CoLab Network

Rapid Review

Switching Calcitonin Gene–Related Peptide Inhibitors for Migraine Prophylaxis

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Key Messages

There are several different formulations of drugs that target calcitonin gene–related peptide (CGRP) available in Canada for preventing migraine. This Rapid Review examines the evidence regarding the effectiveness of different CGRP inhibitors after failure on a first or second CGRP inhibitor due to lack of efficacy or tolerability.

The review includes 1 systematic review of 7 nonrandomized studies, 3 additional nonrandomized studies, and 2 clinical guidelines, all published since 2020. The included studies all examined changes in monthly migraine days after switching to a new CGRP inhibitor. No economic studies were identified.

The findings generally show that patients experience improvement with the second CGRP inhibitor based on reported migraine events. However, the guidelines found there was not enough evidence to consider this practice evidence-based.

All the studies, including the clinical guidelines, were conducted in other countries, so it is not clear how applicable they are to patients in Canada.

All studies had very significant methodological concerns and their results should not be considered conclusive. In particular, all the primary studies were uncontrolled, meaning that bias from regression to the mean could not be ruled out.

Overall, the included studies do not offer clear guidance on the effectiveness of prophylactic CGRP inhibitors in patients with migraine who have failed treatment on a different CGRP inhibitor.

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Abbreviations

CGRP	calcitonin gene–related peptide
CGRPr	calcitonin gene–related peptide receptor
MMD	monthly migraine days
mAb	monoclonal antibody
SR	systematic review

Introduction and Rationale

Background

Disease Background

Migraine is a type of headache characterized by recurrent episodes of moderate to severe throbbing or pulsating pain on 1 side of the head.[1] The pain is caused by the activation of nerve fibres within the walls of the brain blood vessels travelling inside the meninges (3 layers of membranes protecting the brain and spinal cord) and scalp.[2] Untreated migraine episodes can last from 4 hours to 72 hours.[1] Other common migraine symptoms may include nausea, vomiting, and sensitivity to light, noise, and odours.[1] Routine physical activity, movement, or even coughing or sneezing can worsen the pain.[1] Migraine occurs most frequently in the morning, especially upon waking.[1] However, migraine can occur at predictable and unpredictable times in the day.[1] Different factors can increase the risk of having a migraine including emotion, stress, overexertion, sudden changes in weather or environment, strong odours or fumes, loud or sudden noises, too much or too little sleep, motion sickness, low blood sugar, skipped meals, or bright or flashing lights.[1,2]

Migraine is divided into 4 phases that may be present during an episode.[1,2] First, premonitory symptoms (prodrome) occur up to 24 hours or longer before developing a migraine.[1,2] These include food cravings, unexplained mood changes, uncontrollable yawning, fluid retention, or increased urination.[1,2] Next, patients may experience aura, such as flashing or bright lights immediately before or during the migraine, or patients may experience sensory symptoms, such as numbness, tingling, or muscle weakness.[1,2] The pain usually starts gradually and builds in intensity; however, it is possible to have a migraine without a headache.[1,2] Finally, the postdrome is when patients are exhausted or confused following a migraine.[1,2] This period may last up to a day.[1,2] The 2 major types of migraine are migraine with aura or migraine without aura.[1,2] Other types of migraine may include abdominal migraine, hemiplegic migraine, menstrual migraine, retinal migraine, or status migrainosus which is a rare and severe type of migraine with disabling pain and nausea.[1,2]

If patients experience fewer than 15 migraine episodes per month, it is classified as episodic migraine.[1,2] Conversely, chronic migraine is defined as experiencing 15 or more migraine episodes per month.[1,2] Migraine is currently listed as the sixth most disabling disorder globally, and the highest ranking among all neurologic disorders.[2] The etiology of migraine is complex, and it does include a genetic component.[2] Migraine occurs in both children and adults and affects women 3 times more often than men.[1,2] Migraine in women often relates to hormone changes.[1,2] A migraine episode may begin at the start of the menstrual cycle or during pregnancy, and women may experience improvement in migraine symptoms after menopause.[1,2]

Treatment of Migraine

Migraine treatment is aimed at relieving symptoms and preventing future episodes.[1,2] Drug therapy for migraine is divided into acute and prophylactic treatment.[1,2] Acute medications are taken as soon as migraine symptoms occur to relieve pain and restore function.[1,2] Prophylactic treatment involves taking medication daily to reduce the frequency and severity of future episodes.[1,2] Acute treatment for migraine may include triptan drugs, ergot derivative drugs, nonprescription analgesics, combination analgesics, prescription nonsteroidal anti-inflammatory drugs, drugs for nausea relief, and prescribed narcotics.[1,2]

Prophylactic treatment should be considered for patients if they have 4 or more migraine days per month or if it is disabling.[3] Many oral drugs are used (some off-label) to prevent migraine, including anticonvulsants, beta-blockers, calcium channel blockers, and antidepressants.[2,4] OnabotulinumtoxinA (Botox) is an injection indicated to prevent migraine; however, it needs to be administered by a trained health care provider.[2,4] Calcitonin gene–related peptide (CGRP) inhibitors are novel, targeted drugs indicated to prevent migraine.[4] The drug class works by inhibiting the action of CGRP, which reduces both pain transmission and inflammation.[4]

There are 2 major types of drugs that work through inhibiting CGRP for the treatment of migraine. The first are monoclonal antibodies (mAbs) that target either CGRP or the CGRP receptor (CGRPr). Three mAbs are currently approved in Canada that target CGRP: galcanezumab (Emgality), fremanezumab (Ajovy), and eptinezumab (Vyepti). The other approved mAb, which targets the CGRPr, is erenumab (Aimovig). In addition, there are 3 approved small-molecule treatments that target the CGRPr, including atogepant (Qulipta), rimegepant (Nurtec), and ubrogepant (Ubrelvy), which are known collectively as gepants medicines. These drugs have a fast onset of action, convenient dosing, and mild to moderate side effects.[4] CGRP inhibitors are commonly reimbursed by drug plans after patients have experienced inadequate response, intolerance, or contraindication to 2 or more conventional oral migraine prophylactic drugs.[4]

Main Take-Aways

Migraine is a type of serious headache that can lead to disabling symptoms for many people in Canada. Prophylactic treatment of migraine is generally indicated in cases in which patients have weekly or disabling symptoms. There are several treatment options for migraine, including the novel class of CGRP inhibitors, which are generally covered by drug plans when other treatment options have failed.

Policy Issue

While CGRP inhibitors can be effective after failure of conventional therapies, it is unclear how sequencing within this drug class impacts effectiveness in patients experiencing intolerance, suboptimal response, or side effects. It is unclear whether alternative CGRP inhibitors after initial CGRP treatment failure are effective. Subsequent treatment with CGRP inhibitor alternates could lead to wasteful use of health care resources and potential exposure to side effects for patients. Public drug plan reimbursement criteria for CGRP inhibitors make no stipulation regarding prior use of drugs of the same class; therefore, sequencing may be permissible. Evidence is needed to inform policies regulating the use of CGRP inhibitors for migraine prophylaxis for patients who have experienced a previous CGRP inhibitor.

Policy Question

1. Should CGRP inhibitors be reimbursed upon lack or loss of response to a previous CGRP inhibitor for migraine prophylaxis?

Main Take-Aways

While CGRP inhibitor medications have been shown to be effective after failure on conventional migraine therapies, it remains unclear whether switching CGRP inhibitors is an effective and cost-effective treatment option.

Purpose

To review the evidence behind the use of prophylactic CGRP inhibitors in patients with migraine who have experienced a previous CGRP inhibitor.

Research Question

1. What is the effectiveness of prophylactic CGRP inhibitors in patients with migraine who have experienced a previous CGRP inhibitor?

Methods

Literature Search Methods

The research team used a literature search strategy based on a combination of drug names and terms that denoted switching or changing therapies. This strategy consisted of a limited literature search on key resources, including MEDLINE via PubMed, the Cochrane Library, Canadian and major international health technology agencies, as well as a focused internet search. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses, indirect treatment comparisons, clinical trials or observational studies, economic studies, and guidelines. The search was limited to English-language documents with no date restrictions and was conducted on May 14, 2024.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population(s)	Individuals aged 18 years and older with at least 4 migraine days per month previously treated with a CGRP inhibitor.
Subgroups	• Age • Sex or gender
Interventions	• Erenumab (Aimovig) • Galcanezumab (Emgality) • Fremanezumab (Ajovy) • Eptinezumab (Vyepti) • Atogepant (Qulipta) • Rimegepant (Nurtec) • Ubrogepant (Ubrelvy)
Comparators	• Erenumab (Aimovig) • Galcanezumab (Emgality) • Fremanezumab (Ajovy) • Eptinezumab (Vyepti) • Atogepant (Qulipta) • Rimegepant (Nurtec) • Ubrogepant (Ubrelvy) • Placebo • No comparator
Outcomes	• Migraine headache frequency • Migraine headache intensity • Health-related quality of life • Use of concurrent acute pain medication • Health care resource utilization (e.g., emergency department visits)
Study designs	• Systematic reviews • Randomized controlled trials • Nonrandomized studies • Economic evaluations • Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or they were duplicate publications. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines with unclear methodology were also excluded. Conference abstracts, narrative reviews, editorials, case reports, and case series were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A Measurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[5] for SRs, the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I)[6] instrument for nonrandomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[7] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

Main Take-Aways

The literature search identified 404 potential citations, of which 6 met the inclusion criteria. These consisted of 1 SR, 3 nonrandomized observational studies, and 2 clinical guidelines. No randomized controlled studies or economic evaluations were identified.

A total of 404 citations were identified in the literature search. Following screening of titles and abstracts, 365 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 33 publications were excluded for various reasons (Appendix 1), and 6 publications met the inclusion criteria and were included in this report. These publications consisted of 1 SR, no randomized controlled trials, 3 nonrandomized studies, no economic evaluations, and 2 evidence-based guidelines. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study selection. Additional references of potential interest are provided in Appendix 6.

Study Characteristics

Main Take-Aways

The studies included in this review were all published between 2022 and 2024. The studies included in the SR and the nonrandomized studies were all nonrandomized studies of patients who switched between different CGRP mAbs. Studies were generally small and conducted in several different countries. The evidence-based guidelines were developed using a systematic process and were designed for use in Germany and in Europe.

One SR,[8] 3 nonrandomized studies,[9-11] and 2 evidence-based guidelines[12,13] were identified and included in this review. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The SR was published in 2024 and included studies published up to March 17, 2024.[8] The SR[8] had broader inclusion criteria than the present review. Specifically, it reviewed 9 nonrandomized studies. This included 1 case series and 1 nonrandomized study that studied patients who switched CGRP inhibitors due to dosing preference and not due to treatment failure. Thus, these 2 studies were excluded from this review. The 7 remaining nonrandomized studies are described in this report.[14-20] These included studies were published between 2022 and 2024; the outcomes reported were based on changes in monthly migraine days (MMDs). A meta-analysis was not conducted, and a risk of bias assessment was not completed. Due to gaps in the reporting in the SR, the 7 studies were all read individually to ascertain or confirm certain elements (e.g., study design, setting, and industry funding).

The 3 nonrandomized studies were all single-arm, nonrandomized, retrospective cohort studies of patients who started a CGRP inhibitor medication after failure on another due to nonresponse, lack of tolerability, or both. The studies were published in 2023[9,10] and 2024.[11]

The 2 evidence-based clinical guidelines were published 2022 and were intended to guide clinician use of CGRP mAbs in migraine treatment. The first, by Diener et al. (2022),[12] is a guideline on migraine treatment produced by the Deutsche Gesellschaft für Neurologie (German Society for Neurology). The guidelines were based on a systematic literature review and were developed by clinical experts in the field. The second, by Sacco et al. (2022),[13] was developed for the same patient population and was also an update to an existing guideline to address treatment with CGRP inhibitor medications. A systematic literature review was done using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Both studies used clinical opinion if evidence was unavailable; neither guideline reported a rating scale for the quality of the evidence underlying the recommendations.

Country of Origin

The SR[8] was conducted by a team in Italy. The relevant primary studies contained in the SR were from Japan (2 studies), Germany (2 studies), Italy, Germany and Austria, and the UK and Italy. The nonrandomized studies were conducted in the United Arab Emirates,[10] Japan,[9] and the UK.[11] The guidelines were developed for use in Germany[12] and in Europe.[13]

Patient Population

The SR[8] included patients who had switched between different CGRP inhibitor medications. The included studies ranged in size from 20 to 153 patients, with a total of 374 (mean 53) patients. Details regarding the age, sex, gender, and duration of the condition in the patients was not systematically reported. In the majority of the included studies, most patients had switched CGRP inhibitor medication due to nonresponse, with a smaller number of patients switching due to adverse events.

The 3 nonrandomized studies used different observational data sources. Suliman et al. (2024)[10] used clinical records from a single site in the United Arab Emirates. The analysis focused on patients who switched CGRP inhibitor medications during the course of their treatment (largely due to nonresponse), received at least 3 doses of the first CGRP inhibitor medication, and maintained treatment for at least 6 months after switching.

Subanalyses investigated differences in patients who switch from a CGRPr inhibitor to a CGRP inhibitor, those who switch from a CGRP inhibitor to a CGRPr inhibitor, and those who switch between different CGRP inhibitor medications. Suzuki et al. (2023)[9] studied patients who started on CGRP inhibitor medications in a clinic in Japan. A subset of 70 patients had previously used a CGRP inhibitor medication and had an "insufficient" response to either 1 or 2 prior CGRP inhibitor medications. The final nonrandomized study, by Talbot et al. (2024),[11] included patients under the care of a local neurology service in the UK. Patients who had received a minimum of 2 CGRP mAbs and who had submitted 1 or more months of headache diaries were included in the study.

Both clinical guidelines[12,13] targeted the use of CGRP inhibitor medications in patients with migraine. The target population was clinicians working with these patients.

Interventions and Comparators

All the included studies, both in the SR and the nonrandomized studies, focused on switches between 2 or more CGRP mAbs. No studies included switches to or from gepant medications.

The studies included in the SR[8] followed patients who switched between several types of CGRP inhibitor therapies. This included 3 studies that investigated switches from any CGRPr mAb to a CGRP mAb: erenumab to fremanezumab or galcanezumab (2 studies) and erenumab to fremanezumab (1 study). Two studies investigated switches in the opposite direction, from a CGRP mAb to a CGRPr mAb, both of which studied switches from galcanezumab or fremanezumab to erenumab. The other 2 studies investigated changes between any CGRP mAb (1 study) and from galcanezumab, erenumab, or both to fremanezumab (1 study). All the included studies lacked comparators and followed a single population of patients after switching.

The nonrandomized clinical studies all studied switches to multiple different CGRP inhibitor medications. The study by Suliman et al. (2024)[10] used observational data to identify patients that performed 1 of 3 types of CGRP inhibitor medication switches: from a CGRPr inhibitor to a CGRP inhibitor, from a CGRP inhibitor to a CGRPr inhibitor, or from 1 CGRP inhibitor to a different CGRP inhibitor. Patient reports of MMDs at baseline were compared to the rates at 6 months. In the study by Suzuki et al. (2023),[9] patients were switched to erenumab, galcanezumab, and fremanezumab, but the numbers of each in the subset of patients who switched were not provided. In the nonrandomized study by Talbot et al. (2024),[11] patients were switched to 1 of erenumab, fremanezumab, or galcanezumab based on cost, allergy, and individual preferences. None of the 3 studies included a comparator group.

Both guidelines considered various aspects of treatment with CGRP mAbs.[12,13] For the purposes of this review, the focus was on recommendations regarding switching to a different CGRP mAb following nonresponse to a first drug.

Outcomes

The outcomes assessed in the SR[8] were all related to MMDs. Changes in MMDs were reported based on 50% and 30% reduction thresholds (5 studies and 4 studies, respectively), and an overall reduction in the mean (2 studies).

The nonrandomized studies also largely used MMDs as their primary outcome measure and examined the change in outcomes from patients between baseline and a follow-up period, which ranged from 3 to 12 months. Suliman et al. (2024)[10] examined the median change in the reported number of MMDs at baseline and at 6 months, which were collected using patient diaries. Suzuki et al. (2023)[9] also collected information on MMDs from patient diaries, which were collected over a 12-month period. The nonrandomized study by Talbot et al. (2024)[11] used headache diary data collected by patients as a condition of the coverage of their drug. Patients identified "red days" when headaches limited their activities of daily living or required the use of triptan medication, "amber" days with headaches that did not limit activity, and the number of days headache medications were used. In addition, participants completed the Headache Impact Test-6 (HIT-6) each month. Changes in MMDs and the HIT-6 were assessed at 3 months.

Both guidelines focused on reducing the number of days with migraine in patients.[12,13]

Critical Appraisal

Main Take-Aways

All studies reported in the SR and the primary studies had very significant methodological concerns. In particular, all the primary studies were uncontrolled, meaning that bias from regression to the mean could not be ruled out. While the clinical guidelines were developed using a systematic literature search, neither did a formal bias assessment on the evidence.

Systematic Reviews

There were some aspects of the included SR[8] that were well-conducted, but there were large gaps in the reporting on other aspects. The review was clear about the population, intervention, comparison, outcome (PICO) criteria, including the population of interest being patients who switched medications, the intervention being another CGRP inhibitor medication, and the outcome of changes in MMDs. The authors also reported no conflicts of interest that were relevant to the study. The authors also engaged in a substantial discussion about why they observed heterogenous results. However, there was no reporting on the selection of study designs, only a single database was used, the studies did not appear to be reviewed in duplicate, no list of excluded studies was provided, and the risk of bias in the included studies was not assessed. Most of the included studies were small, single-arm, observational studies that were conducted on populations that may not extrapolate to potential patient populations. While the SR did not contain an assessment of potential conflicts of interests, a review of the original studies shows that all had authors with potential conflicts of interest due to relationships with pharmaceutical manufacturers.[14-20]

Nonrandomized Studies

Similar to the studies identified in the SR, there were also very significant sources of potential bias in the other nonrandomized clinical studies. For example, Suliman et al.[10] required that patients who were switched maintain treatment on the new CGRP medication for a minimum of 6 months after switching. This is potentially problematic as it will eliminate patients who stopped the new medication due to either nonresponse and/or side effects. Their analysis also lacked a control group, leaving it very open to several

potential biases. Of note in this context is the potential for regression to the mean because there was no control group to base estimates of secular change. Both these factors would likely bias toward showing effectiveness and tolerability of switching. Similarly, there were major changes in follow-up of patients in the nonrandomized study by Suzuki et al. (2023).[9] Of the 70 patients who had switched from an ineffective CGRP medication, it appears that only 15 patients were available for data estimates at the end of the 12-month follow-up period (based on data in Figure 5 in the original study). Dropout in the switching cohort was not separately reported; however, in the overall cohort there was marked dropout due to "insufficient response" to the CGRP medication, which would bias the findings of the study away from the null. As with the first study, this study also lacked a control group and would thus be subject to the same potential bias of regression to the mean. The study by Talbot et al. (2024)[11] was subject to the same issues with a lack of control group and potential regression to the mean. The authors also carried forward observations to future values if data were missing, which has an unknown impact on their estimates. In terms of generalizability, it is unclear whether the study groups would extrapolate to the overall patient population. However, the proportion of the study population that was female did roughly mirror the epidemiological data on migraine at 79%[10] and 85%.[11]

Guidelines

The guidelines included both their scope and purpose.[12,13] While both included input from professional groups, neither appeared to include patient input in their development. Systematic methods were used to search the literature base in both guidelines, but the methods for assessing the evidence were only systematic in 1 of the 2 guidelines,[13] and neither conducted a formal bias assessment. While applicability was not discussed in either guideline, this may have been a consequence of them being updates rather than full guidelines. Funding and conflicts of interest were disclosed in both.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Findings

Main Take-Aways

Overall, the included studies generally found that patients experience improvement with the second CGRP inhibitor based on the reported number of MMDs. In contrast, the authors of the guidelines concluded that there was not enough evidence to consider switching to a different CGRP inhibitor medication.

Appendix 4 presents the main study findings. Overall, the authors of the SR concluded that "Although there has been a steady increase in data concerning the potential efficacy of CGRP(r) mAb switching, there is still an insufficient body of evidence to make a definitive recommendation on the efficacy of this intervention."[8] The other nonrandomized studies and guidelines generally support this conclusion.

Clinical Effectiveness of Switching CGRP Inhibitor Medications

The findings from the different studies are split into the switch types that were the focus of the original studies.

Switching From CGRPr mAbs to CGRP mAbs

Four of the included studies in the SR[8] investigated switching from any CGRPr mAb to a CGRP mAb. All these studies found a reduction in MMDs after the switch. Two studies showed a decrease of 30% or more in 32% and 36% of patients, and a reduction of 50% or more in 12% and 26% of patients. Another study showed a 50% or more decrease in MMDs in 42.8% of enrolled patients. One nonrandomized study[10] found this type of switching led to an average reduction of 1.6 MMDs at 6 months, but this result was not statistically significant.

Switching From CGRP mAbs to CGRPr mAbs

Two of the included studies in the SR[8] investigated switching from any CGRP mAb to a CGRPr mAb. Both these studies found a reduction in MMDs following the switch. A decrease of 30% or more in MMDs was reported by 45% and 56% of patients. In addition, 1 study showed that 10% of patients experienced a 50% or more reduction in MMDs. One nonrandomized study found this form of switching led to an average decrease of 3.7 MMDs at 6 months.

Switching Between Mixed CGRP mAbs

The other studies included in the SR[8] investigated switching between any CGRP mAb medication to another after failure. The first study reported that 33.1% reported a 50% or more decrease in MMDs following the switch. There was no difference between patients who switched between a CGRPr mAb to a CGRP mAb or vice versa. The final study indicated there was a significant decrease in MMDs, but did not report a response rate. One of the nonrandomized studies[10] found that switching to any other CGRP inhibitor was associated with a reduction in MMDs of 5.0 days at 6 months. Another nonrandomized study[9] found that 60% of patients reported a 50% or more reduction in MMDs at 12 months after switching to a different CGRP inhibitor medication. The final nonrandomized study[11] found that 15% of patients reported a 50% or more reduction in MMDs at 3 months. This study also found no statistically significant change in the HIT-6, the number of days using a triptan, or the number of days using a painkiller.[11]

Switching Between Gepant Medications

No relevant evidence was found that investigating switching to and/or from a CGRP mAb to a gepant medication or vice versa.

Guidelines Regarding Switching CGRP Inhibitor Medications

Both guidelines suggest that switching CGRP inhibitor medications may be an option when patients have failed on a prior CGRP inhibitor medication.[12,13] One guideline specifically suggested a trial of a CGRPr inhibitor medication could be justified after failure on a CGRP inhibitor medication or vice versa.[12] The second guideline also conjectures about switching between CGRP inhibitor medications with a different mechanism of action (from a CGRP inhibitor to a CGRPr inhibitor or vice versa).[13] In both cases, the guidelines are very clear that these recommendations are based on no or low-quality data.

Limitations

In general terms, there are serious limitations in this review beyond the individual study limitations discussed previously. The main drawbacks are the small sample sizes, extremely high risk of internal bias, the external validity of findings, a lack of statistical hypothesis testing in many studies, and that very few studies were authored by individuals who did not have potential conflicts of interest.

The issues with internal validity stem from the entire evidence base consists of low-quality, single-arm, uncontrolled, nonrandomized studies. As noted in the SR,[8] this leaves open the possibility that all these findings were the result of regression to the mean. As placebo response in trials of drugs in this clinical area can be quite high, the lack of controlled studies means that "it is impossible to distinguish these findings from the studies in this manuscript from placebo."[8] The additional studies that were not included in the SR do not alleviate these concerns and the guidelines do not offer any additional evidence base from which to draw conclusions. In short, this means the changes found in every study contained in this review could be critically flawed.

In terms of external validity, the studies included different populations from several countries, but the applicability of many of the results to the Canadian context remains unclear. Several of the studies included specific populations, such as a single headache clinic or hospital. As other treatment practices might differ substantially, this is another source of potential bias in all these uncontrolled studies. In addition, we found very little information on other outcomes of interest, including migraine headache intensity, health-related quality of life, and health care resource utilization (e.g., emergency department visits). Whether the previously described findings would extrapolate to these other outcomes remains unknown.

Conclusions and Implications for Decision- or Policy-Making

Main Take-Aways

The included studies do not offer conclusive evidence in support of switching CGRP inhibitor medications after failure on a first CGRP inhibitor medication. However, existing studies do suggest some potential, particularly when switching between medications with different mechanisms of action (e.g., CGRP inhibitor to CGRPr inhibitor) or after discontinuing a particular therapy due to medication-specific adverse events. Clinical guidelines indicate that this might be a viable strategy in particular circumstances, but also acknowledge the lack of a solid evidence base to make treatment recommendations.

We identified 1 SR[8] that included 7 relevant nonrandomized studies, 3 nonrandomized clinical studies,[9-11] and 2 guidelines[12,13] that examined the potential to switch CGRP inhibitor medications following failure on a first CGRP inhibitor medication. All these studies examined switching between different CGRP mAbs and did not include any assessment of gepant medications. Overall, these studies consistently found that patients with migraine demonstrated reductions in MMDs following a switch in CGRP inhibitor medication.

With respect to clinical effectiveness, all 10 nonrandomized studies included in both the SR and the primary studies indicated a reduction in MMDs following a switch in CGRP medication. However, the scale of these reductions was widely variable. For example, reductions of 50% or more in MMDs ranged from 10% of patients to 60% of patients across various studies. Many of these reductions were not subject to formal statistical testing, so confidence intervals were not available in many instances. While both guidelines suggested switching might be a viable clinical strategy, neither based this recommendation on good evidence.

Overall, these findings should be considered suggestive at best. The entirety of the evidence is based on very weak uncontrolled designs, leaving the potential that significant bias impacted the results. In particular, the potential for all the empirical results to be biased because of regression to the mean should not be understated, especially since this is a well-documented phenomenon in this area of research. In addition, only a small portion of this literature base has been conducted by researchers without industry conflicts. Additional research on the effectiveness of switching patients between CGRP medications following a treatment failure would be valuable in reducing the decision-making uncertainty in this clinical area.

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Authors

Michael Law acquired data, analyzed, and interpreted results, and drafted the report.

Contributors

This project was selected as part of a pilot for early engagement with patients, clinicians, and drug manufacturers. We thank the contributors from each of these impacted groups for providing feedback and expertise throughout this project.

Patient Partner

We thank **Beth Kidd** for providing input into the direction of the research, drawing from lived experience, and providing valuable contributions to this report.

Clinical Experts

These individuals kindly provided comments on this report:

Paul Cooper, MD, FRCPC, FAAN
Professor, Division of Neurology, Department of Clinical Neurologic Sciences
Schulich School of Medicine and Dentistry, Western University

Wasif Hussain, MD, FRCPC
Associate Clinical Professor
University of Alberta

Drug Manufacturers

All CGRP inhibitor drug manufacturers were contacted, and we acknowledge the following 4 who contributed their feedback: AbbVie Canada, Eli Lilly Canada, Lundbeck Canada, and Teva Canada.

Conflicts of Interest

Michael Law disclosed the following:

Payment as Advisor or Consultant
Health Canada – Pharmacare

iTAD Limited – Routine data inLMICs

Canada's Drug Agency – PMDE

Payment as Advisor or Consultant – Expert Witness Reports and Testimony for Labour Unions
Federation of Post-Secondary Educators – Changes to drug benefits plan, (expert witness testimony)

Durham Police Association – Changes to drug benefits plan (expert witness testimony)

Beth Kidd disclosed the following:

Employment
Health Coalition of Alberta – patient advocacy

Volunteer Member
Canada's Drug Agency – Acting Chair of the Patient and Community Advisory Committee

Dementia Network Calgary – Strategic Council

Migraine Warriors Alberta – co-administrator of a virtual patient support group

Research Canada – Board of Directors

Paul Cooper disclosed the following:

Participation in Advisory Board Meetings
Teva – fremanezumab

Abbvie – ubrogepant and atogepant

Abbvie – onabotulinumtoxinA

Novartis – erenumab

Lundbeck – eptinezumab

Pfizer – rimegepant

Educational Lectures
Teva – anti-CGRP monoclonal antibodies

Lilly – treatment of migraine

Speaker Training Session
Lundbeck - eptinezumab
Canada's Drug Agency – Participated in reviews of erenumab and galcanezumab

Wasif Hussain disclosed the following:

Speaking Engagements
Abbvie/Allergan – Botox, Ubrogepant, Atogepant
Miravo – Cambia, Suvexx
Eli Lilly – galcanezumab
Lundbeck – eptinezumab
Teva - fremanezumab

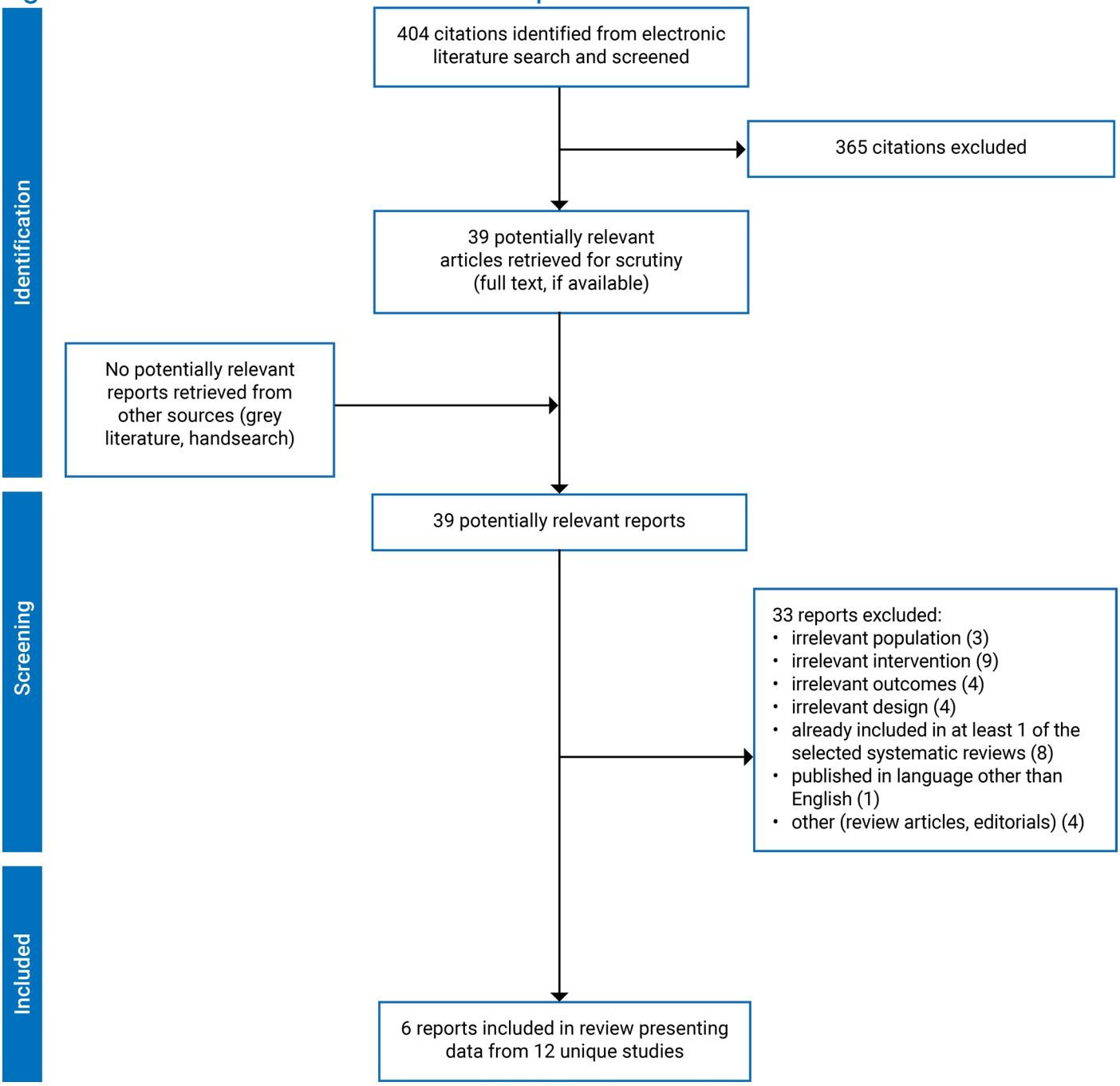
Payment as Advisor or Consultant – Advisory Boards
Abbvie/Allergan – Botox, Ubrogepant, Atogepant
Eli Lilly – galcanezumab
Lundbeck – eptinezumab
Miravo – Cambia, Suvexx
Eisai – lecanemab

No other conflicts of interest were declared.

Appendix 1: Selection of Included Studies

Note that this appendix has not been copy-edited.

Figure 1: PRISMA Flow Chart of Selected Reports



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Wells-Gatnik et al. (2024)[8] Italy **Funding source:** None	**Study Design:** 7 primary studies, all single-arm nonrandomized studies **Settings:** Several countries	**Inclusion criteria:** Patients who switched CGRP inhibitor medication due to efficacy or side effects **Age:** NR **Sex:** NR	**Intervention:** Switching CGRP inhibitor after failure **Comparator**: None	**Outcomes:** > 30% reduction MMDs > 50% reduction MMDs Change in MMDs **Follow-up:** NR

CGRP = Calcitonin Gene-related Peptide; MMD = monthly migraine days; NR = not reported

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Suliman et al. (2024)[10] UAE **Funding source:** None	**Study Design:** Single-arm, uncontrolled, nonrandomized study **Setting:** Single clinic	Individuals who switched from 1 CGRP to another **Number of patients:** 53 **Mean Age (SD):** 39.2 (11.0) **Sex:** 42 women (79%)	**Intervention:** New CGRP medication **Comparator**: None	**Outcomes:** reduction in MMDs (≥ 50% for chronic migraine and ≥ 30% for episodic migraine), adverse events **Follow-up:** 6 months
Suzuki et al. (2023)[9] Japan **Funding source:** None (but author conflicts are present)	**Study Design:** Single-arm, uncontrolled, nonrandomized study **Setting:** Single outpatient clinic	Subgroup of prior CGRP users who initiated new therapy **Number of patients:** 70 **Mean Age (SD):** NR **Sex:** NR	**Intervention:** New CGRP medication **Comparator**: None	**Outcomes:** ≥ 50% reduction in MMDs **Follow-up:** 12 months
Talbot et al. (2023)[11] UK **Funding source:** None (but author conflicts are present)	**Study Design:** Single-arm, uncontrolled, nonrandomized study **Setting:** Neurology service patients	Individuals with chronic migraine that switched CGRP treatment **Number of patients:** 54 **Mean Age (SD):** 48.9 (13.8) **Sex:** 46 women (85%)	**Intervention:** New CGRP medication **Comparator**: None	**Outcomes:** MMDs, ≥ 50% reduction in MMDs, ≥ 30% reduction in MMDs, HIT-6 **Follow-up:** 3 months

CGRP = Calcitonin Gene-related Peptide; MMD = monthly migraine days; NR = not reported; SD = standard deviation

Table 4: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Diener et al. (2022)[12]						
Intended users: German clinicians **Target population:** Patients with migraine	CGRP medications	Reduction in headache days	Systematic literature search based on specific search terms	Based on selection of authors for each section	Development of each recommendation by authors	Delphi process of expert input and validation, voting on recommendations
Sacco (2022)[13]						
Intended Users: European clinicians **Target Population:** Patients with migraine	CGRP medications	Reduction in migraine days	Systematic literature search based on specific search terms, expert opinion	GRADE approach	Structured process including drafting and interaction	None mentioned

CGRP = Calcitonin Gene-related Peptide; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[5]

Strengths	Limitations
Wells-Gatnik and Martelletti (2024)[8]	
• Clearly stated PICO criteria, including population, intervention, and outcome • Discussion and explanation for observed heterogeneity of the results • Authors reported no potential sources of conflict of interest	• Very little information on how the review was conducted, including whether the methods were predetermined and how study designs were selected • Studies were sourced from only one database and were not explicitly selected or reviewed in duplicate • No list of excluded studies was provided • No risk of bias assessment was conducted, nor was this used as an inclusion or discussion criteria • Funding of the included studies was not discussed

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; PICO = patient, population, intervention, outcome

Table 6: Strengths and Limitations of Clinical Studies Using ROBINS-I

Strengths	Limitations
Suliman et al. (2024)[10]	
• Intervention groups were clearly defined • There were no deviations away from the intervention from what would be expected in normal practice • Measurements were made based on predetermined instruments and used a standard measure	• The analysis was uncontrolled, leaving it open to bias due to regression to the mean (likely bias away from null) • Patients were required to adhere to the prescribed regimen for a period of 6 months • Selection of participants into the study was predicated on them finishing 6 months of therapy on the new medication, which is a serious potential source of bias as it would exclude users who did not respond or had adverse events occur early (likely bias away from null) • An unknown number of patients were excluded due to a lack of 6-month follow-up (unclear bias) • The outcome could have been influenced by knowledge of receipt of a new medication (unpredictable source of bias)
Suzuki et al. (2023)[9]	
• Intervention groups were clearly defined • There were no deviations away from the intervention from what would be expected in normal practice • Measurements were made based on predetermined instruments and used a standard measure	• The analysis was uncontrolled, leaving it open to bias due to regression to the mean (likely bias away from null) • Patients were required to adhere to the prescribed regimen for a period of 12 months • Selection of participants into the study was predicated on them completing 12 months of follow-up, which is a serious potential source of bias as dropout was concentrated in nonresponders (likely away from null) • 55/70 patients were excluded due to a lack of 12-month follow-up

Strengths	Limitations
	(unclear bias) • The outcome could have been influenced by knowledge of receipt of a new medication (unpredictable source of bias)
Talbot et al. (2023)[9]	
• Intervention groups were clearly defined • There were no deviations away from the intervention from what would be expected in normal practice • Measurements were made based on predetermined instruments and used a standard measure	• The analysis was uncontrolled, leaving it open to bias due to regression to the mean (likely bias away from null) • Data were carried forward to the next observation in the case of missing data; this impacted 17 observations at the 3-month time point (likely bias away from the null if related to ineffectiveness or side effects) • The outcome could have been influenced by knowledge of receipt of a new medication (unpredictable source of bias)

ROBINS-I = Risk Of Bias In Nonrandomized Studies - of Interventions

Table 7: Strengths and Limitations of Guidelines Using AGREE II[7]

Item	Diener et al. (2022)[12]	Sacco et al. (2022)[13]
Domain 1: Scope and purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of development		
7. Systematic methods were used to search for evidence.	Unclear	Yes
8. The criteria for selecting the evidence are clearly described.	No—authors who wrote each section of the guideline selected the relevant literature	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	No	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes

Item	Diener et al. (2022)[12]	Sacco et al. (2022)[13]
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts before its publication.	Yes	No
14. A procedure for updating the guideline is provided.	No	No
Domain 4: clarity of presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: applicability		
18. The guideline describes facilitators and barriers to its application.	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	No
20. The potential resource implications of applying the recommendations have been considered.	No	No
21. The guideline presents monitoring and/or auditing criteria.	Yes	No
Domain 6: editorial independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; CGRP = Calcitonin Gene-related Peptide

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 8: Summary of Findings by Outcome — Headache

Type of medication switch	Wells-Gatnick et al. (2024)[8]	Suliman et al. (2024)[10] nonrandomized study	Suzuki et al. (2023)[9] nonrandomized study	Talbot et al. (2023)[11] nonrandomized study
≥ 30% reduction in MMDs				
CGRPr to CGPR	Two studies, 32% and 36% of patients	NR	NR	NR
CGRP to CGRPr	Two studies, 45% and 56% of patients	NR	NR	NR
Any Change	NR	NR	NR	33% of patients
≥ 50% reduction in MMDs				
CGRPr to CGPR	Three studies, 12%, 26% and 42.8% of patients	NR	NR	NR
CGRP to CGRPr	One study, 10% of patients	NR	NR	NR
Any Change	One study, 33.1% of patients	NR	60% of patients	15% of patients
Mean MMDs				
CGRPr to CGPR	NR	Median 6-month difference −1.6 (P = 0.109)	NR	NR
CGRP to CGRPr	NR	Median 6-month difference −3.73 (P < 0.001)	NR	NR
CGRP to another CGRP	NR	Median 6-month difference −3.47 (P = 0.001)	NR	NR
Any change	Decrease in 1 study, scale not reported	Median 6-month difference −5.0 (< 0.001)	Reduction of between 7 and 10 MMD suggested in Figure 5 (P < 0.001)	−1.2 days (95% CI, −2.7 to 0.3)
HIT-6 Score				
Any change	NR	NR	NR	−0.8 (95% CI, −3.6 to 2.0, P = 0.52)

CGRP = Calcitonin Gene-related Peptide; CGRPr = Calcitonin Gene-related Peptide receptor; MMD = monthly migraine days; HIT-6 = Headache-impact test-6; NA = not applicable; NR = not reported.

Note: Data are presented as percentages, which represents the proportion of the population in the study that reported that reduction in MMDs at follow-up.

Table 9: Summary of Findings by Outcome — Medication Use

Outcome	Wells-Gatnick et al. (2024)[8]	Suliman et al. (2024)[10] nonrandomized study	Suzuki et al. (2023)[9] nonrandomized study	Talbot et al. (2023)[11] nonrandomized study
Triptan days	NR	NR	NR	−1.0 (P = 0.16)
Painkiller days	NR	NR	NR	−1.5 (P = 0.18)

NR = not reported.

Table 10: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Diener et al. (2022)[12]	
"Data from uncontrolled trials suggests that switching from one monoclonal antibody to another was useful if one is ineffective, especially when accompanied by a change in drug class." "Whether it makes sense to switch from one ligand antibody to another cannot be conclusively answered at present with the available literature, but can certainly be considered pragmatically in individual cases."	The guideline clearly states that the data comes from uncontrolled trials, and cites 1 such trial.
Sacco et al. (2022)[13]	
The guideline notes that all CGRP medications have good tolerability, but these issues may lead to discontinuation. The guideline suggests that "If the reported side effect is specific for a given CGRP-mAb (e.g., constipation related to erenumab), switching to a different CGRP-mAb may be appropriate based on clinical experience."	Based on expert opinion.
In the case of inefficacy, the guideline notes that "considerations to support the switch from one CGRP-mAb to another, include differences in the mechanism of action (action on the ligand or on the receptor), difference in administration schedule (monthly versus quarterly) and to a lesser extent difference in formulations (subcutaneous versus intravenous) Eptinezumab is the only CGRP mAb available in an intravenous formulation." *Recommendation: In individuals with migraine with inadequate response to 1 monoclonal antibody targeting the CGRP pathway, there is insufficient evidence on the potential benefits of antibody switch but switching may be an option.*	"Some observational studies provide information to support this possibility; however, bias cannot be excluded, and those data cannot be considered sufficient to recommend a switch." "Considering the above reported reasons, the panel expressed a consensus statement to recognize the lack of adequate scientific evidence but at the same time we acknowledge that, for some individuals with migraine, a switch may represent the best therapeutic option. RCTs to test a CGRP-mAb switch in individuals with inadequate response to the first CGRP-mAb are needed to provide information on this issue."

CGRP = Calcitonin Gene-related Peptide

Appendix 6: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

Small Molecule Calcitonin Gene-Related Peptide Receptor Antagonists for the Acute Treatment of Migraine. Ottawa: CADTH; 2020 Mar. (CADTH Issues in Emerging Health Technologies; issue 184). https://www.cadth.ca/sites/default/files/hs-eh/eh0081-cgrp-for-acute-treatment-of-migraine-final.pdf

Emerging non-opioid drugs for the management of chronic non-cancer pain. Ottawa: CADTH; 2018. (Environmental scan; no. 69). https://www.cadth.ca/sites/default/files/pdf/ES0322_Non-Opioid%20Drugs%20for%20Non-Cancer%20Pain.pdf

For more information on CoLab and its work visit **colab.cadth.ca**

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