flow diagram.[23]

Study records

Data management

The search strategy identified abstracts to extract from the databases. Duplicate citations were removed, and the abstracts were imported into Covidence, a Cochrane tool for systematic review management.

Selection process

All abstracts were reviewed independently by two reviewers (IM, SC), and potentially relevant citations were selected for full review. Any disagreements as to whether studies should be included were resolved by discussion. Where multiple publications were associated with an included study, those providing the most recent data and/or unique information regarding outcomes of interest were retained. The process of study selection is described using a PRISMA flow diagram in Appendix 1.

Risk of bias in individual studies

Risk of bias (ROB) assessments were carried out on each study independently by two review team members (IM and SC) using the Cochrane ROB 2 tool. If conflicts could not be resolved by discussion, ML or CS were available to cast a final vote.

Data collection process

Data extraction was performed independently by two reviewers (IM, SC), who compared their findings and reached agreement. Data to be gathered from each study included details regarding publication characteristics, aspects of design, participant enrollment criteria and demographics, setting, interventions compared, outcomes measured and AEs from all study arms.[24] Data was recorded using a standardized worksheet that was piloted and refined at the beginning of the data abstraction process.

Data synthesis

Data synthesis was done by one author (IM), although the data used was extracted independently and verified by two team members (IM and SC). For more details on data synthesis, please consult Appendix 1. We analyzed the doses which showed the best treatment responses, and we reported all the outcomes based on those doses. Meta-analyses were performed using random effects models where possible. We did meta-analyses where there were multiple studies with the same treatments. For all analyses, data for episodic migraine and chronic migraine was analyzed separately. To assess for publication bias, funnel plots and comparison-adjusted funnel plots were planned if sufficient studies were available; however, these were not undertaken because we did not have any treatment with more than 10 studies.[25] Findings from the review are reported based upon updated guidance from the PRISMA.[26]

Confidence in cumulative evidence

A modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to determine confidence in evidence for each outcome. In this process, the evidence was analyzed based on various parameters of ROB (multiple types), consistency, directness, precision and publication bias.[27] This has been the standard for neurology guidelines.[1,28]

Across each intervention analyzed, we summarized all outcomes available from those we have prespecified by building a GRADE summary of finding tables,[27] created using the GRADE profiler (GRADEpro) software.[29] Outcome importance was ranked a priori into the groupings of critical in all outcomes.[30] The quality of evidence for all critical outcomes is reported in Appendix 2, but in this document, we report the lowest quality of evidence for critical outcomes. We identified the quality of evidence as high when we were confident the true effect was close to the estimate given, moderate when we felt that it was somewhat likely we were close to the true effect, low when we were not sure our estimate was close to the true effect and very low when we had little confidence in the effect estimate as we highlight in Table 1.[17,31]

After arriving at the quality of evidence for the evidence base, a modified Delphi consensus process[32] with members of the Steering Committee and the Recommendation Committee consisting of a panel of experts within the CHS was undertaken to provide recommendations, using Welphi. Welphi *is an online survey platform that implements the Delphi method.*[33] *Multiple rounds were circulated to the group until a 70% consensus was achieved.*

A strong recommendation was made when the Recommendation Committee members were confident that the intervention could be used for most patients and that the benefits of therapy outweigh the potential risks. A weak recommendation was made when the Recommendation Committee members were less confident that the desirable effects probably outweighed the undesirable effects. The treatment may be considered in some but may not be appropriate in others, and the consideration may depend on the patient and clinical situation. These categories are highlighted in Table 2.

Results

In the abstract review stage, 4459 studies were reviewed from our search and 3 additional studies as detailed in the PRISMA flow diagram in Appendix 1. A total of 398 studies were excluded, and 442 full-length articles were reviewed. For this review, 381 studies were excluded in the full-text stage, and the reasons for exclusion are detailed in the PRISMA flow diagram in Appendix 1. Finally, 61 studies were included in this evidence update. We outline these below in the text by treatment category, and their ROB is

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Table 2. GRADE recommendation and certainty of evidence explained

Recommendation GRADE	Benefits versus risks clinical implication	Clinical implication
Strong – high quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients in most circumstances
Strong – moderate quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients, but there is a chance the recommendations may change with more research
Strong – low quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients, but there is a good chance the recommendations could change with more research
Weak – high quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances
Weak – moderate quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances, but there is less certainty about when it should be used
Weak – low quality evidence	Benefits are more closely balanced with risks and burdens for many patients	There is considerable uncertainty about when to use this medication

documented in Appendix 3. The meta-analyses and summary of findings tables are outlined in Appendix 2.

Table 3 presents all evidence incorporated into decision-making regarding the quality of evidence, from which panel came up with strength of recommendation.

More details on the systematic review and individual studies are available in Appendix 2. For all the studies, the efficacy outcomes and adverse effects are summarized in Table 2. A summary of the evidence synthesis is also provided, specifically how we arrive at the certainty of evidence and reasons for downgrade for each outcome in Table 3.

Studies were identified by the systematic review across seven different therapeutic categories as follows:

CGRP-blocking agents

Atogepant: We found two studies for episodic migraine[34,35] and one for chronic migraine,[36] and one was found for treatment-resistant migraine patients.[37] For episodic migraine, there was moderate certainty in evidence, and for chronic migraine, a high certainty in evidence.

Eptinezumab: We identified one study for episodic migraine[38] and two for chronic migraine,[39,40] and one was found for treatment-resistant migraine patients.[41] For episodic migraine, there was moderate certainty in evidence and for chronic migraine, a high certainty in evidence.

Erenumab: For the treatment of episodic migraine, we identified five studies,[42–46] and for chronic migraine, two studies.[39,40] One study was found in treatment-resistant episodic migraine.[47] For episodic migraine, there was high certainty in evidence, and for chronic migraine, a high certainty in evidence.

Fremanezumab: For the treatment of episodic migraine, we identified three studies,[48–50] and for chronic migraine, two studies.[51,52] One study was found in treatment-resistant episodic migraine.[53] For episodic migraine, there was moderate certainty in evidence, and for chronic migraine, a high certainty in evidence.

Galcanezumab: For the treatment of episodic migraine, we identified five studies,[54–58] and for chronic migraine, one study.[59] One study was found in treatment-resistant episodic migraine.[60] For episodic migraine, there was moderate certainty in evidence, and for chronic migraine, a high certainty in evidence.

Rimegepant: For the treatment of episodic migraine, we identified one study,[61] and although this study included some patients with chronic migraine, there was no subgroup analysis provided for the primary outcome in this group, and this was overall a small population. This data was of moderate certainty in evidence for episodic migraine patients.

Toxins

OnabotulinumtoxinA: For the treatment of chronic migraine, one study was found,[62] and it provided high certainty in evidence. This chronic migraine study is a pooled study of Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1[63] and PREEMPT 2.[64] We note that PREEMPT 1[64] was negative on its primary outcome of change in headache episodes; however, this is not one of the outcomes we looked for in our review, nor is it a standard outcome in the field; this study was positive on all its secondary outcomes including migraine day reduction, which is one of the primary outcomes we looked for in our systematic review. There is an ongoing study in episodic migraine. The results are pending.[65]

Antihypertensives

Candesartan: One new study in episodic migraine was found,[66] and one study from the previous guidelines was integrated in our analysis.[67] This data provided a moderate certainty of evidence of this medication's efficacy.

Enalapril: One new study was found for this treatment in episodic migraine[68] and provided a very low certainty of evidence of this medication's efficacy.

Propranolol: One new study was found for this treatment in chronic migraine;[69] this was a non-inferiority study with top-iramate. This study provided a moderate certainty of evidence of this medication's efficacy.

Antiepileptics

Gabapentin: One new study was found for this treatment in episodic migraine;[70] this was a negative study. Previous studies reviewed in previous guideline were positive studies,[71,72] but these were less well powered. This study provided a very low certainty of evidence of this medication's lack of efficacy.

Levetiracetam: We found three studies in episodic migraine prevention: two used a placebo comparator[73,74] and one used valproic acid as a comparator.[75] These studies provided low certainty of evidence of this medication's efficacy.

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Table 3. Summary of evidence table

Trial information				Outcomes (from meta-analysis if multiple studies where possible)			
Publication	**Name of study**	**Treatment and comparator**	**N per group**	**MDR vs comparator (95% CI)**	**OR 50%RR (95% CI)**	**RR 50%RR**	**OR AE (95% CI)**
CGRP Blocking Medications							
ATOGEPANT							
Episodic Migraine							
Ailani 2021	ADVANCE phase 3	Atogepant and placebo	222–230	1.2 days lower (0.66 to 1.64)	2.43 (1.19 to 4.97)	1.63 (1.07 to 2.49)	1.19 (0.58 to 2.24)
Goadsby 2020	Phase 2b/3	Atogepant and placebo	183–186				
Chronic Migraine							
Pozo Rosich 2023	PROGRESS	atogepant and placebo	246–256	1.8 days lower (0.8 to 2.9)	1.98 (1.35 to 2.89)	1.58 (1.22 to 2.04)	1.76 (1.24 to 2.50)
EPTINEZUMAB							
Episodic Migraine							
Ashina 2020	PROMISE-1 phase 3	Eptinezumab and placebo	221–223	1.1 days lower (0.54 to 1.68)	2.16 (1.48 to 3.16)	1.51 (1.23 to 1.85)	0.93 (0.64 to 1.35)
Chronic Migraine							
Dodick 2019	Phase 2b	Eptinezumab and placebo	131–134	2.6 days lower (1.79 to 3.41)	2.32 (1.79 to 3.01)	1.52 (1.33 to 1.74)	1.27 (0.98 to 1.63)
Lipton 2020, Silberstein 2020	PROMISE-2 phase 3	eptinezumab and placebo	356–366				
ERENUMAB							
Episodic migraine							
Dodick 2018	ARISE phase 3	Erenumab and placebo	286–291	1.56 days lower (1.19 to 1.93)	2.30 (1.71 to 3.08)	1.64 (1.33 to 2.02)	0.84 (0.71 to 1.00)
Goadsby 2017	STRIVE phase 3	Erenumab and placebo	317–319				
Reuter 2018	LIBERTY	Erenumab and placebo	121–125				
Sakai 2019	Phase 2	Erenumab and placebo	135–137				
Sun 2016	Phase 2	Erenumab and placebo	107–108				
Wang 2021	EMPOWER	Erenumab and placebo	224–338				
Chronic Migaine							
Tepper 2017	Phase 2	Erenumab and placebo	188–282	2.09 days lower (1.22 to 2.95)	1.84 (1.24 to 2.72)	1.48 (1.09 to 2.01)	1.12 (0.76 to 1.65)
Yu 2022	DRAGON	Erenumab and placebo	278–279				
FREMANEZUMAB							
Episodic Migraine							
Bigal 2015	Phase 2b	Fremanezumab and placebo	96–104	2.33 days lower (1.24 to 3.42)	2.99 (1.84 to 4.87)	2.08 (1.41 to 3.08)	1.08 (0.69 to 1.69)
Dodick 2018_2		Fremanezumab and placebo	290–294				
Sakai 2021_2	Phase 2b/3	Fremanezumab and placebo	117–121				
Chronic Migaine							
Sakai 2021	Phase 2b/3	Fremanezumab and placebo	189–191	1.76 days lower (1.10 to 2.43)	2.73 (2.05 to 3.63)	2.11 (1.70 to 2.63)	1.18 (0.86 to 1.61)

(*Continued*)

Table 3. Summary of evidence table (*Continued*)

Trial information				Outcomes (from meta-analysis if multiple studies where possible)			
Publication	**Name of study**	**Treatment and comparator**	**N per group**	**MDR vs comparator (95% CI)**	**OR 50%RR (95% CI)**	**RR 50%RR**	**OR AE (95% CI)**
Silberstein 2017	Phase 3	Fremanezumab and placebo	375–379				
GALCANEZUMAB							
Episodic Migraine							
Hu 2022	PERSIST phase 3	Galcanezumab and placebo	259–261	1.97 days lower (1.29 to 2.65)	2.77 (2.30 to 3.33)	1.74 (1.41 to 2.15)	1.37 (1.01 to 1.84)
Sakai 2020	Phase 2	Galcanezumab and placebo	115–230				
Skljarevski 2018	EVOLVE-2 phase 3	Galcanezumab and placebo	223–461				
Skljarevski 2018_2	Phase 2b	Galcanezumab and placebo	70–137				
Stauffer 2018		Galcanezumab and placebo	213–433				
Chronic Migaine							
Detke 2018	REGAIN phase 3	Galcanezumab and placebo	273–558	2.1 days lower (0.99 to 3.21)	2.02 (1.42 to 2.87)	1.74 (1.32 to 2.29)	1.39 (1.04 to 1.87)
RIMEGEPANT							
Migraine							
Croop 2021	Phase 2/3	Rimegepant and placebo	373–374	0.8 days lower (0.2 to 1.5)	1.38 (1.01 to 1.84)	1.18 (1.00 to 1.40)	1.00 (0.74 to 1.34)
Toxins							
ONABOTULINUM TOXIN							
Chronic Migraine							
Dodick 2010	PREEMPT 1 and 2	Onobotulinum toxin and placebo	688–696	2.0 days lower (1.27 to 2.67)	1.65 (1.25 to 1.92)	1.34 (1.18 to 1.53)	1.55 (1.25 to 1.92)
Anti-hypertensives							
CANDESARTAN							
Episodic Migraine							
Tronvik 2003		Candesartan and placebo	57–57	1.2 days lower	4.00 (2.04 to 7.86)	2.76 (1.66 to 4.60)	NA
Stovner 2014		Candesartan and placebo	64–67	0.58 days lower			
ENALAPRIL							
Migraine							
Sonbolestan 2013		enalapril and placebo	19–21	4.42 days lower	7.72 (1.41 to 42.17)	4.52 (1.13 to 10.08)	NA
PROPRANOLOL							
Chronic Migraine compared to other active							
Chowdhury 2022	TOP-PRO	Propranolol and topiramate	82–93	1.7 days lower (0.39 higher to 3.82 lower)	1.35 (0.64 to 2.87	1.28 (0.70 to 2.34	1.10 (0.59 to 2.05)
Anti-epileptics							

GABAPENTIN							
Migraine							
Silberstein 2013	Phase 2	Gabapentin and placebo	128–134	0.3 days lower (0.60 higher to 1.1 lower)	1.12 (0.72 to 1.74)	1.12 (0.72 to 1.74)	NA
LEVETIRACETAM							
Episodic Migraine							
Verma 2013		Levetiracetam and placebo	32–33	2.25 days lower	7.51 (3.06 to 18.40)	3.31 (1.83 to 6.00)	NA
Sadeghian 2015		Levetiracetam, valproate and placebo	35	4 days lower			
TOPIRAMATE							
Chronic Migraine							
Diener 2007		Topiramate and placebo	27–32	2.3 days lower (0.5 to 4.1)	1.69 (1.07 to 2.68)	1.43 (1.04 to 1.98)	2.65 (1.58 to 4.44)
Silberstein 2007 and Silberstein 2009		Topiramate and placebo	153				
Migraine compared to other active							
Reuter 2022	HERMES	Topiramate and erenumab	388	1.84 days higher (1.25 to 2.43)	0.36 (0.27 to 0.48)	0.56 I0.47 TO 0.67)	3.47 (2.51 to 4.80)
Nutraceuticals							
GINGER							
Episodic migraine							
Martins 2020		Ginger and placebo	53–54	Not significantly different	1.08 (0.45 to 2.58)	1.05 (0.62 to 1.77)	NA
MELATONIN							
Migraine							
Alstadhaug 2010		Melatonin 2 mg and placebo	46	0.80 days lower (2.27 lower to 0.66 higher	2.32 (0.55 to 9.77)	1.72 (0.59 to 4.26)	0.81 (0.40 to 1.64)
Goncalves 2016		Melatonin 3 mg and placebo	59–60				
NMDA Receptor Antagonist							
MEMANTINE							
Migraine							
Noruzzadeh 2016		Memantine and placebo	30	3.47 days lower (1.70 to 5.25)	NA	NA	1.44 (0.46 to 4.53)
Shanmugam 2019		Memantine and placebo	30		5.60 (1.55 to 20.23)	1.66 (1.13 to 3.43)	
Statins							
ATORVASTATIN ACTIVE COMPARATOR OR ADD ON							
Episodic Migraine							
Ganji 2021		Atorvastatin + valproic acid vs placebo + valproic acid	34	2.00 days lower - CI not available	NA	NA	1.61 (0.53 to 4.88)

(*Continued*)

Table 3. Summary of evidence table (*Continued*)

Trial information				Outcomes (from meta-analysis if multiple studies where possible)			
Publication	**Name of study**	**Treatment and comparator**	**N per group**	**MDR vs comparator (95% CI)**	**OR 50%RR (95% CI)**	**RR 50%RR**	**OR AE (95% CI)**
Hesami 2018		Atorvastatin vs valproic acid	30	NA	0.72 (0.28 to 1.86)	0.90 (0.67 to 1.21)	0.27 (0.11 to 0.69)
ROSUVASTATIN ADD ON							
Migraine							
Mzadeh 2020		Rosuvastatin + propranolol vs propranolol	45–55	1.53 days lower - CI not available	NA	NA	NA
SIMVASTATIN							
Migraine							
Beuttner 2015		Simvastatin + vit D vs placebo	28–29	9.80 days lower (13.50 to 6.00)	9.33 (1.06 to 81.77)	7.25 (0.95 to 55.20)	0.40 (0.13 to 1.22)

Trial information	Grade MDR outcome			Grade 50% RR outcome			Grade AE outcome		
Publication	**Grade 2 ROB**	**Certainty**	**Reasons for change**	**Grade 2 ROB**	**Certainty**	**Reasons for change**	**Grade 2 ROB**	**Certainty**	**Reasons for change**
CGRP Blocking Medications									
ATOGEPANT									
Episodic Migraine									
Ailani 2021	Low	High	None	Low	Moderate	Inconsistency - p value significant, high I^2	Low	Moderate	Inconsistency - p value significant, high I^2
Goadsby 2020	Low			Low			Low		
Chronic Migraine									
Pozo Rosich 2023	Low	High	None	Low	High	None	Low	High	None
EPTINEZUMAB									
Episodic Migraine									
Ashina 2020	Low	Moderate	Imprecision	Low	High	None	Low	High	None
Chronic migraine									
Dodick 2019	Low	High	None	Low	High	None	Low	High	None
Lipton 2020, Silberstein 2020	Low			Low			Low		
ERENUMAB									
Episodic Migraine									
Dodick 2018	Low	High	None	Low	High	None	Low	High	None
Goadsby 2017	Low			Low			Low		
Reuter 2018	Low			Low			Low		
Sakai 2019	Low			Low			Low		
Sun 2016	Low			Low			Low		
Wang 2021	Low			Low			Low		

Chronic Migaine									
Tepper 2017	Low	High	None	Low	High	None	Low	High	None
Yu 2022	Low			Low			Low		
FREMANEZUMAB									
Episodic Migraine									
Bigal 2015	Low	High	None	Low	Moderate	Inconsistency - p value significant, high I2	Low	High	None
Dodick 2018_2	Low			Low			Low		
Sakai 2021_2	Low			Low			Low		
Chronic Migaine									
Sakai 2021	Low	High	None	Low	High	None	Low	High	None
Silberstein 2017	Low			Low			Low		
GALCANEZUMAB									
Episodic Migraine									
Hu 2022	Low	Moderate	Inconsistency	Low	High	None	Low	Moderate	Inconsistency
Sakai 2020	Low			Low			Low		
Skljarevski 2018	Low			Low			Low		
Skljarevski 2018_2	Low			NA			Low		
Stauffer 2018	Low			Low			Low		
Chronic Migaine									
Detke 2018	Low	High	None	Low	High	None	Low	High	None
RIMEGEPANT									
Migraine									
Croop 2021	Low	Moderate	Imprecision	Low	Moderate	Imprecision	Low	High	None
Toxins									
ONABOTULINUM TOXIN									
Chronic Migraine									
Dodick 2010	Low	High	None	Low	High	None	Low	High	None
Anti-hypertensives									
CANDESARTAN									
Episodic Migraine									
Tronvik 2003	Low	Moderate	Imprecision	Low	Moderate	Inconsistency - quite high I2			NA
Stovner 2014	Low			Low					
ENALAPRIL									
Migraine									
Sonbolestan 2013	Some concerns	Low	ROB	Some concerns	Very Low	ROB, imprecision	NA		

(*Continued*)

Table 3. Summary of evidence table (*Continued*)

Trial information	Grade MDR outcome			Grade 50% RR outcome			Grade AE outcome		
Publication	**Grade 2 ROB**	**Certainty**	**Reasons for change**	**Grade 2 ROB**	**Certainty**	**Reasons for change**	**Grade 2 ROB**	**Certainty**	**Reasons for change**
PROPRANOLOL									
Chronic Migraine compared to other active									
Chowdhury 2022	Low	Moderate	Indirectness	Low	Moderate	Indirectness	Low	Moderate	Indirectness
Anti-epileptics									
GABAPENTIN									
Migraine									
Silberstein 2013	Low	Very low	Inconsistency with previous studies	Low	Very low	Inconsistency with previous studies	Low	NA	
LEVETIRACETAM									
Episodic Migraine									
Verma 2013	High	Low	ROB	High	Low	ROB			NA
Sadeghian 2015	High			High					
TOPIRAMATE									
Chronic Migraine									
Diener 2007	High	Very low	ROB, imprecision	High	Very low	ROB, imprecision	High	Low	ROB
Silberstein 2007 and Silberstein 2009	High			NA			High		
Migraine compared to other active									
Reuter 2022	Low	High	None	Low	HIgh	None	Low	High	None
Nutraceuticals									
GINGER									
Episodic migraine									
Martins 2020	Low	High	None	Low	High	None	Low		
MELATONIN									
Migraine									
Alstadhaug 2010	Low	Very low	ROB, inconsistency and imprecision	Low	Very low	ROB, inconsistency and imprecision	Low	Moderate	ROB
Goncalves 2016	High			High			High		
NMDA Receptor Antagonist									
MEMANTINE									
Migraine									

Noruzzadeh 2016	Low	Moderate	Imprecision	Low	Moderate	Imprecision	Low	Moderate	Imprecision
Shanmugam 2019	Low			Low			Low		
Statins									
ATORVASTATIN ACTIVE COMPARATOR OR ADD ON									
Episodic Migraine									
Ganji 2021	Low	Low	Imprecision, inconsistency	NA	Very low	Imprecision, inconsistency, ROB	Low	Very low	Imprecision, inconsistency, ROB
Hesami 2018	NA			High			High		
ROSUVASTATIN ADD ON									
Migraine									
Mzadeh 2020	High	Very low	Imprecision, indirectness, ROB	NA	NA	NA	NA	NA	NA
SIMVASTATIN									
Migraine									
Beuttner 2015	Low	Very low	Imprecision, inconsistency, indirectness	Low	Very low	Imprecision, inconsistency, indirectness	Low	Very low	Imprecision, inconsistency, indirectness

Note: N = number; MDR = migraine day reduction; OR 50%RR = odds ratio of 50% response rate; RR 50%RR = relative risk of 50% response rate; OR AE = odds ratio of adverse events; ROB = risk of bias.

Table 4. New recommendations

Recommended for use in episodic migraine		
Drug	**Recommendation strength**	**Quality of evidence**
Atogepant	Strong	Moderate
Eptinezumab	Strong	Moderate
Erenumab	Strong	High
Fremanezumab	Strong	Moderate
Galcanezumab	Strong	Moderate
Candesartan	Strong	Moderate
Topiramate	Weak	Moderate
Rimegepant	Weak	Moderate
Memantine	Weak	Moderate
Levetiracetam	Weak	Low
Enalapril	Weak	Very low
Melatonin	Weak	Very low
Recommended for use in chronic migraine		
Drug	**Recommendation strength**	**Quality of evidence**
Atogepant	Strong	High
Erenumab	Strong	High
Eptinezumab	Strong	High
Fremanezumab	Strong	High
Galcanezumab	Strong	High
OnabotulinumtoxinA	Strong	High
Propranolol	Strong	Moderate
Topiramate	Weak	Very low
Not recommended for use in episodic migraine (DO NOT USE)		
Drug	**Recommendation strength**	**Quality of evidence**
Ginger	Strong	High
Gabapentin	Weak	Very low
Statin alone or add-on	Weak	Very low

Topiramate: There was a new study comparing the use of topiramate to erenumab in episodic migraine[76] and another new study comparing the use of topiramate to amitriptyline in episodic migraine.[77] These studies showed that topiramate is less well tolerated and overall, less effective than erenumab, with a high certainty of evidence. In chronic migraine, there were three publications of two studies;[78–80] these studies overall provided low certainty evidence of medication's efficacy.

Nutraceuticals

Ginger: There was a single study looking at this as a preventive treatment in episodic migraine.[81] This study provided high certainty evidence that the treatment is not effective.

Melatonin: There were two studies looking at this preventive treatment in episodic migraine.[82,83] The study with a low ROB but a lower dose of 2 mg nightly was negative,[82] whereas the study with a high ROB but at a higher dose of 3 mg nightly was a positive study.[83] These studies provided very low certainty of evidence of efficacy of melatonin and raised the possibility of a dose effect.

Table 5. Previous recommendations still in effect

Previous recommendations for episodic migraine in effect from 2012		
Drug	**Recommendation strength**	**Quality of evidence**
Propranolol	Strong	High
Metoprolol	Strong	High
Amitriptyline	Strong	High
Nadolol	Strong	High
Butterbur	Strong	Moderate
Riboflavin	Strong	Moderate
Coenzyme Q10	Strong	Low
Magnesium citrate	Strong	Low
Divalproex	Weak	High
Flunarizine	Weak	HIgh
Pizotifen	Weak	High
Venlafaxine	Weak	Low
Verapamil	Weak	Low
Lisinopril	Weak	Low
Not recommended for use in episodic migraine (DO NOT USE)		
Onabotulinum toxin type A	Strong	High
Feverfew	Strong	Moderate

N-Methyl-D-aspartate (NMDA) receptor antagonist

Memantine: There were two studies looking at this medication for episodic migraine;[84,85] these provided moderate certainty of evidence of efficacy of memantine.

Statins

We identified two studies looking at statin added to another preventive[86,87] and two studies looking at a statin versus placebo[88] or another active comparator.[89] Overall, these studies provided very low certainty of evidence of efficacy of statins alone or as an add-on to another preventive, and additionally, none of the therapies was used in more than a single trial.

By undertaking a Delphi consensus process, the Recommendation Committee arrived at the treatment recommendations outlined below in Table 4. We also provide the previous recommendations from the 2012 guideline that have not been modified in Table 5.

Notably, we have provided new recommendations for CGRP-blocking medications in episodic and chronic migraine that are currently in use, and most of these medications receive a strong recommendation in episodic and chronic migraine. Rimegepant is not currently approved for use in Canada as a preventive treatment but may be in the future. We have given it a weak recommendation, which could change pending future clinical studies. We upgraded candesartan to a strong recommendation for episodic migraine. We downgraded gabapentin to a weak recommendation against its use in episodic migraine. We downgraded topiramate to a weak recommendation for use in episodic migraine. Additionally, the weak recommendation for memantine, levetiracetam, enalapril and melatonin in episodic migraine is new. We additionally made recommendations for propranolol (strong) and topiramate (weak) use in chronic migraine.

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Part 2: Treatment Strategies Based on Expert Consensus

Questions applicable to clinical practice were developed by the Steering Committee. These were presented to the Recommendation Committee as well as to two patient representatives. The questions were discussed, opinions exchanged and consensus obtained.

Questions for consideration in migraine prevention

1. ***Who should receive preventive treatment?***[17]
   a. ***Patients with 4 or more moderate or severe headache days a month not responding to acute medication.***
   b. Patients with 8 or more headache days a month, even when acute medications are effective, as the risk of medication overuse headache (MOH) is increased in this group.
   c. Patients who have migraine attacks with a significant impact on their life, despite using acute medications and trigger management/lifestyle modification strategies. The number of migraine days may be 3 or less in these situations if the impact is severe.
2. ***What should be considered when choosing a migraine preventive drug?*** [17]
   a. Efficacy: What is the confidence in the evidence and expected size of the effect of the drug in reducing migraine frequency?
   b. Drug side effect profile: How safe and well tolerated is the drug?
   c. Comorbid disorders (depression, anxiety, insomnia, obesity, hypertension, history of renal calculi, constipation, vascular disorders).
   d. Patient disability and migraine severity.
   e. Pregnancy planning and appropriate contraception.
   f. Patient preference.
3. ***What constitutes an adequate preventive trial?***
   a. Drugs should be continued at a target dose for at least 2 months for an adequate trial unless side effects make drug discontinuation necessary.[17]
   b. In the case of anti-CGRP mAbs, the majority of patients can be evaluated for response after 3 months. However, especially in patients with a history of treatment-resistant chronic migraine, the improvement might be subtle over the first 3 months but become more apparent and clinically significant over 6 months.[90,91]
   c. In the case of onabotulinumtoxinA, patients should have a minimum of two quarterly injections, and three quarterly injections could be reasonable.[92]
4. ***When should preventive therapy be considered effective?***[17]
   a. Headache diaries are important in evaluating treatment effectiveness, and we recommend patients use one of the mobile applications available or a paper diary.[93,94]
   b. Headache frequency or intensity is reduced by 50% or more, although less reductions of headache frequency may be worthwhile, particularly if the drug is well tolerated.
   c. Reduction in headache intensity and migraine-related disability also need to be considered.[17,95]
      For example:
      (i) Migraine Disability Assessment (MIDAS) Score
         • Reduction of ≥5 points for a baseline score between 11 and 20
         • Reduction of >30% for a baseline score >20
      (ii) Headache Impact Test with 6 items (HIT-6) Score
         • Reduction of ≥5 points
5. ***How long should successful preventive therapy be continued?***[17]

This opinion is from expert consensus, as there are no randomized studies providing clear guidance on the optimal duration of migraine preventive treatments. This broadly generalized approach may not be appropriate, and this may have to be assessed on a case-by-case basis. Longer duration of treatment may be particularly important with patients with a long history of chronic migraine.[96]

While using conventional oral preventive drugs, it is reasonable to consider tapering off medications at 12 months, especially if patients are doing well with a meaningful response to therapy and have reverted to an infrequent episodic pattern of headache (ideally 4–6 headache days) with good control with acute therapies, no risk of medications overuse headache and minimal disability. If headaches or migraine symptoms recur as the dose is decreased or as the drug is discontinued, the dose should be increased again, or the drug be restarted.

For those on newer agents such as onabotulinumtoxinA or anti-CGRP mAbs, discontinuation can also be considered based on patient preference. We recommend this only if there is an episodic pattern of migraine with very minimal disability for a period of at least 12 months. For onabotulinumtoxinA, a proposed method of attempting this is to increase the interval between injections and see if there is no worsening, the treatment can be stopped.[97] There are no long-term safety concerns with onabotulinumtoxinA to warrant discontinuation in patients who want to continue.[98] For anti-CGRP mAbs, this can also be attempted in a similar way with increasing the interval and restarting therapy if there is a worsening of attacks. There is some evidence that stopping anti-CGRP therapies leads to increased attacks, so patients should be warned accordingly.[98,99] There are presently no known safety concerns with use that require stopping these medications after a specific treatment interval,[99] but patients should be monitored for the possibility of new onset hypertension or worsening of existing hypertension.[100–103]

What advice should be given to the patient with medication overuse when prevention is being considered?[17]

a. When preventive therapy is started, patients should be evaluated for the presence of medication overuse and instructed accordingly regarding the appropriate amount of medication to use monthly, and the frequency of acute medication use should also be followed.
b. Evidence suggests that in many cases, a withdrawal may not be necessary and starting preventive therapy alone may be adequate. Still, a withdrawal may be necessary for some patients.[104–106]
c. As opioid and barbiturate-induced MOH is more likely to occur,[107] and in clinical experience may be less likely to respond to prevention, we recommend taper in these situations.[108]

Chronic migraine and overlap with high-frequency episodic migraine (HFEM)

The previous CHS Guideline of 2012 did not address chronic migraine. In the current definition of ICHD3, chronic migraine is currently defined as 15 or more headache days per month, with at least 8 days having migrainous features or response to migraine-specific medications.[19] This definition is somewhat arbitrary,[109] and in fact chronic migraine and HFEM have a lot of similarities as we discuss below.

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The following have been shown to be efficacious in the treatment of chronic migraine: propranolol, topiramate, onabotulinumtoxinA, erenumab, galcanezumab, fremanezumab, eptinezumab and atogepant.

Recent papers have highlighted that the disability burden experienced by migraine patients is driven by the number of migraine days per month and patients with episodic migraine who have 8 or more migraine days per month experience a high degree of disability, similar to chronic migraine patients who have 8 or more migraine days per month.[110,111] The degree of disability does tend to increase with the number of migraine days overall, and severe disability can start even at HFEM.[111,112] This has led to the suggestion that the requirement for 15 or more headache days be dropped from the future ICHD definition of chronic migraine.[110,111]

Special considerations for anti-CGRP therapies

The CGRP-blocking medications are widely used in migraine. However, their place in first-line migraine prevention may not be cost-effective in all instances.[21,113–117] As guideline developers in constrained resource settings, we must consider this aspect.[118,119] Additionally, a network meta-analysis performed by the Institute for Clinical and Economic Review found these medications not to be superior in efficacy to older medications for episodic migraine prevention however using older trials that may not be comparable.[120] For chronic migraine, only comparison possible was with topiramate.[120] Now we have a head-to-head trial of topiramate versus erenumab, this showed the superiority of erenumab both in terms of efficacy and tolerability.[76] These medications are also likely better tolerated in clinical practice when compared to oral preventives.[121–123]

In a Canadian context, Canadian Agency for Drugs and Technologies in Health (CADTH) found the use of these newer treatments first line to not be cost-effective when looking only at direct costs.[113–117] For chronic migraine and likely HFEM, cost-effectiveness on direct costs is likely not the only consideration. The quite high indirect costs are important,[124] along with the high burden of disability of these patients[10,111,125] and the evidence of poor tolerability of older medications in the context of these patients likely needing long-term use.[121,122] The only study in patients where no prior preventive failure was required (the population we are proposing these medications be used in) looking at indirect costs shows that these medications are cost-effective in chronic migraine patients[126] at a threshold likely acceptable in a Canadian setting.[127] In this particular study, their use is not cost-effective in episodic migraine patients, but there was no separate HFEM group.[126]

In patients with moderate-frequency episodic migraine (MFEM) (4 or more migraine days up to 7), we would consider it reasonable to allow the use of these medications after failure or intolerance of two preventive therapies unless data shows this to be cost-effective as first-line use.

In a Canadian context, the indirect and direct costs of chronic migraine and HFEM are similar and significantly higher than low-frequency episodic migraine.[124] We believe it is reasonable to recommend that all patients with HFEM (8 or more migraine days, but less than 15 headache days) with moderate disability and all patients with chronic migraine (8 or more migraine days and 15 or more headache days) get access for first-line use of these medications with other medications, given the high indirect costs incurred by these patients, and because likely the use of these medications leads to savings overall on indirect costs.[128] Should the ICHD incorporate HFEM into the definition of chronic migraine in the future, then we would recommend that the requirement to demonstrate moderate disability be removed.

Indication for treatment with CGRP targeting agents (atogepant, eptinezumab, galcanezumab, erenumab, fremanezumab)

A. MFEM (4–7 MMD)
   (i) Intolerance/contraindication or inadequate response to an 8-week trial of at least two non-CGRP targeting oral preventive therapies.
B. HFEM (8–14 MMD)
   (i) At least moderate disability as shown by one of:
      a. MIDAS score ≥11
      b. HIT-6 score >50
      c. Clinical impression
   (ii) If condition (i) met, no requirement for a trial of non-CGRP oral preventive therapies
C. Chronic migraine
   No requirement for MIDAS, HIT-6 or trial of non-CGRP targeting oral preventive therapies.
   Treatment options include:
   (i) Atogepant, eptinezumab, galcanezumab, erenumab, fremanezumab
   (ii) OnabotulinumtoxinA
   (iii) Propranolol
   (iv) Topiramate

The choice among the different treatment options for episodic and chronic migraine would depend on the healthcare practitioner's assessment of the clinical situation as well as patient preference.

We would like to acknowledge that the possibility of unknown and perhaps serious side effects is present with many new medications up to 10 years after their introduction in up to a third of drugs, and we should remain vigilant with these newer therapies and may revise our recommendations.[129,130]

Further considerations in clinical use:

a. Before starting these therapies, we recommend individualized clinical assessment of vascular disease and risk factors. Generally, anti-CGRP therapies have had a good cardiovascular and cerebrovascular safety profile in patients with no active cardiovascular or cerebrovascular disease,[131,132] but caution should be exercised especially in patients with recent cerebrovascular or cardiovascular events as this population was excluded from clinical studies.
b. There have been reports of worsening and new onset Raynaud's phenomena[130,133–135] and alopecia,[130] and individualized decision-making should be considered.
c. In patients with severe constipation, erenumab and atogepant should be used with caution.[34–36,46,136]
d. There are reports of worsening of hypertension or de novo hypertension in some patients on erenumab and possibly other anti-CGRP therapies.[102]
e. Switching in cases of treatment failure should also be considered, some observational studies indicate that after the failure of one anti-CGRP therapy, it is possible that an individual may respond to another anti-CGRP therapy,[137–139] and there is also the option of class switching from a receptor antibody to a ligand antibody and vice versa.[140,141]

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f. We do recommend that switching between anti-CGRP therapies in cases of side effects or patient preference:

- switching from erenumab or atogepant to a CGRP ligand blocker in cases of constipation
- switching to eptinezumab in cases of injection site reactions
- switching from erenumab to fremanezumab in cases of hypertension[102]
- switching to an antibody with quarterly dosing for patients preferring this option instead of monthly dosing.

Clinical strategies for migraine prevention[17]

1. ***First-time strategy***
   (a) Beta-blocker strategy: Propranolol, nadolol, metoprolol
   (b) Candesartan: With caution in patients of childbearing potential regarding safety issues in pregnancy
   (c) CGRP-blocking strategy: Erenumab *, galcanezumab*, fremanezumab *, eptinezumab *, atogepant * in HFEM (with moderate disability using MIDAS, HIT-6 or clinical impression) and chronic migraine. For the anti-CGRP mAbs, caution should be exercised in patients of child-bearing age.
   (d) Toxin strategy: OnabotulinumtoxinA should be considered first line in chronic migraine (≥8 migraine days per month and ≥15 headache days).
   (e) Tricyclic strategy: Amitriptyline
2. ***Low side effect strategy***
   (a) Candesartan
   (b) Herbal/vitamin/mineral: Magnesium citrate, riboflavin, coenzyme Q10, melatonin
   (c) CGRP-blocking strategy: Erenumab *, galcanezumab*, fremanezumab *, eptinezumab *, atogepant *
   (d) Toxin strategy: OnabotulinumtoxinA in chronic migraine.
3. ***Increased body mass index strategy***
   Topiramate
   Atogepant *
4. ***Hypertension strategy***
   Propranolol, candesartan, nadolol, metoprolol
5. ***Depression/anxiety strategy***
   Amitriptyline, venlafaxine
6. ***Medications that can be considered in certain patients – weak recommendation***
   These treatments are also recommended for use as monotherapy, in addition to the strategies outlined above.
   Levetiracetam* memantine* and rimegepant*, **
   Topiramate, valproic acid, pizotifen, flunarizine and verapamil
   *New treatments added since 2012 CHS Guideline
   ** Not approved for use in Canada
7. ***Refractory patient strategy***[17]
   Refractory migraine is defined as a condition in which symptoms cause significant interference with the ability to function or quality of life despite the use of acute and preventive treatment.[17,113–115] Treatment-resistant migraine is defined as a patient with a failure of properly dosed trials of medications from at least two classes of prophylactic medications.[113–115] In refractory patients, there is ample evidence that anti-CGRP mAbs[41,47,53,60] and atogepant[37] can be effective even after other treatments fail. In all episodic migraine patients having failed other preventive therapies, anti-CGRP mAbs and atogepant should be offered.[41,47,53,60]

Layering of treatment can also be considered in refractory patients. There is a rationale behind the layering of drugs; it is likely that different prophylactic drugs work by different mechanisms, and therefore, the effects of two drugs may be synergistic in reducing migraine frequency. Here are some strategies to consider and rationale:

i. There are observational studies showing increased benefit from using onabotulinumtoxinA and anti-CGRP mAbs or gepants in combination.[116–118] This is reasoned to be due to the combined blockade of Adelta and C fibers CGRP signaling, likely adding synergistic benefit not seen with either therapy alone.[119] Based on expert consensus, we recommend considering layering of anti-CGRP therapies with onabotulinumtoxinA in refractory patients.
ii. There are observational studies on layering of older therapies with anti-CGRP therapies (erenumab), and although these studies are not randomized, there have been encouraging results with improvement in migraine days and acute medication use.[21,22] This strategy is recommended in other recent guidelines.[23] Based on expert consensus, we recommend considering layering of older medications with anti-CGRP therapies in refractory patients, especially in cases where onabotulinumtoxinA can't be used.
iii. There are observational studies showing improvement looking at combinations of older therapies beta-blockers or flunarizine with topiramate[15,16] and also valproate and beta-blockers.[17] There was a negative randomized study looking at combining amitriptyline and topiramate; however, patient impression in this study was in favor of the combination.[18] Combination therapy using older therapies for refractory patients has been commonly recommended by other expert groups as well.[19,20] In cases where newer anti-CGRP or toxin strategies can't be used, we recommend considering layering of older therapies, being cognizant of possible side effects and interactions.
iv. There is also evidence for the use of other strategies such as behavioral interventions and neuro-modulation, but we have not reviewed these strategies for the current guideline.[24]

For further guidance, a review should be consulted,[24] and when possible, these patients should be considered for referral to a headache specialist for management.

These strategies are proposals. If a patient fits better in one strategy versus another, then the best medication should be used.

8. ***Migraine during pregnancy and lactation strategy***[90]
   (a) Migraine drug prophylaxis is best avoided during pregnancy and lactation, if possible. Strategies involving trigger avoidance and lifestyle factors should be considered.
   (b) If migraine drug prophylaxis is necessary during pregnancy or lactation, the best choice is a beta-blocker (propranolol or metoprolol), and if these are contraindicated or ineffective, amitriptyline can be considered.[120,121]
   (c) There is some evidence on the safety of onabotulinumtoxinA in patients exposed to it during pregnancy[122–124] and also lactation.[125] In patients with disabling treatment-resistant chronic migraine, this may be considered, but we caution that this data includes a small number of patients and can't

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Table 6. Recommendations for migraine prevention summary

		Episodic migraine		Chronic migraine				
Class	**Medication**	**Recommendation**	**Certainty**	**Recommendation**	**Certainty**	**Dose**	**Side effects**	**Caution indicated**
CGRP Blocking	Atogepant	↑↑ STRONG	⊕⊕⊕◯ MODERATE	↑↑ STRONG	⊕⊕⊕⊕ HIGH	60 mg PO daily, can also consider for 30 mg daily if side effects	Dizziness, drowsiness, constipation, hypertension and weight loss	Kidney or liver disease, are pregnant or planning on pregnancy or are breastfeeding
	Eptinezumab	↑↑ STRONG	⊕⊕⊕◯ MODERATE	↑↑ STRONG	⊕⊕⊕⊕ HIGH	100 mg IV every 3 months to start, can increase to 300 mg	Nasopharyngitis, nausea and constipation, fatigue, anaphylaxis and possibly as a class effect hypertension	Active or recent cardiovascular, cerebrovascular or peripheral vascular disease including raynaud's, and in those planning on pregnancy in the next 6 months or those who are breastfeeding.
	Erenumab	↑↑ STRONG	⊕⊕⊕⊕ HIGH	↑↑ STRONG	⊕⊕⊕⊕ HIGH	70 mg SC monthly, can increase to 140 mg	Constipation, hypertension, injection site reaction, alopecia, anaphylaxis and muscle cramps	Active or recent cardiovascular, cerebrovascular or peripheral vascular disease including raynaud's, and in those planning on pregnancy in the next 6 months or those who are breastfeeding.
	Fremanezumab	↑↑ STRONG	⊕⊕⊕◯ MODERATE	↑↑ STRONG	⊕⊕⊕⊕ HIGH	225 mg SC monthly or 675 mg SC every 3 months	Constipation, injection site reaction, alopecia, anaphylaxis, hypertensionand muscle cramps	Active or recent cardiovascular, cerebrovascular or peripheral vascular disease including raynaud's, and in those planning on pregnancy in the next 6 months or those who are breastfeeding.
	Galcanezumab	↑↑ STRONG	⊕⊕⊕◯ MODERATE	↑↑ STRONG	⊕⊕⊕⊕ HIGH	240 mg SC first month and 120 mg monthly thereafter	Constipation, injection site reaction, alopecia, hypertension, anaphylaxis and muscle cramps	Active or recent cardiovascular, cerebrovascular or peripheral vascular disease including raynaud's, and in those planning on pregnancy in the next 6 months or those who are breastfeeding.
	Rimegepant	↑ WEAK	⊕⊕⊕◯ MODERATE			75 mg PO every other day	Dizziness, drowsiness, constipation and possibly hypertension	Kidney or liver disease, are pregnant or planning on pregnancy or are breastfeeding
Anti-Epileptics	Levetiracetam	↑ WEAK	⊕⊕◯◯ LOW			250 mg daily up to 1000 mg in two daily divided doses	Dizziness, drowsiness, mood or behavior changes	Those at risk for depression or aggressive behavior
	Topiramate	↑ WEAK DOWNGRADE	⊕⊕⊕◯ MODERATE	↑ WEAK	⊕◯◯◯ VERY LOW	25 mg nightly and increase up to 100 mg in one or two divided doses	Paresthesias, cognitive changes, weight loss, nephrolithiasis and acute angle closure glaucoma	In those planning pregnancy as teratogenic, should not be used in those at risk of kidney stones.
	Valproic acid	↑ WEAK	⊕⊕⊕⊕ HIGH			250 mg daily up to 1000 mg in two daily divided doses	GI discomfort, tremors, fatigue, weight gain, hair thinning, Parkinsonism with long term use, rare hepatic and pancreatic toxicity	Liver disease.
Anti-Depressants	Amitriptyline	↑↑ STRONG	⊕⊕⊕⊕ HIGH			10 mg nightly up to 50 mg nightly	Drowsiness, dry eyes, dry mouth, constipation, weight gain and rarely arrhythmia	Multiple serotonergic medicaitons, cardiac disease or risk of arrythmia, correlation with increased risk of dementia with long term use
	Venlafaxine	↑ WEAK	⊕⊕◯◯ LOW			37.5 mg daily, but increase up to 150 mg daily as this was effective dose only	Nausea, sweating, dry mouth, dizziness, fatigue or insomnia	Multiple serotinergic medicaitons, those at risk for long qt.

Anti-Hypertensives	Candesartan	↑↑ STRONG UPGRADE	⊕⊕⊕◯ MODERATE			8 mg daily and up to 16 mg daily	Hypotension, dizziness	Acute kidney injury or if planning pregnancy
	Enalapril	↑ WEAK	⊕◯◯◯ VERY LOW			2.5 mg daily up to 5 mg twice daily	Hypotension, dizziness, cough and angioedema	Acute kidney injury or if planning pregnancy
	Flunarizine	↑ WEAK	⊕⊕⊕⊕ HIGH			5 mg daily up to 10 mg daily	Sedation, weight gain, depression and extra-pyramidal symptoms	History of depression or ongoin parkinsonism
	Lisinopril	↑ WEAK	⊕⊕◯◯ LOW			10 mg daily up to 20 mg daily	Hypotension, dizziness, cough and angioedema	Acute kidney injury or if planning pregnancy
	Nadolol	↑ WEAK	⊕⊕⊕⊕ HIGH			20 mg daily up to 240 mg/day	Hypotension, dizziness, fatigue and exercise intolerance, erectile dysfunction and rarely depression	Asthma, diabetes, bradycardia
	Propranolol	↑↑ STRONG	⊕⊕⊕⊕ HIGH	↑↑ STRONG	⊕⊕⊕◯ MODERATE	40 mg daily up to 80 mg twice daily	Hypotension, dizziness, fatigue and exercise intolerance, erectile dysfunction and rarely depression	Asthma, diabetes, bradycardia
	Verapamil	↑ WEAK	⊕⊕◯◯ LOW			Start at 40 mg twice or three times daily	Hypotension, dizziness, constipation, lower extremity edema and rarely arrythmia	Bradycardia, arrythmia, avoid use with beta-blockers
Toxins	OnabotulinumtoxinA	↓↓ STRONG	⊕⊕⊕⊕ HIGH	↑↑ STRONG	⊕⊕⊕⊕ HIGH	Start at 155 U every 12 weeks, can increase to 195 units	Worsening headache or neck pain for a few days, cosmetic changes such as brow ptosis, neck or shoulder weakness	Neuromuscular disease such as myasthenia, pregnancy, infection at site.
NMDA Antagonists	Memantine	↑ WEAK	⊕⊕⊕◯ MODERATE			5 mg daily up to 10 mg twice daily	Confusion, dizziness, drowsiness, headache, hallucinations	Ongoing depression or psychiatric disease
Nutraceuticals	Coenzyme Q10	↑↑ STRONG	⊕⊕◯◯ LOW			start at 100 mg per day and up to 300 mg	Abdominal discomfort, insomnia	Pregnancy or if on warfarin
	Magnesium citrate	↑↑ STRONG	⊕⊕◯◯ LOW			100 mg daily up to 400 mg total daily dose	Diarrhea	Renal failure
	Melatonin	↑ WEAK	⊕◯◯◯ VERY LOW			3 mg nightly	Drowsiness	
	Riboflavin	↑↑ STRONG	⊕⊕◯◯ LOW			200 mg up to 400 mg daily dose	Discolored urine	Pregnancy
Serotonergic Antagonists	Pizotifen	↑ WEAK	⊕⊕⊕⊕ HIGH			0.5 mg daily up to 1.5 mg	Drowsiness, dry eyes, dry mouth, constipation, weight gain and rarely arrhythmia	Significant drug interactions (mao inhibitors, glucuronidation)

Note: In dark font are the new updated guidelines, and in light font are previous guideline recommendations, which were not updated.
PO = oral; SC = subcutaneous; IV = intravenous.

ascertain rare AEs. We recommend clinicians consider the use of onabotulinumtoxinA during pregnancy on a case-by-case basis.

(d) There is some limited post-marketing data on the safety of anti-CGRP mAbs and gepants in pregnancy,[126] but this data includes very small numbers of patients and can't ascertain AEs. As CGRP crosses the placenta[127] and is involved in uteroplacental circulation,[21] patients should not actively try to become pregnant until the treatment has been stopped for 6 months for anti-CGRP mAbs. For gepants, it should be sufficient to discontinue for a week before attempting to get pregnant based on the half-life of these agents. Patients should be advised accordingly.

(e) Anti-CGRP mAbs are large molecules and would likely be destroyed in the gastrointestinal tract. They are not likely to be absorbed and transferred into breast milk. They may be safe, but there is a paucity of data available,[129–132] and their use in lactation is currently not recommended. For available gepants, there is no data available on transfer to breast milk and infants, and their use in lactation is currently not recommended. Rimegepant, which is not approved for prevention in Canada, shows very low secretion in breast milk.[133,134]

9. ***Drugs not recommended***

(a) OnabotulinumtoxinA is not recommended for prophylaxis of episodic migraine, but there is an ongoing study, and as such, this recommendation may need to be reconsidered when more is known about the result of this study.[65]

(b) Gabapentin is not recommended for prophylaxis of episodic migraine.

(c) Statins alone or add-on are not recommended for prophylaxis of episodic migraine.

(d) Ginger is not recommended for prophylaxis of episodic migraine.

Discussion

We provide updated guidelines on the treatments to be utilized in the prevention of migraine in Canada. We summarize the recommendations and the use of these medications in Table 6 above.

Specific strengths of our study are a well-conducted search and using GRADE methodology with two reviewers throughout all stages of the process. We opted not to update the previous recommendations and certainty of evidence for medications where there was no new evidence, so as to not duplicate the work already completed by our colleagues. We felt that it was unlikely that we were going to change the recommendations for those therapies. It would be informative and useful for future guidelines to have direct comparative studies looking at older medications such as amitriptyline or propranolol, where we have strong recommendations for their use, and seeing how they fare in non-inferiority studies with newer anti-CGRP therapies. In cases such as topiramate, gabapentin and candesartan, where there was substantial new evidence, we did undertake a revision of the previous studies and upgraded or downgraded previous recommendations.

Conclusions

In summary, we provided a systematic review of all studies in migraine prevention since the previous CHS Guideline in 2012 and significantly for all studies in chronic migraine prevention. Based on the evidence synthesis, we provide updated recommendations for the prevention of episodic and chronic migraine utilizing treatments available in Canada. The anti-CGRP agents provide new treatment options for episodic and chronic migraine. We have strong evidence for their use in all patients and in many cases first line, and we caution against denying them in any treatment-resistant patients. There is evidence for the use of propranolol, topiramate and onabotulinumtoxinA in addition to anti-CGRP agents as treatments for chronic migraine. Given the high burden of disability experienced by these patients as well as the efficacy and favorable side effect profile of the newer treatments, we have recommended that onabotulunumtoxinA and the anti-CGRP agents be considered first line among other treatments for chronic migraine. In the event of a change in the ICHD definition of chronic migraine to capture HFEM, we would make the same recommendation for HFEM. Topiramate has a weak recommendation for use, and gabapentin has a weak recommendation against its use in episodic migraine, so both have been downgraded. There is new evidence on the use of memantine, levetiracetam and enalapril in episodic migraine and in certain situations for the use of melatonin in episodic migraine.

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Competing interests. To minimize conflicts of interest, we have undertaken a process of declaring conflicts using standard declaration sheets[1] and bringing these to the CHS board and the guideline panel, to obtain consensus on how to best collectively eliminate those with unmanageable conflicts[1] and to manage these conflicts in those not deemed unmanageable.[1,2] Detailed auditable documents are held with the guideline panel on rules followed for conflict declarations,[1] ongoing conflicts in panel members and management strategies.

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