CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine Prevention
The Guidelines and Beyond

Suzanne Christie, MD, FRCPC
Ioana Medrea, MD, MSc, FRCPC

Disclosures: Suzanne Christie, MD, FRCPC

Consultant/Advisory Boards: Lundbeck, AbbVie, Organon

Speaker: Lundbeck, AbbVie, Teva

Educational Grants (research or education):

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Disclosures: Ioana Medrea, MD, MSc, FRCPC

Consultant/Advisory Boards: Click Therapeutics, Pfizer

Speaker: Lundbeck

Educational Grants (research or education):

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Learning Objectives

Upon completion of this activity, learners will be able to

- Review migraine prevention strategies, first line and beyond
- Go over special situations for migraine prevention such as treatment refractory patients, pregnancy, lactation
- Review of pertinent literature since last search

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

CHS 2024 Updated to Guideline For Migraine Prophylaxis

Evidence-Based Recommendations

- 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

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

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

CHS 2024 Updated to Guideline For Migraine Prophylaxis

Evidence-Based Recommendations

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 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

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 1: Sara

- 21F with past medical history of asthma, uses an inhaler rarely. She is attending university and studying architecture. She works part time in an office job and is studying full time.
- She has 10-12 headache days/mo, worse since starting university. She is missing some school. She finds that rizatriptan 10 mg works well for her and her headache is aborted, but she is using it more often in the last year. All have nausea or light and sound sensitivity and all are at least moderate in intensity and throbbing
- She has no plans to have children, She has an IUD.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 1: Sara

- 21F with past medical history of asthma, uses an inhaler rarely. She is attending university and studying architecture. She works part time in an office job and is studying full time.
- She has 10-12 headache days/mo, worse since starting university. She is missing some school. She finds that rizatriptan 10 mg works well for her and her headache is aborted, but she is using it more often in the last year. All have nausea or light and sound sensitivity and all are at least moderate in intensity and throbbing
- She has no plans to have children, She has an IUD.

What else would you ask this patient?

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 1: Sara

- She has been on no previous migraine preventative treatment
- She is otherwise completely healthy. She is not allergic to any medications is not taking any other medications
- Her mother and sister both have migraine
- She is under considerable stress trying to manage school and working and but does make a point exercising, eating meals regularly trying to maintain good hydration and regular sleep hours

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 1: Sara

- She has been on no previous migraine preventative treatment
- She is otherwise completely healthy. She is not allergic to any medications is not taking any other medications
- Her mother and sister both have migraine
- She is under considerable stress trying to manage school and working and but does make a point exercising, eating meals regularly trying to maintain good hydration and regular sleep hours

What is her diagnosis?

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Spectrum of Migraine

- Low Frequency Episodic Migraine (LFEM): 1-3 MMD
- Moderate Frequency Episodic Migraine (MFEM): 4-7 MMD
- High Frequency Episodic Migraine (HFEM): 8-14 MMD
- Chronic Migraine (CM): ≥ 15 MHD with ≥ 8 MMD

Diagnosis

High-frequency episodic migraine

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Question

Based on the 2024 CHS Migraine Prevention Guidelines, what would you recommend?

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Treatment Strategies Based on Expert Consensus

Migraine Prevention

First Time Strategy

a) Beta blocker: Propranolol, nadolol, metoprolol

b) Tricyclic: Amitriptyline

c) Candesartan (caution regarding pregnancy)

d) 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.

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

* New agents added since 2012

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 1: Sara

- 21F with past medical history of asthma, uses an inhaler rarely. She has 10-12 headache days/mo, worse since starting university. She is missing some school. She finds that rizatriptan 10 mg works well for her and her headache is aborted, but she is using it more often in the last year. She has no plans for children; she has an IUD.
- Assessment: High frequency episodic migraine
- Plan: First line therapy, beta blocker contra-indicated due to asthma. We discuss candesartin and amitriptyline and the steps required to start targeted therapy
- Unfortunately for now insurance is not approving anti-CGRP agents as first line We disagree and will continue to lobby for our patients

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine Prevention

Low Side Effect Strategy

- Drug: Candesartan
- Herbal/vitamin/mineral: magnesium citrate, riboflavin, coenzyme Q10, melatonin*
- CGRP blocking strategy: Erenumab *, galcanezumab*, fremanezumab *, eptinezumab *, atogepant *
- Toxin strategy: OnabotulinumtoxinA in chronic migraine.

* New agents added since 2012

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

Migraine Prevention

Increased Body Mass Index Strategy:

- Topiramate, atogepant*

Hypertension Strategy:

- Propranolol, candesartan, nadolol, metoprolol, lisinopril

Depression/anxiety strategy:

- Amitriptyline, venlafaxine

* New agents added since 2012

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

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

* New agents added since 2012

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

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

* New agents added since 2012

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

Case 1: Sara

- You are seeing Sara 5 years later in clinic. She has been doing well on candesartan, but now is planning pregnancy. She would like you to discuss options with her. At present she has 2-3 headache days/mo. She often finds that she can used OTC Advil as she forgets to carry her rizatriptan around, and most of the time this is enough. She is on candesartan 8 mg.
- Shared decision making is key, for prevention we can try no therapy, and we discuss nerve blocks with lidocaine if headache worsening initially, in most cases should improve as pregnancy goes on.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Pregnancy and Lactation Strategy

- Migraine drug prophylaxis is best avoided during pregnancy and lactation.
- If not possible, the best choice is a beta-blocker (propranolol or metoprolol) and if these are contraindicated or ineffective, amitriptyline can be considered.
- There is some evidence on the safety of onabotulinumtoxin A in patients exposed to it during pregnancy
- Allergan Global Safety Database: prevalence rate of major fetal defects among live births is consistent with the rates reported in the general population
- Lactation: Large molecule, protein bound, makes transfer to breast milk unlikely or in very low concentration
- Lack of robust large-scale prospective data for pregnancy and lactation
- We recommend the use of Onabotulinum toxin A in pregnancy and lactation on a case-by-case basis

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285
Brin et al, Neurology 2023
Smirnoff et al, Frontiers in Pain Research 2022
Wong et al, The Journal of Headache and Pain 2020

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Pregnancy and Lactation Strategy

- 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
- 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
- Anti-CGRP mAbs are large molecules and likely little to no transfer to breast milk
- Would likely be destroyed in the infant gastrointestinal tract.
- 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.

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285 Noseda et al, Cephalalgia 2023 Baker et al, Breastfeeding Medicine 2022

CANADIAN HEADACHE CONFERENCE COAST TO COAST

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.

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

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.

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

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

Medrea et al, CJNS(2025), 52, 450–472 doi:10.1017/cjn.2024.285

CANADIAN HEADACHE CONFERENCE COAST TO COAST

New and Not Included Studies

Methodology:

– updated search from guidelines to find new studies since then on Medline and Embase

- Since we focused on medication treatments for guideline, additionally looked at certain studies we did not look at in our previous search
- This is not an inclusive list; it is a summary of what was deemed most of interest

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Fremanezumab and Co-morbid Depression

JAMA Neurology

RCT: Fremanezumab for the Treatment of Patients With Migraine and Comorbid Major Depressive Disorder

POPULATION

43 Males, 310 Females

Adults with episodic or chronic migraine and comorbid major depressive disorder

42.9 (SD, 12.3) y

INTERVENTION

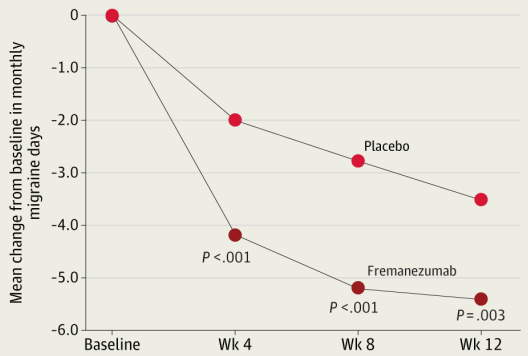
353 Patients randomized

175 Fremanezumab
225 mg monthly via subcutaneous injection

178 Placebo
Matched subcutaneous placebo injection

FINDINGS

Treatment with fremanezumab resulted in significant reductions over placebo in monthly migraine days



Mean change from baseline in MMD during the 12-wk double-blind period
Fremanezumab: -5.1; 95% CI, -6.09 to -4.13; *P* <.001
Placebo: -2.9; 95% CI, -3.89 to -1.96; *P* <.001

SETTINGS / LOCATIONS

55 Centers across 12 countries

PRIMARY OUTCOME

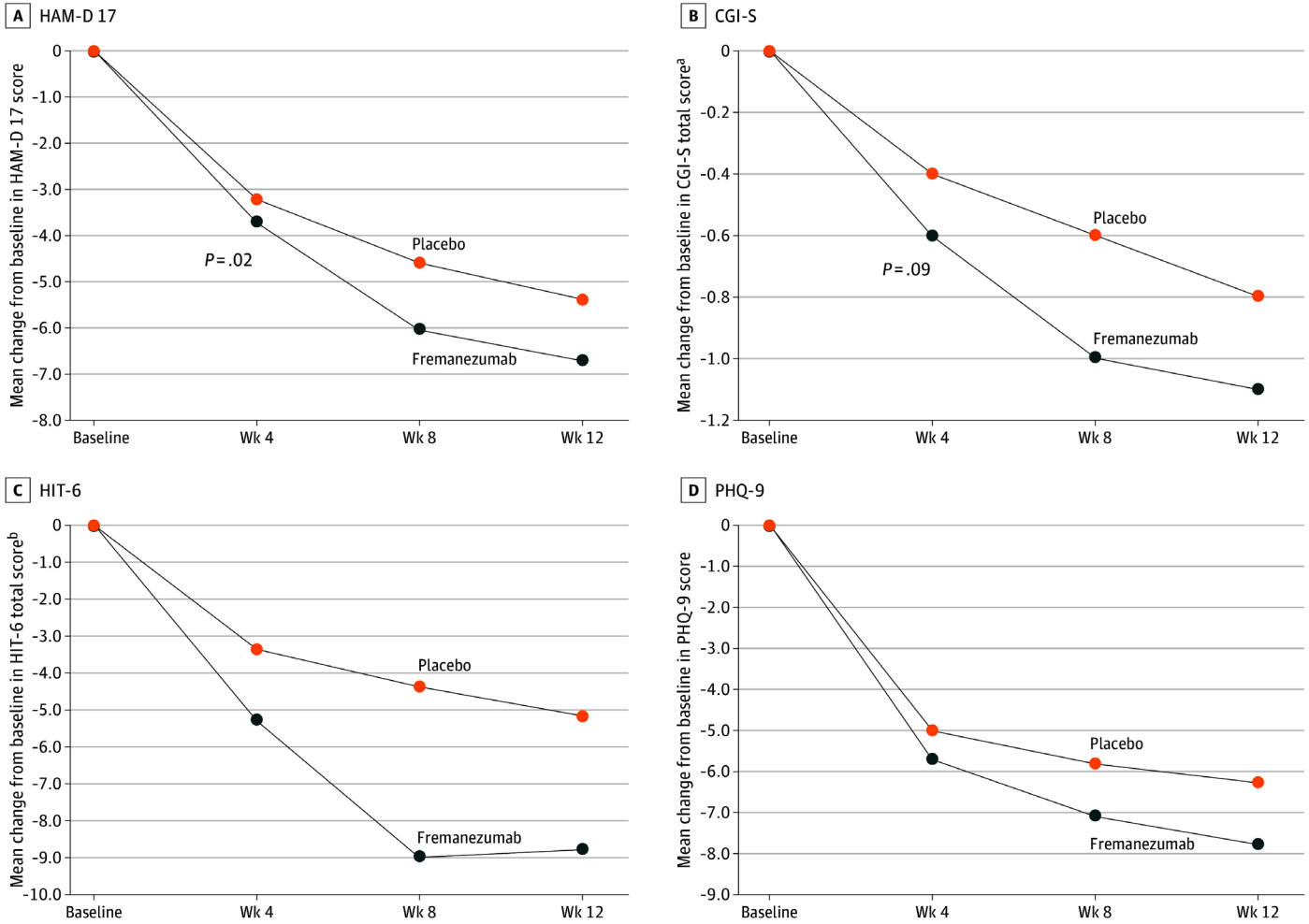
Mean change from baseline in monthly migraine days (MMD) during the 12-week double-blind period in adults with episodic or chronic migraine and major depressive disorder

Lipton RB, Ramirez Campos V, Roth-Ben Arie Z, et al. Fremanezumab for the treatment of patients with migraine and comorbid major depressive disorder: the UNITE randomized clinical trial. *JAMA Neurol.* Published online May 5, 2025. doi:10.1001/jamaneurol.2025.0806

Lipton RB, JAMA Neurol. 2025 Jun 1;82(6):560-569.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

CGRP and Depression? Future Directions



Lipton RB, JAMA Neurol. 2025 Jun 1;82(6):560-569.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Challenge-Mig – Head to Head Trial of Galcanezumab and Rimegepant in Episodic Migraine Prevention

Rimegepant is not approved for migraine prevention in Canada yet. It is approved for episodic migraine prevention in the USA.

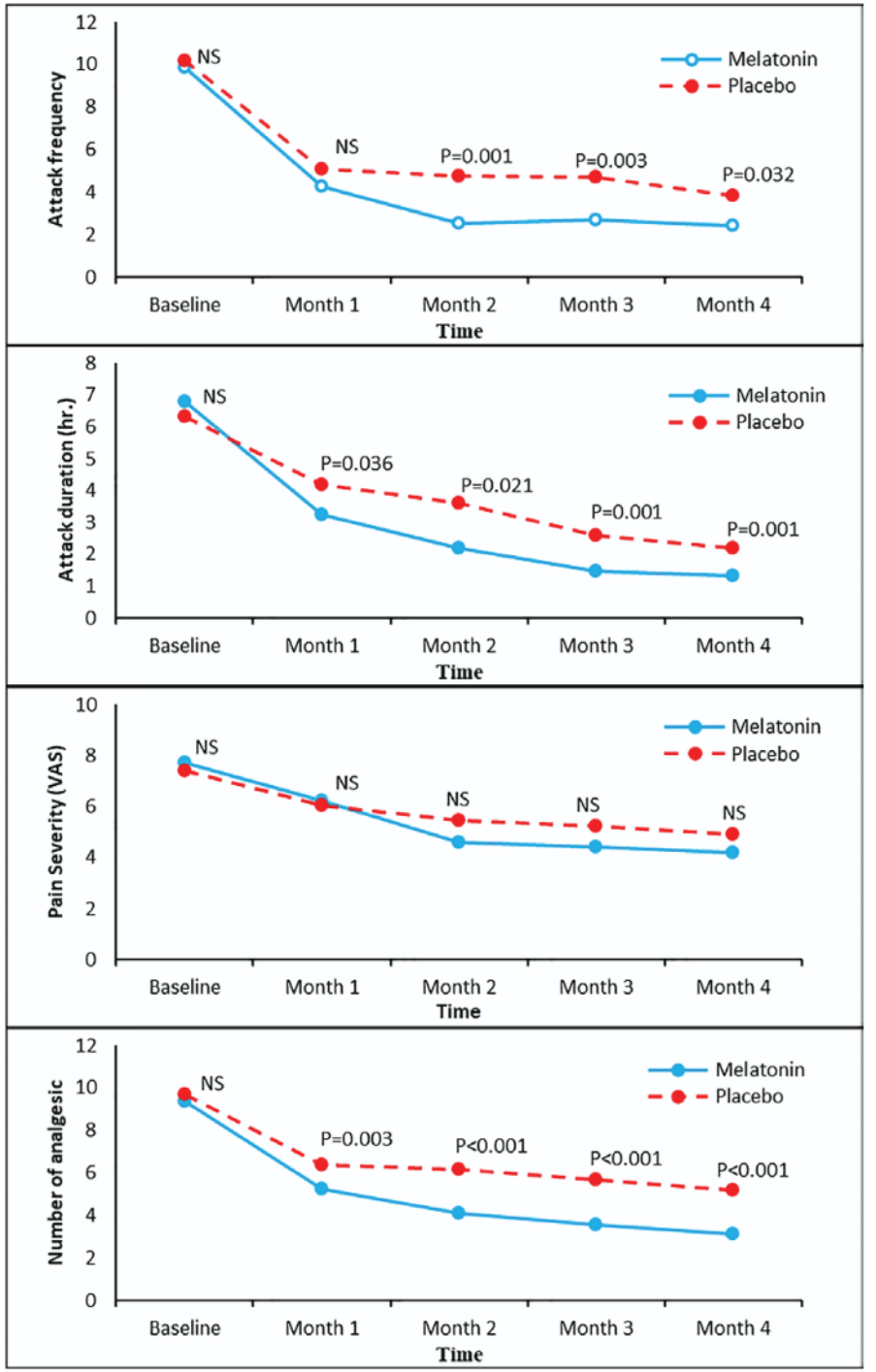
Endpoint	Treatment[a]	*N*	% response rate (SE)/LSMean change from baseline (SE)	Odds ratio/LSMean change difference (95% CI)[b]
Primary endpoint: ≥ 50% response[c]	Galcanezumab	269	62.0 (2.0)	1.1 (0.8, 1.4)[d]
	Rimegepant	284	61.0 (2.0)	
Key secondary endpoints[e]				
Number of monthly migraine headache days[f]	Galcanezumab	269	– 4.8 (0.17)	– 0.4 (– 0.8, 0.1)
	Rimegepant	284	– 4.4 (0.16)	
≥ 75% response[c]	Galcanezumab	269	37.0 (2.0)	1.2 (0.9, 1.6)
	Rimegepant	284	33.0 (2.0)	
Number of monthly migraine headache days at month 3[g]	Galcanezumab	249	– 5.1 (0.2)	– 0.2 (– 0.7, 0.4)
	Rimegepant	259	– 4.9 (0.2)	

Schwedt TJ et al Journal of the Neurological Sciences. 2023 Dec 1;455.

CANADIAN HEADACHE CONFERENCE COAST TO COAST

Melatonin – New study

- Dose of 3 mg nightly versus placebo
- Significant difference in headache attacks was not maintained past month 4, but other measures were.
- Again, melatonin may be useful.



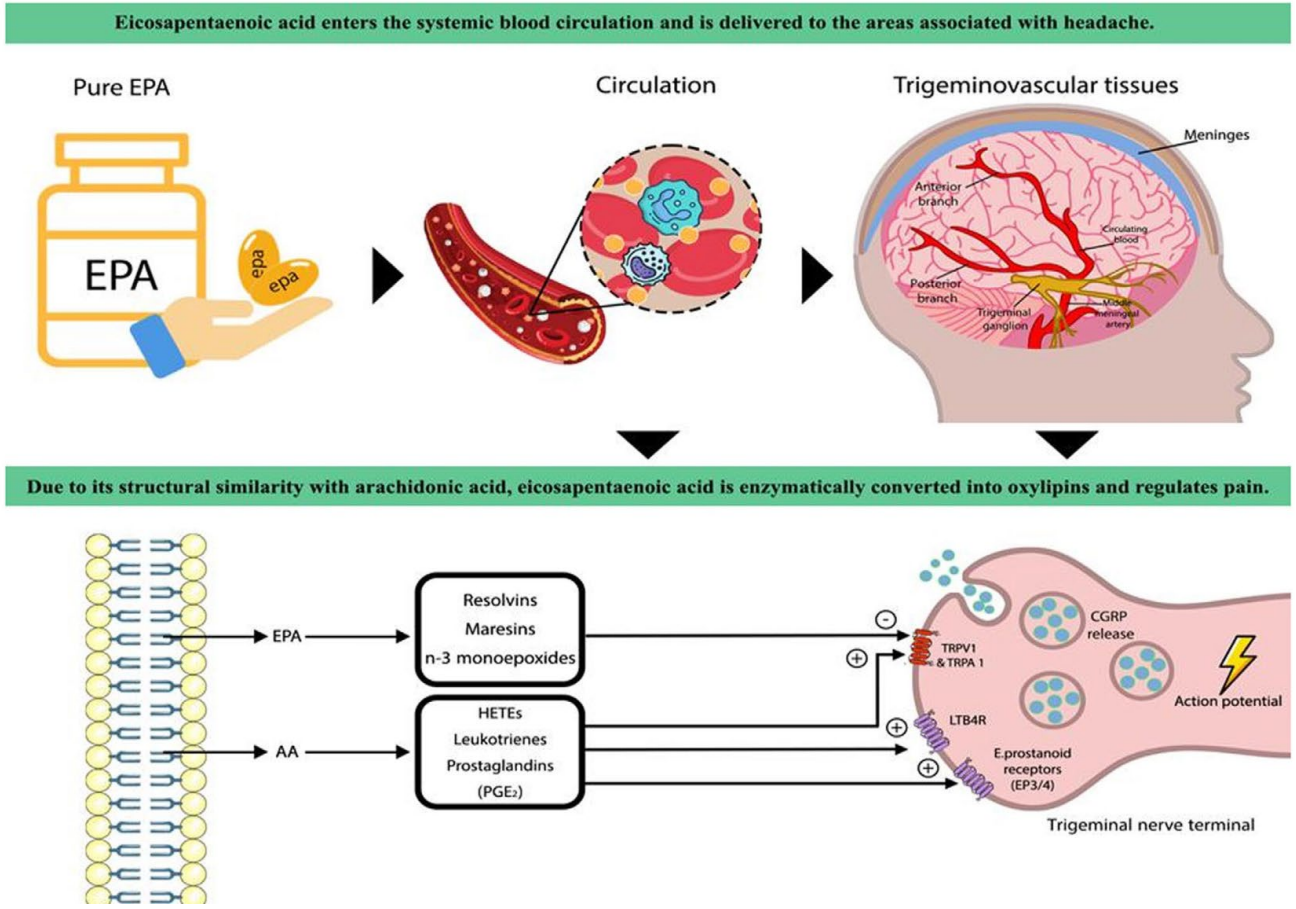
Mehramiri, et al 2024. *Iranian Journal of Medical Sciences*, *49*(5), p.313.

Supplements – Eicosapentaenoic Acid in EM and CM

Eicosapentaenoic acid (EPA), is a polyunsaturated fatty acid (PUFA) currently utilized in clinical practice for cardiovascular risk reduction and hypertriglyceridemia.

EPA can supplant arachidonic acid in inflammatory pathways, generating anti-inflammatory mediators instead of inflammatory molecules.

Within pain processing pathways, EPA acts as a precursor for synthesizing oxylipins with antinociceptive properties, such as resolvins. These oxylipins activate G-protein coupled receptors and transient receptor potential, thereby modulating trigeminal nerve activation and localized release of calcitonin gene-related peptide.



Mohammadnezhad et al (2025). *Headache: The Journal of Head and Face Pain.*, *65*(1), 153–163.

Supplements – Eicosapentaenoic Acid in CM

- Patients were kept on stable preventive therapy and were started on 1000 mg EPA twice daily or placebo.
- Augmenting the treatment regimen with 2000 mg/day of EPA alongside standard prophylactic pharmacotherapy exhibits
- Notable improvements in CM attacks, MHD, and overall HRQoL.
  Medication was overall well tolerated with gastrointestinal upset, such as nausea and vomiting, being the primary AE reported.

MHD, mean (SD)				
Follow-up	Baseline	18.66 (3.80)	17.60 (3.61)	0.270
	Week 4	11.26 (3.26)	14.83 (3.14)	**<0.001**
	Week 8	8.90 (3.36)	13.0 (3.79)	**<0.001**
	Mean difference	−9.76 (4.15)	−4.60 (4.87)	**<0.001**

Mohammadnezhad et al (2025). *Headache: The Journal of Head and Face Pain.*, *65*(1), 153–163.

CANADIAN HEADACHE CONFERENCE COAST TO COAST

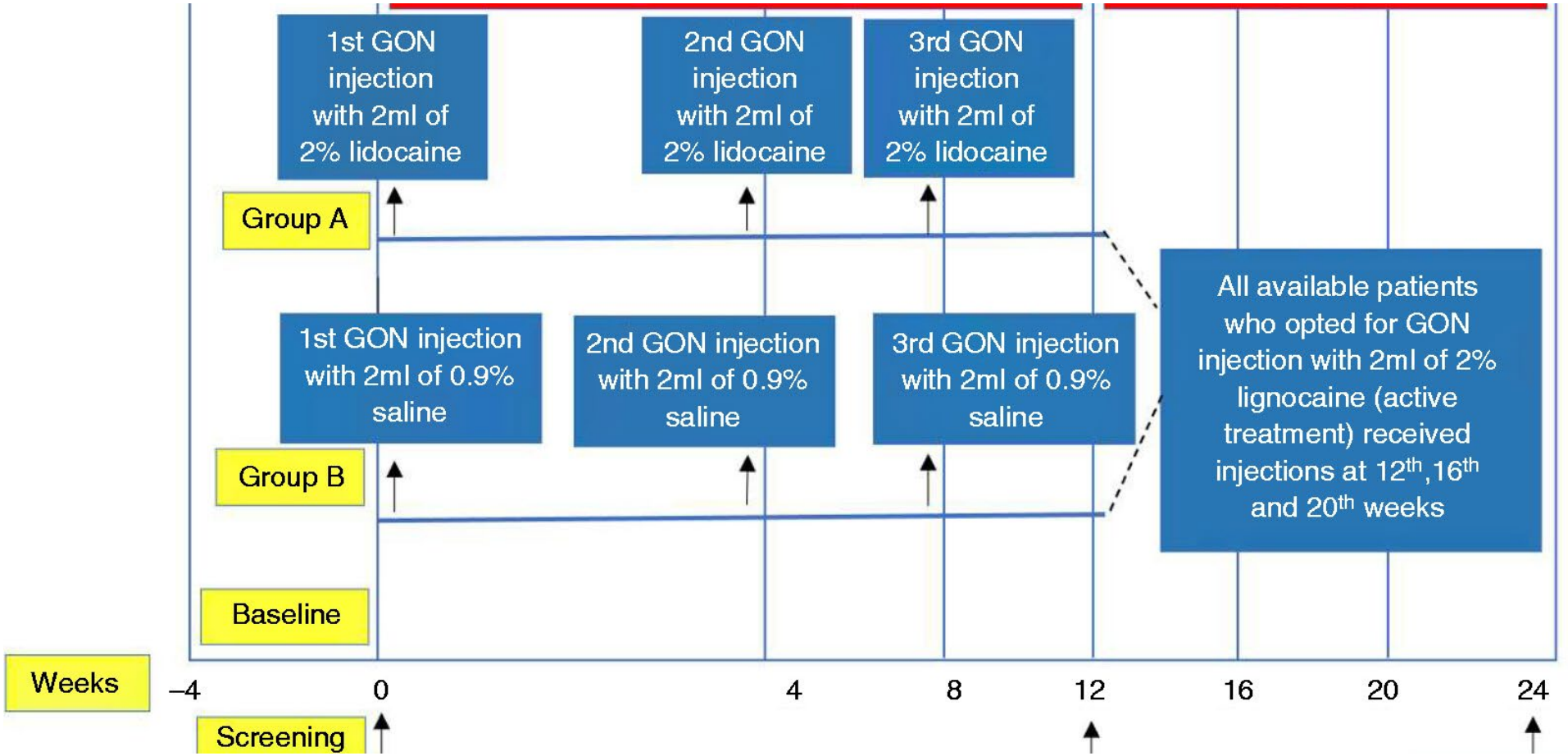
Supplements – Eicosapentaenoic Acid in EM

- Patients were started on 900 mg EPA twice daily or placebo.
- Medication was overall well tolerated . In the EPA group, three participants (8.5 %) reported the following AEs: eructations (n = 1, 2.85 %), nausea (n = 1, 2.85 %), and dyspepsia (n = 1, 2.85 %). Meanwhile, in the placebo group, two participants (5.7 %) reported the following AEs: eructations (n = 1, 2.85 %) and diarrhea (n = 1, 2.85 %).
- All AEs were mild and self-limiting, and no participants withdrew from the study because of intolerable AEs. There were no discernible between-group differences in the occurrence of AEs.

	Placebo				EPA				Change (△After-Before)			
	Before	After	Statistic	*P* value	Before	After	Statistic	*P* value	Placebo	EPA	Statistic	*P* value
All												
Migraine frequency (days/month)	6.7 ± 4.6	6.1 ± 3.5	t = -0.95; DF = 34	0.347	7.4 ± 5.0	3.0 ± 2.0	t = -5.08; DF = 34	< 0.0001	−0.6 ± 3.5	−4.4 ± 5.1	t = 3.63; DF = 68	0.001
Frequency of acute headache medication usage (days/month)	3.5 ± 3.2	3.6 ± 3.3	t = 0.15; DF = 34	0.884	2.9 ± 3.2	1.6 ± 1.7	t = -2.61; DF = 34	0.013	0.1 ± 2.3	−1.3 ± 3.0	t = 2.16; DF = 68	0.035
Headache severity (VAS score)	5.3 ± 1.6	5.3 ± 1.8	t = -0.08; DF = 34	0.940	5.5 ± 2.0	4.2 ± 2.6	t = -3.09; DF = 34	0.004	0.0 ± 2.2	−1.3 ± 2.4	t = 2.22; DF = 68	0.030
PSQI score 《	5.7 ± 3.1	5.9 ± 3.3	t = 0.35; DF = 34	0.731	6.6 ± 3.3	5.5 ± 3.0	t = -1.63; DF = 34	0.113	0.2 ± 3.9	−1.1 ± 4.0	t = 1.4; DF = 68	0.166
MIDAS score	15.3 ± 11.0	17.9 ± 16.7	t = 0.77; DF = 34	0.448	17.9 ± 17.4	4.8 ± 7.1	t = -4.8; DF = 34	<0.0001	2.6 ± 20.2	−13.1 ± 16.2	t = 3.59; DF = 68	0.001

Hsueh-Fang Wang et al Brain, Behavior, and Immunity, Volume 118, 2024, Pages 459-467

Occipital Nerve Blocks and Migraine Prevention – CM

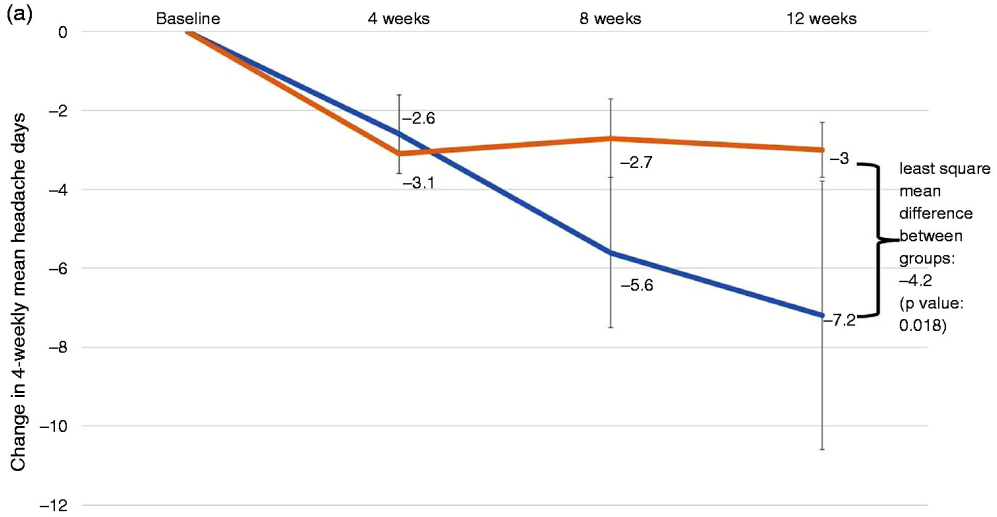


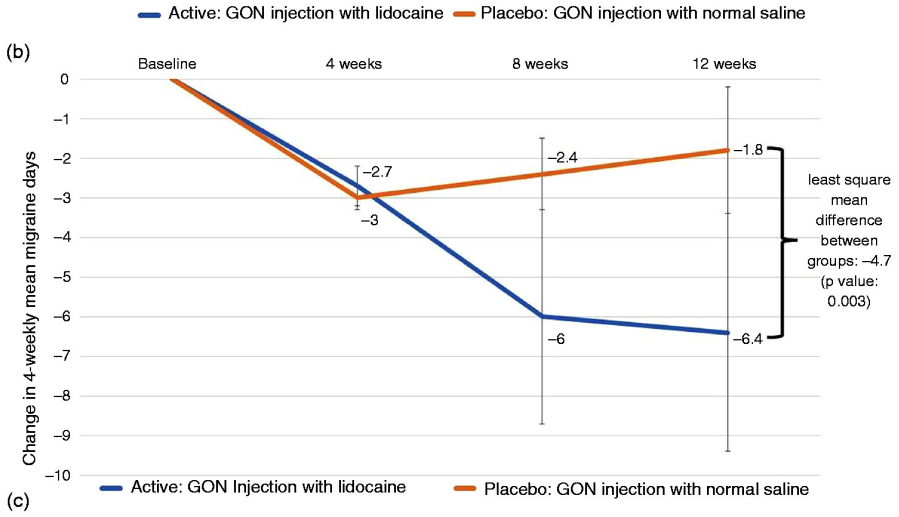
All patients were blinded by also getting a lidocaine patch at site of injection, to not identify paresthesia

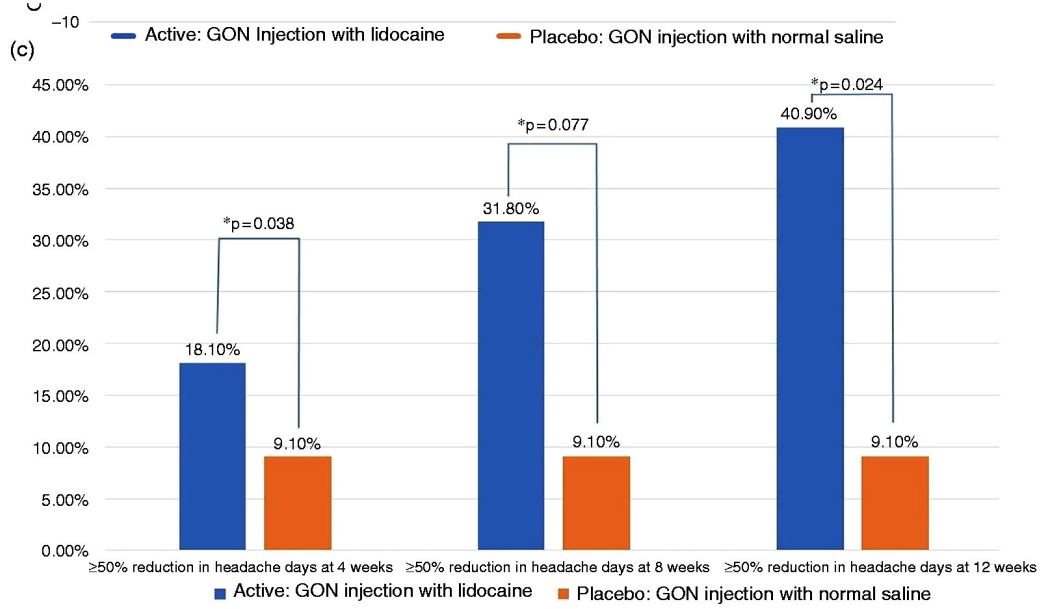
Chowdhury D et al, *Cephalalgia*. 2023;43(2).

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Occipital Nerve Blocks and Migraine Prevention – CM







Chowdhury D et al, *Cephalalgia*. 2023;43(2).

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 2: Helene

- 42F with daily and continuous chronic migraine, she works as a teacher. Has tried multiple preventive classes, beta-blockers (2), anti-epileptics (3), calcium channel blockers (2), angiotensin receptor blockers (1), TCA and SNRI, the side effects are inevitable for her, and she can't really tolerate most medications.
- She has had onabotulinumToxin with some good effect in past, and has started fremanezumab therapy in the last 5 months with some good effect. She thinks with onabotulinumToxin her headache intensity went from 7-9/10 to 5-7/10, and additionally with fremazenumab it has improved and she finally has some headache free days, about 3 per month.
- Her insurance will not cover both therapies. Her last onabotulinumToxin therapy was 6 months ago, and she is exasperated, she is back to daily and continuous headache 7/10, which is better for about 2 weeks with the anti-GRP injection, **but she feels like she is going backwards and is worried she may have to take a leave from work again.**

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 2: Helene

- We discuss and start nerve blocks as a temporizing preventive measure while we explore other options and while she is figuring out possible insurance coverage changes and we draft yet another appeal.
- Discuss doing a psychotherapeutic program, there now is evidence for CBT, MBSR and ACT therapies in migraine, work with a therapist to provide this for your patients.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Take Home Points

- Review the first line therapies in those without preventive use
- Consider for early targeted therapy in all patients
- Consider pregnancy recommendations
- Consider refractory strategies
- New considerations for depression with anti-CGRP therapies, some new nutraceutical options, and reconsideration of occipital nerve block evidence especially in pregnancy, treatment refractory and patients in crisis.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Canadian Headache Society Migraine Prevention Guideline Update

Medrea I, Cooper P, Lagman-Bartolome AM, et al. Updated Canadian Headache Society Migraine Prevention Guideline with Systematic Review and Meta-analysis. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 2025;52(3):450-472.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

THANK YOU