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Preventive Treatment Guidelines

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Why new guidelines

- Pringsheim et al 2012 Canadian migraine prevention guidelines are recognized as excellent
- Calcitonin gene-related peptide-blocking treatments are now available in the form of monoclonal antibodies and gepants
- Did not include chronic migraine and its relevant treatments
- There are newer studies of preventive therapies recommended in previous guidelines that may change the previous recommendations

Pringsheim T et al. Can J Neurol Sci. 2012;39(2 Suppl 2):S1-59.

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Steering Committee

<u>Chair:</u> Christie, S MD – Division of Neurology, University of Ottawa

<u>Co-Chair:</u> Medrea, I MD, MSc – Division of Neurology, SUNY Upstate Medical University

Cooper, P MD – Division of Neurology, Division of Neurology, University of Western Ontario

Lagman, M MD – Division of Neurology, Division of Neurology, University of Western Ontario

Sandoe, C MD – Division of Neurology, University of Toronto

Hussain W, MD – Division of Neurology, University of Alberta

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CHS 2024 Update to Guidelines for Migraine Prophylaxis

The guideline is divided into 2 parts:

1. Evidence-based recommendations
2. Treatment strategies based on expert consensus

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Evidence-based Recommendations

CHS 2024 Update to Guidelines for Migraine Prevention

Systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

Moher et al. Epidemiology. 2011;22(1):128.

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Search Strategy

- The 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
- Using the multifile option and deduplication tool available on the Ovid platform, we searched Ovid MEDLINE® ALL, Embase, and Cochrane CENTRAL
- The strategies utilized a combination of controlled vocabulary (e.g., “Migraine Disorders”, “Calcitonin Gene-Related Peptide Receptor Antagonists”,) and keywords (e.g., “migraine”, “CGRP monoclonal antibody”, “migraine prevention medication”)

McGowan et al J Clin Epidemiol. 2016;75:40–6.

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PICO (Population Intervention Comparator Outcome)

We identified randomized controlled trials conducted in adults with episodic and chronic migraine, as defined by the International Classification of Headache Disorders (ICHD)

Interventions included treatment versus placebo or comparator trials when one of the comparators was known to be effective in the treatment of migraine

Outcome parameters included the following:
(a) Reduction in monthly migraine days (alternatively, headache days if migraine days not reported)
(b) 50% responder rates
(c) Safety and tolerability

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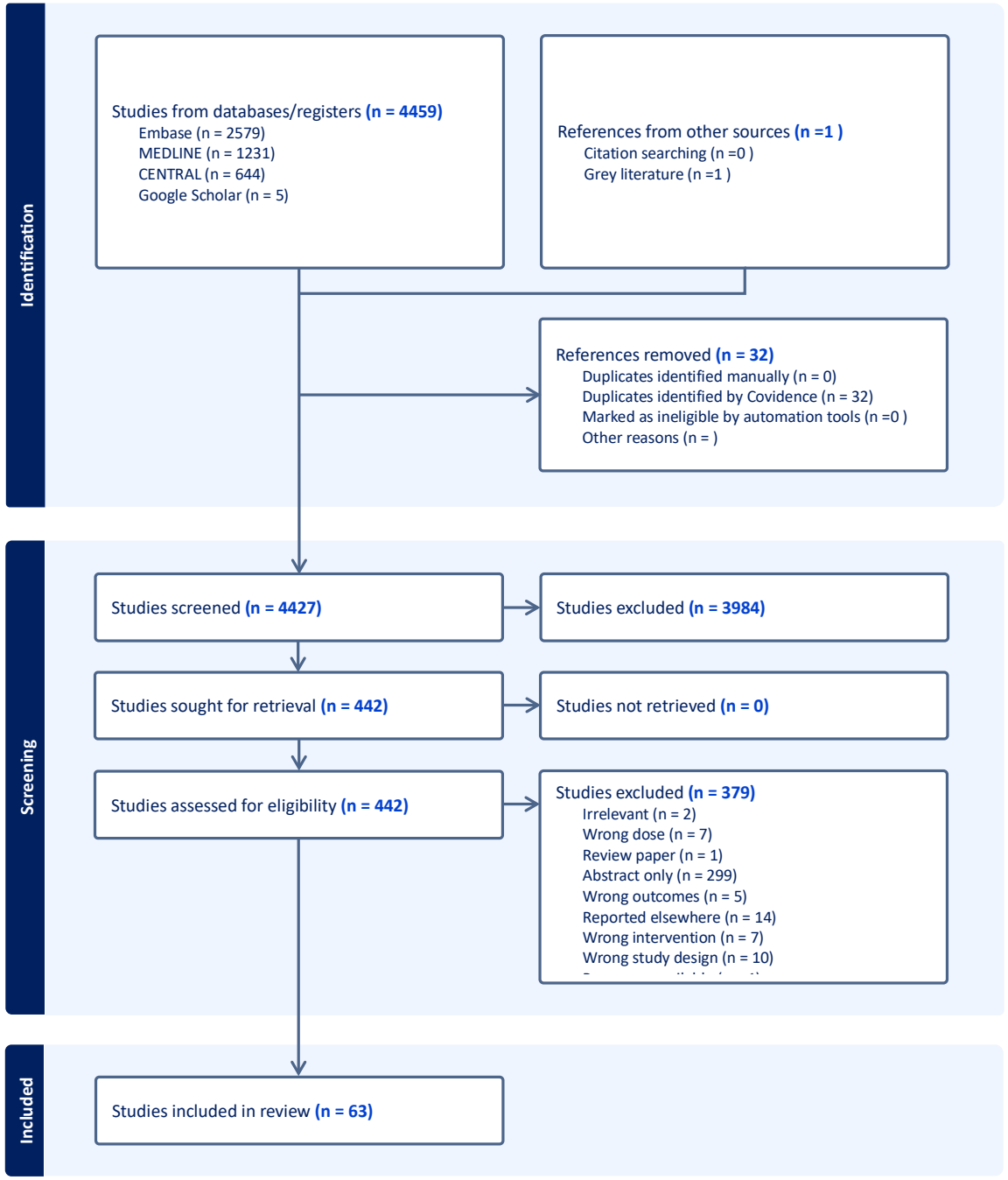
Identification
Studies from databases/registers (n = 4459)
Embase (n = 2579)
MEDLINE (n = 1231)
CENTRAL (n = 644)
Google Scholar (n = 5)
References from other sources (n =1)
Citation searching (n =0)
Grey literature (n =1)
References removed (n = 32)
Duplicates identified manually (n = 0)
Duplicates identified by Covidence (n = 32)
Marked as ineligible by automation tools (n =0)
Other reasons (n =)
Screening
Studies screened (n = 4427)
Studies excluded (n = 3984)
Studies sought for retrieval (n = 442)
Studies not retrieved (n = 0)
Studies assessed for eligibility (n = 442)
Studies excluded (n = 379)
Irrelevant (n = 2)
Wrong dose (n = 7)
Review paper (n = 1)
Abstract only (n = 299)
Wrong outcomes (n = 5)
Reported elsewhere (n = 14)
Wrong intervention (n = 7)
Wrong study design (n = 10)
Included
Studies included in review (n = 63)

From Evidence to Recommendations

- Screening was done in Covidence by two reviewers at the abstract and full-text stage (IM, SC)
- Included studies were analyzed and extracted by two reviewers (IM,SC)
- Cochrane RoB2 tool was used to assess for bias (IM, SC)
- Revman was used to input study data and do meta-analysis (IM)
- Final quality of evidence was determined using the GRADE system (IM)

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From Evidence to Recommendations

- Grade PRO GDT was used to create Summary of Evidence Tables (IM)
- The Summary of Evidence Tables were presented to the Recommendation Committee
- Recommendations were obtained through consensus according to the Dephi method, we used **Welphi** which is an online survey platform
- Consensus was reached at 70% agreement

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Levels of Evidence: GRADE System

Level of Evidence	Definition
High	We are confident that the true effect lies close to the estimate given by the evidence available.
Moderate	We are moderately confident in the effect estimate, but there is a possibility 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.

Guyatt et al. Journal of clinical epidemiology. 2011;64(4):383–94

Balshem H et al. Journal of clinical epidemiology. 2011;64(4):401–6.

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Strength of Recommendation GRADE

STRONG

The Recommendation Committee members are confident that the intervention could be used for most patients, and that the benefits of therapy outweigh the potential risks

WEAK

The Recommendation Committee members are less confident and understand that desirable effects probably outweigh the undesirable effects in most but may not be appropriate in others as this may depend on the patient and clinical situation

Pringsheim T et al. Can J Neurol Sci. 2012;39(2 Suppl 2):S1-59.
Andrews et al. Journal of clinical epidemiology. 2013;66(7):719–25.

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Recommendation Committee

- Suzanne Christie, MD, FRCPC, University of Ottawa
- Ioana Medrea, MD, FRCPC, SUNY Upstate Medical University
- Paul Cooper, MD, FRCPC, University of Western Ontario
- Farnaz Amoozegar, MD, FRCPC, University of Calgary
- Marissa Lagman, MD, FRCP, University of Western Ontario
- Claire Sandoe, MD, FRCPC, University of Toronto
- Ana Bradi, MD, FRCPC, University of Ottawa
- Jessica Dawe, MD, FRCPC, Dalhousie University
- Meagan Guay, MD, FRCPC, McMaster University
- Francois Perreault, MD, FRCPC, University of Montreal
- Stuart Reid, MD, FRCPC, Queen's University
- Candice Todd-Azziz, MD, FRCPC, University of Toronto

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CHS 2024 Update to Guideline For Migraine Prevention

- New recommendations for episodic migraine for CGRP blocking medications, memantine, levetiracetam, melatonin and enalapril

- Updated the recommendations for topiramate-weak for and gabapentin-weak against

- We provide recommendations in chronic migraine for the first time, for CGRP blocking medications and also for onabotulinumtoxinA and topiramate and propranolol

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
Onabotulinum Toxin A	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

Treatment Strategies Based on Expert Consensus

Migraine Prevention

First time strategy

a) Beta blocker: Propranolol, nadolol, metoprolol

b) Candesartan (caution regarding pregnancy)

c) CGRP blocking: Erenumab *, galcanezumab*, fremanezumab *, eptinezumab *, atogepant * in high frequency episodic migraine (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 childbearing age.

d) Toxin strategy: OnabotulinumtoxinA should be considered first line in chronic migraine (≥8 migraine days per month and ≥15 headache days).

e) Tricyclic: Amitriptyline

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Migraine Prevention

Low side effect strategy

(a)Drug: 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.

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Migraine Prevention

Increased body mass index strategy:

- Topiramate, atogepant*

Hypertension Strategy:

- Propranolol, candesartan, nadolol, metoprolol, lisinopril

Depression/anxiety strategy:

- Amitriptyline, venlafaxine

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Migraine Prevention

Medications that can be considered in certain patients – weak recommendation:

- Topiramate, divalproex, pizotifen, flunarizine and verapamil
  - (Rimegepant) – not yet approved for this use in Canada
  - Levetiracetam and memantine

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Chronic Migraine

Propranolol, topiramate

OnabotulinumtoxinA*

Erenumab *, galcanezumab *, fremanezumab *, eptinezumab *

Atogepant *

- CGRP blocking therapies and onabotulinum toxin A should be included amongst first-line treatments in chronic migraine prevention, and for anti CGRP also in high frequency episodic migraine with moderate disability

- The newer agents are at least comparable to propranolol and topiramate in efficacy and to date, have had a favorable side effect profile

- The decision on which preventive therapy to use should be determined by the treating health care provider’s assessment of the clinical situation

- Factors to consider may include tolerance to side effects, body mass index, hypertension and patient preference

Pregnancy and Lactation Strategy

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.

c. There is some evidence on the safety of onabotulinumtoxinA in patients exposed to it during pregnancy, and also lactation. 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 ascertain rare adverse events. We recommend clinicians consider the use of onabotulinumtoxinA during pregnancy on a case-by-case basis.

Mitchell et al, Neurology 2023
Smirnoff et al, Frontiers in Pain Research 2022
Wong et al, The Journal of Headache and Pain 2020

Pregnancy and Lactation Strategy

a. There is some limited post marketing data on the safety of anti-CGRP mAbs and Gepants in pregnancy, but this data includes very small numbers of patients and can't ascertain adverse events. As CGRP crosses the placenta and is involved in uteroplacental circulation, 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 half-life of these agents. Patients should be advised accordingly.

b. Anti-CGRP mAbs are large molecules and would likely be destroyed in the gasto-intestinal tract. They are not likely to be absorbed and transfer into breast milk. They may be safe, but there is a paucity of data available. Use in lactation is currently not recommended. For available gepants there is no data available on transfer to breast milk and infants, and use in lactation is currently not recommended. For rimegepant which is not approved for prevention in Canada, it shows very low secretion in breast milk.

Noseda et al, Cephalalgia 2023
Baker et al, Breastfeeding Medicine 2022

Refractory Patient Strategy

- Refractory migraine is defined when symptoms cause significant interference with the ability to function or quality of life despite use of acute and preventive treatment.
- Treatment resistant migraine is defined as a patient with a failure of properly dosed trials of medications from at least 2 classes of preventive medications.
- Layering of treatment can also be considered in refractory patients. There is a rationale behind layering of drugs, it is likely that different prophylactic drugs work by different mechanisms and therefore the effects of 2 drugs may be synergistic in reducing migraine frequency.

Refractory Patient Strategy

- Combinations of anti-CGRP therapies and onabotulinum toxin have some observational evidence of efficacy, as does addition of older therapies to anti-CGRP therapies. If these strategies are not possible can consider for layering of older medication, being cognizant of possible side effects and interactions.
- 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.

Conclusions

- Newer anti-CGRP medications have added to our arsenal in episodic and chronic migraine
- We have strong evidence for their use in treatment-resistant patients, and in chronic migraine and high-frequency episodic migraine (with moderate disability) patients as first-line amongst other options
- Topiramate has a weak recommendation for and gabapentin has a weak recommendation against in episodic migraine, so both have been downgraded
- There is new evidence on use of memantine and levetiracetam in episodic migraine, and in certain situation for the use of melatonin
- There is evidence for the use of propranolol, topiramate and also onabotulinumtoxinA in addition to anti-CGRP in chronic migraine

Thank you

To the Canadian Headache Society and the chair Dr Christie, our steering committee and all our recommendations panel members!

- Suzanne Christie, MD, FRCPC, University of Ottawa
- Ioana Medrea, MD, FRCPC, SUNY Upstate Medical University
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Medrea I MD MSc ; Cooper P MD; Lagman M MD; Sandoe CH MD MSc; Amoozegar, F MD; Hussain, MW MD ; Bradi AC MD ; Dawe J MD ; Guay M MD ; Perreault F MD ; Reid S MD; Todd C MD MSc ; Skidmore B; Christie SN MD Updated Canadian Headache Society Systematic Review, Pairwise Meta-analysis and Guideline for Migraine Prevention –In Publication, The Canadian Journal of Neurological Sciences

Paper should be available in the next few weeks

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THANK YOU