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Canadian Headache Society Guideline for Migraine Prophylaxis

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ABSTRACT: ***Objectives:*** The primary objective of this guideline is to assist the practitioner in choosing an appropriate prophylactic medication for an individual with migraine, based on current evidence in the medical literature and expert consensus. This guideline is focused on patients with episodic migraine (headache on ≤ 14 days a month). ***Methods:*** Through a comprehensive search strategy, randomized, double blind, controlled trials of drug treatments for migraine prophylaxis and relevant Cochrane reviews were identified. Studies were graded according to criteria developed by the US Preventive Services Task Force. Recommendations were graded according to the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. In addition, a general literature review and expert consensus were used for aspects of prophylactic therapy for which randomized controlled trials are not available. ***Results:*** Prophylactic drug choice should be based on evidence for efficacy, side-effect profile, migraine clinical features, and co-existing disorders. Based on our review, 11 prophylactic drugs received a strong recommendation for use (topiramate, propranolol, nadolol, metoprolol, amitriptyline, gabapentin, candesartan, butterbur, riboflavin, coenzyme Q10, and magnesium citrate) and 6 received a weak recommendation (divalproex sodium, flunarizine, pizotifen, venlafaxine, verapamil, and lisinopril). Quality of evidence for different medications varied from high to low. Prophylactic treatment strategies were developed to assist the practitioner in selecting a prophylactic drug for specific clinical situations. These strategies included: first time strategies for patients who have not had prophylaxis before (a beta-blocker and a tricyclic strategy), low side effect strategies (including both drug and herbal/vitamin/mineral strategies), a strategy for patients with high body mass index, strategies for patients with co-existent hypertension or with co-existent depression and / or anxiety, and additional monotherapy drug strategies for patients who have failed previous prophylactic trials. Further strategies included a refractory migraine strategy and strategies for prophylaxis during pregnancy and lactation. ***Conclusions:*** There is good evidence from randomized controlled trials for use of a number of different prophylactic medications in patients with migraine. Medication choice for an individual patient requires careful consideration of patient clinical features.

RÉSUMÉ: Ligne directrice de la Canadian Headache Society concernant la prophylaxie de la migraine. ***Objectifs :*** L'objectif principal de cette ligne directrice, fondée sur les données actuelles de la littérature médicale et sur des consensus d'experts, est d'aider le médecin traitant à choisir une médication prophylactique appropriée pour un patient migraineux. Cette ligne directrice cible les patients qui présentent de la migraine épisodique (céphalée présente ≤ 14 jours par mois). ***Méthode :*** Nous avons identifié, par une stratégie de recherche exhaustive, des études randomisées, à double insu et contrôlées, de traitements médicamenteux prophylactiques de la migraine et des revues Cochrane pertinentes. Les études ont été classifiées selon les critères élaborés par le US Preventive Services Task Force. Les principes du Grading of Recommedations Assessment, Development and Evaluation (GRADE) Working Group ont été utilisés pour classifier les recommandations. De plus, une revue de la littérature et un consensus d'experts ont été utilisés pour les aspects du traitement prophylactique pour lesquels aucun essai randomisé n'était disponible. ***Résultats :*** Le choix du médicament prophylactique devrait être basé sur des données démontrant son efficacité et son profil d'effets secondaires, et sur les caractéristiques cliniques de la migraine et les maladies coexistantes chez le patient. Suite à notre étude, 11 médicaments ont fait l'objet d'une forte recommandation pour cette utilisation (le topiramate, le propranolol, le nadolol, le métoprolol, l'amitriptyline, la gabapentine, le candésartan, le pétasite, la riboflavine, le coenzyme Q10 et le citrate de magnésium) et 6 ont fait l'objet d'une faible recommandation (le divalproex sodique, la flunarizine, le pizotifen, la venlafaxine, le vérapamil et le lisinopril). La qualité des données sur les différentes médications variait d'élevée à faible. Des stratégies de traitement prophylactique ont été développées pour aider le médecin à choisir un médicament prophylactique adapté à des situations cliniques spécifiques telles : des stratégies pour les patients qui n'ont jamais utilisé de traitement prophylactique (une stratégie bêta bloqueur et tricyclique), des stratégies qui comportent peu d'effets secondaires (stratégies tant avec des médicaments qu'avec des plantes médicinales / vitamines / minéraux), une stratégie pour les patients qui ont un indice de masse corporelle élevé, des stratégies pour les patients qui souffrent également d'hypertension ou de dépression et / ou d'anxiété et des stratégies additionnelles de monothérapie pour les patients chez qui les traitements prophylactiques antérieurs ont échoué. De plus, des stratégies pour la migraine réfractaire au traitement et pour la prophylaxie pendant la grossesse et la lactation ont été élaborées. ***Conclusions :*** Il existe des données de bonne qualité provenant d'essais contrôlés, randomisés, pour appuyer l'utilisation de différentes médications prophylactiques chez les patients migraineux. La médication doit être choisie judicieusement pour chaque patient, en tenant compte des caractéristiques cliniques du patient.

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Contributions to the Guideline - Authors

Pringsheim, T - Completed the literature search, did the systematic review, wrote initial drafts of Section 2, participated in consensus groups, and reviewed all draft manuscripts. *Davenport, WJ* - Contributed to the systematic review, contributed to the design of the guidelines, participated in consensus groups, and reviewed all draft manuscripts. *Mackie G* - Contributed to the guidelines in terms of an initial literature review, participated in all consensus groups, and reviewed all manuscript drafts. *Worthington, I* - Was the primary author of Table 2, Section 3, participated in consensus groups, and reviewed all manuscript drafts. *Aubé, M* - Participated in consensus groups, and provided extensive feedback on manuscript drafts. *Christie, S* - Participated in all consensus groups, and provided feedback on manuscript drafts. *Gladstone, J* - Participated in consensus groups, and provided extensive feedback on manuscript drafts. *Becker WJ* - Was the primary author of Sections 1, 3, 4, and 5, and of all three appendices, and wrote the final draft of the manuscript, participated in abstract review for the systematic review, and participated in all consensus groups.

Other members of the Canadian Headache Society Prophylactic Guidelines Development Group

Participated in consensus groups and/or provided feedback on manuscript drafts.

External reviewers

We are very grateful to our external reviewers who reviewed draft manuscripts and provided extensive feedback. They did not review the final manuscript, and the authors take full responsibility for the content of this guideline.

Conflict of Interest

Pringsheim, T - Dr. Pringsheim has received an educational grant from Teva Neuroscience. *Becker, WJ* - Dr. Becker has served on Advisory boards and/or done clinical trials for and/or received speaker's honoraria from: Allergan, Merck, AGA Medical, Medtronic, Teva, Johnson and Johnson, and Pfizer. W*orthington, I* - Ms. Worthington has served on Advisory Boards and/or received honoraria (speaker, consultation, and travel to headache conferences) from: Merck Frosst, Glaxo Smith Kline, and Astra Zeneca. *Aubé, M* - Dr. Aubé has served on Advisory boards and/or done clinical trials for and /or received speaker's honoraria from: Merck, Teva, Johnson and Johnson, and Pfizer. *Christie, SN* - Dr. Christie has served on Advisory Boards and/or received Research Grants, Speaker Honoraria/Educational Grants from Merck Frosst, Allergan, Pfizer, Teva and Johnson and Johnson. *Gladstone JP* - Dr. Gladstone has served on Advisory Boards and/or been involved with clinical trials for and/or received educational grants/speaker's honoraria from: Allergan, Merck, Teva, Johnson & Johnson and Pfizer. He holds investments in Allergan. *Gawel, M* - Dr. Gawel has served on advisory boards and/or received research funding from GlaxoSmithKline, Pfizer Allergan, Merck, Janssen, Neuraxon, Allergan, Astra Zeneca and Abbott. *Leroux E* - Dr. Leroux has served on advisory boards for and/or received honoraria from Allergan, Merck, Pfizer, and Johnson and Johnson. Her institution (Hôpital Notre-Dame, Montreal, QC, Canada) has received grants from Pfizer, Merck, and Teva Neuroscience. *Robinson, G* - Dr. Robinson has served on Advisory boards and /or received speaker's honoraria from Allergan, Merck, Teva, Johnson and Johnson, and Pfizer. *Richer, L* - Dr. Richer has served on advisory boards and / or participated in clinical trials with Janssen-Ortho, Allergan, and Merck. *Giammarco R* - Dr. Giammarco has served on advisory boards for or received honoraria from Merck, Allergan, Pfizer, and Johnson and Johnson. *Purdy RA* - Dr. Purdy has served on advisory boards and/or given continuing professional development presentations for Merck Canada and Pfizer. *Shapero G* - Dr. Shapero has been a consultant or speaker for Merck Frosst, Pfizer, Astra Zeneca, Mcneil, GlaxoSmith-Kline, Teva, Allergan, and Johnson and Johnson.

Guideline Structure

This guideline is divided into five sections and three appendices. The systematic review in section 2 is the core of the guideline, but Sections 1 and 3 address many other issues important for migraine prophylaxis for which randomized controlled trial information is not available. A guideline summary for primary care physicians and a summary for patients are also provided.

The appendices provide a detailed summary of how the guideline was developed. They also have information on behavioural aspects of migraine therapy, and provide several tools for use in migraine prophylaxis including a patient information sheet.

The sections and appendices are listed below. Each contains its own references in order to allow it to be used on its own, and to allow for easier updating.

Section 1:	Introduction to the Guideline, and General Principles of Migraine Prophylaxis
Section 2:	Systematic Review: Medications for Migraine Prophylaxis
Section 3:	Treatment Strategies: Pharmacological Prophylaxis
Section 4:	Migraine Prophylactic Guideline Summary for Primary Care Physicians
Section 5:	Migraine Preventive Medication Guideline: A Summary for Patients and Their Families
Appendix 1:	Headache Triggers, Lifestyle Factors, and Behavioural Therapies in Migraine
Appendix 2:	Guideline Development Summary
Appendix 3:	Tools for use in Migraine Prophylaxis

Introduction to the Guideline, and General Principles of Migraine Prophylaxis - Section I

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ABSTRACT: ***Objectives:*** To provide an overview of the objectives and target population of the guideline and to review the general principles of pharmacological migraine prophylaxis. ***Methods:*** A general literature review and several consensus groups were used to formulate an expert consensus for the general use of migraine prophylactic medications. ***Results:*** The objective of the guideline is to assist the physician in choosing an appropriate prophylactic medication for an individual with frequent migraine, and thereby reduce migraine-related disability. Prophylactic therapy should be considered when migraine has a substantial impact despite use of acute medications, or when high attack frequency puts patients at risk for medication overuse headache. A specific prophylactic medication is chosen based on evidence for efficacy, tolerability, and on the presence of co-existing disorders. A prophylactic trial should consist of at least two months at the target dose (or at the maximum tolerated dose if the usual target dose is not tolerated) before the medication is considered ineffective. It is usually considered effective if migraine frequency is reduced by 50% or more. ***Conclusions:*** This guideline provides advice on the use of prophylactic medications including when to initiate prophylaxis, how to choose a prophylactic drug, and for how long to continue prophylactic therapy.

RÉSUMÉ: Introduction à la ligne directrice et principes généraux de la prophylaxie de la migraine – Section I. ***Objectifs :*** Le but de cet article est de fournir un aperçu des objectifs et de la population-cible de la ligne directrice et de réviser les principes pharmacologiques généraux de la prophylaxie de la migraine. ***Méthode :*** Nous avons eu recours à une revue générale de la littérature et à plusieurs groupes de consensus pour formuler un consensus expert pour l'utilisation générale de médicaments prophylactiques contre la migraine. ***Résultats :*** L'objectif de la ligne directrice était d'aider les médecins à choisir un médicament prophylactique approprié pour un individu qui présente des migraines fréquentes et ainsi réduire l'invalidité due à la migraine. Un traitement prophylactique devrait être envisagé quand la migraine a un impact substantiel malgré l'utilisation d'une médication en phase aiguë ou quand la fréquence est telle que le patient risque de surutiliser la médication antimigraineuse. Le choix d'une médication prophylactique spécifique est basé sur les preuves de son efficacité et de son innocuité, et sur la présence de maladies coexistantes. Un essai de médication prophylactique devrait durer au moins deux mois à la dose-cible (ou à la dose maximale tolérée si la dose-cible usuelle n'est pas tolérée) avant que la médication ne soit considérée inefficace. Le médicament est habituellement considéré comme efficace si la fréquence de la migraine est diminuée de 50% ou plus. ***Conclusions :*** Cette ligne directrice fournit des conseils sur l'utilisation des médicaments prophylactiques y compris quand commencer la prophylaxie, comment choisir une médication prophylactique et combien de temps l'administrer.

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Migraine is a common neurological disorder and often causes significant disability. The lifetime prevalence of migraine in Canada has been shown to be approximately 24% in women and 9% in men[1-3]. Migraine is ranked 19th among all health disorders in terms of causing years of life lived with disability by the World Health Organization[4].

Migraine pharmacotherapy is complex, and poses a significant challenge for the physician and the patient. The medications used can be divided into two broad categories: symptomatic or acute medications to treat individual migraine attacks and prophylactic or preventive medications which are used to reduce migraine attack frequency.

All the drugs used for migraine prophylaxis have incomplete efficacy, and most produce adverse effects in many patients. Which drug should be tried first is a clinical decision which is usually based on a number of factors. When prophylaxis should be started is a matter of clinical judgement as precise evidence on which to base this decision is lacking. Finally, drug prophylaxis is no substitute for careful attention to patient lifestyle and migraine trigger management. All patients for whom migraine drug prophylaxis is being considered should be educated regarding the common migraine triggers and the important lifestyle factors which may potentially influence their headache frequency (see Appendix 1).

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Acute migraine therapy, although helpful for many patients, is not adequate treatment for all. Patients with frequent migraine attacks may retain significant disability despite appropriate acute therapy, and when acute medications are used too frequently, they can result in increased headache frequency and medication overuse headache[5,6]. In the Canadian Headache Outpatient Registry and Database (CHORD) study, 21% of patients referred to headache specialists in Canada who received a migraine diagnosis had acute medication overuse[7].

Guideline objectives and target population

Objectives

The primary objective of this guideline is to assist the physician in choosing an appropriate prophylactic medication for an individual with migraine, based on current evidence in the medical literature. Additional objectives include assisting the practitioner in determining which patients need prophylaxis, and how long prophylaxis should be continued. Systematic evidence is not available in the literature for all the clinical decisions which must be made, and an effort has been made in this guideline to place the evidence that exists into a clinical context based upon the medical literature and the experience of experts in headache medicine.

The main clinical question which this guideline aims to help answer for the medical practitioner is, *"Which prophylactic drug should be prescribed for an individual patient in a specific clinical situation"*.

The primary goal of pharmacological migraine prophylaxis is to reduce headache frequency, and headache frequency-related outcome measures are the main outcome measures used in clinical trials evaluating the efficacy of putative prophylactic drugs. The ultimate purpose of this guideline is to reduce the headache-related disability suffered by individuals with migraine. Headache frequency is one factor leading to patient disability.

Target Population

This guideline is focused on patients with episodic migraine (headache on ≤ 14 days a month) who:

1. Suffer a significant degree of disability as a result of their migraine, and for whom acute medication treatment has not proved sufficient to minimize this disability.
2. May be responding well to their symptomatic medications, but in whom a high frequency of acute medication use may place them at risk for medication overuse headache or significant systemic side effects.

Although it is likely that physicians may extrapolate from the evidence presented here and use it for the care of patients with higher migraine frequencies, the literature reviewed for these guidelines did not include patients with chronic migraine (headache on > 14 days a month).

Who Should Use This Guideline?

This guideline is intended primarily for physicians who provide care to patients with migraine, including both family physicians and specialists, and for other health professionals involved in the care of the patient with migraine. Some family physicians, given their broad spectrum of practice, may wish to become familiar with the use of only some of the medications described in this guideline. In that case, this guideline should be helpful in identifying which medications should be considered in patients with migraine undergoing prophylactic therapy for the first time, or who have tried only a few prophylactic medications previously. Other family physicians who have a major interest in migraine treatment, and specialists who treat patients with headache may wish to utilize the full spectrum of medications discussed in this guideline.

Migraine is a chronic medical condition. Successful management usually requires that the patient actively partner with the health professional in determining the optimal management plan. Individuals with migraine and their families are a secondary target audience for this guideline, and this guideline includes a patient-friendly summary (see Section 5).

Further information on some of the features of this guideline and how it was produced is summarized in Appendix 2. Primary care physicians may want to consult Section 4 which provides a summary of this guideline for primary care physicians, and also Appendix 3 which provides some tools to assist in patient care.

Expert Consensus and Recommendations

The core of this guideline is Section 2 "Systematic Review: Medications for Migraine Prophylaxis". The recommendations in this section are based on a systematic review as described in that section. Evidence from randomized controlled trials is not available, however, to guide clinicians with regard to many aspects of migraine prophylaxis where clinical decisions must nevertheless be made. To recognize this, treatment suggestions made in other sections of these guidelines are labelled as "Expert consensus", as they are based on a general literature review and on the expert opinion of clinicians experienced in migraine treatment.

Migraine Prophylaxis: General Considerations

When should migraine prophylaxis be considered?

Prophylactic therapy should be considered in patients whose migraine attacks have a substantial impact on their lives despite appropriate use of acute medications, or where the frequency of their migraine attacks is such that reliance on acute medications alone puts them at risk for medication overuse headache[8]. Some guidelines have suggested that prophylactic treatment should be considered when a patient has three or more severe migraine attacks per month that fail to respond adequately to symptomatic drug treatment[9]. Although attack frequency is helpful in determining the need for prophylactic therapy, the decision to discuss prophylaxis with the patient should be individualized, and all aspects of the patient's migraine syndrome, including the risk of acute medication overuse, need to be considered. Based on expert consensus, some guidelines indicate that prophylactic therapy may also be considered in patients who have severe or prolonged auras even if attacks are relatively infrequent[8].

The population of migraine sufferers who might potentially benefit from prophylaxis is large. Epidemiological studies have shown that 21% of patients with migraine have four or more headache days per month and an additional 5% have migraine on three days a month, but suffer severe impairment or require bed rest during their attacks[10]. It has been estimated that approximately 25% of all migraine sufferers should be offered prophylactic therapy[10]. It is generally considered that

prophylactic medications are underutilized. For patients with migraine referred to headache specialists in Canada in the CHORD study, at the time of specialist consultation 31% of patients were taking a prophylactic drug. Once seen by the specialist, a preventative was recommended or prescribed for 70% of patients[7]. Nevertheless, most medications used for migraine prophylaxis have potential side effects, and the risk-benefit ratio for an individual patient needs to be considered whenever prophylaxis is initiated.

If migraine prophylaxis is defined as therapy directed at reducing migraine frequency, it is important to note that not all migraine prophylactic therapies are pharmacological. Trigger management and lifestyle factors have already been mentioned (see Appendix 1). A number of behavioural therapies can also be used to reduce migraine frequency, and offer an alternative to pharmacological prophylaxis for some patients, or can be used in conjunction with medications. These behavioural therapies include the mastery of relaxation techniques, cognitive behavioural therapy including stress management, biofeedback, and the mastery of pacing and self monitoring skills (see Appendix 1).

EXPERT CONSENSUS

i. Migraine prophylactic therapy should be considered in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management / lifestyle modification strategies.

ii. Migraine prophylactic therapy should be considered when the frequency of migraine attacks is such that reliance on acute medications alone puts patients at risk for medication overuse (rebound) headache. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, ASA, NSAIDs) on 15 days a month or more,

iii. Migraine prophylaxis should be considered for patients with greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective because of the risk of medication overuse headache.

iv. Migraine prophylaxis may be considered in some patients with relatively infrequent attacks according to patient preference and physician judgement, for example in patients with hemiplegic migraine.

v. Migraine prophylaxis may be particularly useful for patients with medical contraindications to acute migraine therapies.

When should migraine prophylactic therapy be stopped?

When migraine prophylactic therapy is initiated, one of three outcomes can be anticipated:

1) The patient may develop intolerable side effects. As a result, the drug may need to be discontinued within days or weeks of initiation of therapy.
2) The drug may show insufficient efficacy. By one month after initiation of treatment, most prophylactic drugs already show some efficacy as measured in patient groups, although the therapeutic effect may increase for several months thereafter[11-13]. If the patient shows no benefit after two months of therapy at the target dose, prophylactic treatment should probably be stopped, and if indicated, another medication tried.
3) The patient may show significant benefit, usually defined as a reduction in migraine frequency or days with headache of 50% or more. The decision as to whether worthwhile benefit has occurred needs to be individualized, and can be greatly enhanced by use of a headache diary. Although the primary effect of prophylactic medications is to reduce migraine attack frequency, anecdotally some patients may also benefit from reduced headache intensity, duration, and / or their attacks may respond better to symptomatic medications. Large clinical trials with anticonvulsant prophylactics (divalproex, topiramate) have generally been unable to demonstrate a significant reduction in headache intensity as a result of prophylaxis[11,12,14] or have shown only minor or equivocal changes[13,15]. One study was unable to show enhanced responsiveness to triptans when patients went on topiramate prophylaxis[16]. It has been reported, however, that both amitriptyline and propranolol reduce the severity of migraine attacks[17].

There is little evidence with regard to how long successful migraine prophylaxis should be continued. Although it is hoped that successful prophylaxis will stabilize a patient's migraine disorder so that attack frequency will remain diminished for a significant period of time after drug discontinuation, the evidence suggests that most patients do relapse to some extent after cessation of prophylactic therapy. One study found that 75% of patients developed increased migraine frequency when successful prophylaxis was stopped[18], and although the time to relapse was highly variable from patient to patient, it occurred on average six months after cessation of prophylaxis. Another study which randomized patients to placebo or continued topiramate therapy after 26 weeks of topiramate prophylaxis found that within one month patients on placebo had deteriorated significantly in terms of migraine frequency as compared to those who continued topiramate therapy[15]. However, even after 26 weeks on placebo, headache frequency had not increased to the baseline frequency which had been present before starting topiramate prophylaxis. This may have been due to "regression to the mean" in their attack frequency rather than representing a long term effect of topiramate prophylaxis. Data from placebo controlled crossover trials indicates that, at least after short term prophylactic therapy (usually three months), the benefits of prophylaxis begin to wane within four weeks of stopping prophylaxis for valproate[14] and flunarizine[19].

In conclusion, there is little evidence to indicate how long successful migraine prophylaxis, once initiated, should be continued. Existing guidelines either do not address this issue[20], or recommend tapering of the prophylactic drug after three to six months if the headaches are well controlled[8], or after "several" months[9]. Given the evidence that the effects of prophylactic drugs begin to wane quickly after prophylaxis is stopped, it might seem prudent to continue prophylaxis for much longer in patients with difficult migraine which has caused major disability in the past. As discussed below in relation to migraine progression, it may be prudent to continue prophylaxis for long periods of time in patients with a long history of relatively high migraine frequency.

The ultimate decision would also depend not only on the benefit experienced by the patient, but also on whether any

significant side effects are present. Although a patient may have initially tolerated a prophylactic medication well and experienced significant improvement, over the long term significant side effects, for example excessive weight gain or ongoing fatigue, may require re-evaluation and at times discontinuation of the medication. Patient follow up is important, for if the initial benefits of the prophylactic drug eventually disappear, there would appear to be little purpose in continuing it. Diary documentation of migraine attack frequency and days with headache per month can be helpful in making these decisions. A headache diary form can be downloaded by patients from www.headachenetwork.ca.

EXPERT CONSENSUS

i. A prophylactic medication trial should consist of at least two months at the target or optimal dose (or at the maximum tolerated dose if the usual target dose is not tolerated) before a prophylactic drug is considered ineffective.

ii. A prophylactic medication is usually considered effective if migraine attack frequency or the number of days with headache per month is reduced by 50% or more, although lesser reductions in migraine frequency may be worthwhile, particularly if the drug is well tolerated.

iii. In addition to reduction in migraine attack frequency or in the number of days with headache per month, reductions in headache intensity and migraine-related disability need to be considered when judging the effectiveness of prophylactic therapy.

iv. Patients on migraine prophylaxis require periodic re-evaluation both to monitor potential side effects, and to assess efficacy.

v. Because of its utility in assessing the effectiveness of prophylactic therapy, patients should be strongly encouraged to keep a headache diary / calendar.

vi. After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the prophylactic medication in many patients, although others may benefit from a much longer duration of prophylactic therapy. If headache frequency increases as the prophylactic drug dosage is reduced, the dosage can be increased again or the drug restarted if it has been discontinued.

Choosing a prophylactic drug

There is no ideal or 1st line prophylactic drug. In choosing a drug for an individual patient, the following need to be considered.

1. *Efficacy:* How strong is the evidence that the drug reduces migraine frequency?
2. *Drug side effect profile:* How safe is the drug, and how well tolerated?
3. *Co-existing medical and/or psychiatric disorders:* Does the patient have depression, anxiety, insomnia, obesity, hypertension, a history of renal calculi, associated tension-type headaches, or another disorder which might influence drug choice?

This guideline will focus on the current evidence regarding the efficacy of selected migraine prophylactic agents.

Recommendations regarding the use of each agent will be made based on the quality of the available evidence (Section 2). A later section of this guideline focuses on pharmacological prophylactic treatment strategies (Section 3), and discusses in more detail how to choose an appropriate prophylactic medication for a specific patient.

Medication over-use

Overuse of acute headache medications is generally considered to render migraine prophylaxis less effective, and cessation of medication overuse is recommended to improve the chances of success when initiating prophylactic therapy[8,9]. Promoting cessation of medication overuse is an important treatment strategy. Of interest, however, several clinical trials have suggested that topiramate can be effective in reducing migraine frequency in the presence of medication overuse, and results in a reduction in symptomatic medication use[21,22]. Studies on the use of onabotulinumtoxinA for prophylaxis of chronic migraine (migraine with headache on more than 14 days-a-month) have also suggested that patients with medication overuse respond to prophylaxis[23,24]. Other prophylactic medications may also be helpful in patients with medication overuse[25]. Based on current evidence, it would appear most advantageous for patients with migraine and medication overuse to both stop their medication overuse and at the same time to start a prophylactic medication.

It is important to recognize that analgesics taken by the patient for other painful conditions (for example back pain) may result in medication overuse headache in the migraine sufferer. Patients may neglect to mention these medications during a headache consultation unless specifically asked.

EXPERT CONSENSUS

i. When prophylactic drug therapy is started, the patient should also be evaluated for the presence of acute medication overuse, and cessation of medication overuse should be strongly encouraged to optimize the chances of success. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, ASA, NSAIDs) on 15 days a month or more.

Migraine progression

A minority of patients with migraine develop a very frequent headache pattern over time, either in association with medication overuse, or due to an apparent progression of their migraine disorder to chronic migraine. Patients with a higher frequency of migraine attacks appear to be at greater risk for further progression to chronic migraine[26]. It is possible, although not proven, that use of prophylactic therapy might prevent or delay patient progression to chronic migraine. An analysis of several large placebo-controlled topiramate treatment trials has provided some evidence that this might be the case[27]. However, in a sample of patients with high-frequency migraine, topiramate prophylaxis did not result in a statistically significant reduction in the proportion of patients who went on to develop chronic daily headache (headache on more than 14 days a month) over a six month time period as compared to placebo[28].

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Systematic Review: Medications for Migraine Prophylaxis - Section II

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ABSTRACT: ***Objective:*** To assess the evidence base for drugs used for prophylaxis of episodic migraine (headache on ≤ 14 days a month) in Canada. ***Methods:*** A detailed search strategy was employed to find relevant published clinical trials. All abstracts were reviewed for eligibility by two reviewers. Only double-blind randomized clinical trials with placebo or active drug controls were included in the analysis. Studies were graded with respect to methodological quality according to the US Preventative Services Task Force. Recommendations were graded according to the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, using a consensus group. ***Results:*** Nineteen medications were evaluated. Seventeen were recommended for use in migraine prophylaxis. Four received a strong recommendation – high quality evidence (topiramate, propranolol, metoprolol, and amitriptyline), four received a strong recommendation – moderate quality evidence (nadolol, gabapentin, candesartan, butterbur), and three received a strong recommendation – low quality evidence (riboflavin, co-enzyme Q10, and magnesium citrate). Three medications received a weak recommendation – high quality evidence (divalproex sodium, flunarizine, and pizotifen), and three received a weak recommendation – low quality evidence (venlafaxine, verapamil, and lisinopril). A strong recommendation was made not to use two medications in patients with episodic migraine: botulinum toxin type A (high quality evidence), and feverfew (moderate quality evidence). ***Conclusion:*** Our systematic review formulated recommendations for the available medications for migraine prophylaxis according to the GRADE method. This should be helpful for practitioners who prescribe medications for migraine prophylaxis.

RÉSUMÉ: Revue systématique sur les médicaments utilisés en prophylaxie de la migraine – Section II. ***Objectif :*** Le but de l'étude était d'évaluer les données factuelles concernant les médicaments utilisés pour la prophylaxie de la migraine épisodique (céphalée présente ≤ 14 jours par mois) au Canada. ***Méthode :*** Une stratégie de recherche détaillée a été utilisée pour identifier les essais cliniques publiés qui étaient pertinents. Tous les résumés ont été révisés par deux réviseurs pour déterminer s'ils pouvaient être inclus dans l'étude. Seuls les essais cliniques randomisés, à double insu avec placebo ou un médicament actif comme comparateur, ont été inclus dans l'analyse. Les études étaient classées selon la qualité de la méthodologie telle que déterminée par la US Preventative Services Task Force. Les recommandations étaient classées selon les principes du Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, par un groupe de consensus. ***Résultats :*** Dix-neuf médicaments ont été évalués. Dix-sept étaient recommandés en prophylaxie de la migraine. Quatre ont reçu une forte recommandation – données probantes de haute qualité (le topiramate, le propranolol, le métoprolol et l'amitriptyline), quatre ont reçu une forte recommandation – données de qualité modérée (le nadolol, la gabapentine, le candésartan et le pétasite) et trois ont reçu une forte recommandation – données de faible qualité (la riboflavine, le coenzyme Q10, le citrate de magnésium). Trois médicaments ont reçu une faible recommandation – données de haute qualité (le divalproex sodique, la flunarizine et le pizotifen) et trois ont reçu une faible recommandation – données de faible qualité (la venlafaxine, le vérapanil et le lisinopril). Il a été fortement recommandé de ne pas utiliser deux médicaments chez les patients qui souffrent de migraine épisodique : la toxine botulique de type A (données probantes de haute qualité) et la grande camomille (données probantes de qualité modérée). ***Conclusion :*** Suite à notre revue systématique et en nous servant de la méthode GRADE, nous avons formulé des recommandations pour l'utilisation des médicaments disponibles pour la prophylaxie de la migraine. Ces recommandations devraient être utiles aux médecins qui prescrivent des médicaments pour la prophylaxie de la migraine.

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Many medications have been used for migraine prophylaxis, and a number are widely used. Because evidence for efficacy is one of the factors used in choosing a prophylactic medication for a patient, it is important to understand what evidence is available for each medication. This systematic review describes the evidence available for each commonly used medication for which randomized controlled clinical trial data is available, assesses the quality of this evidence, and provides a recommendation for or against the use of each medication based on the GRADE method.

A number of other medications which have been promoted by some for use in migraine prophylaxis and which are either rarely used or for which little or no randomized controlled trial data is available are also discussed, based on a general literature review and expert consensus.

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Methodology

A systematic review as outlined below was completed to assess the available evidence for the use of each prophylactic medication. For further details on the general principles of prophylactic medication use, please see Section 1 of this guideline. Appendix 2 provides more information on the development of this guideline. Section 3 provides more details on choosing a specific prophylactic drug for an individual patient, and the clinical use of each medication.

Criteria for Considering Studies for this Guideline

Studies evaluated for this guideline were required to be prospective, randomized, double blind, controlled trials of drug treatments used to prevent the occurrence of migraine attacks. Trials comparing treatments to placebo or an active comparator were included. Both parallel group and cross-over designs were acceptable.

Study participants in the trials were required to be adults and meet International Headache Society[1] or Ad Hoc[2] criteria for the diagnosis of migraine headache, or trial publications had to provide sufficient detail of the headache characteristics to support the diagnosis of migraine (for studies conducted prior to development of Ad Hoc criteria). Trials of patients with chronic daily headache (headache on ≥ 15 days per month), chronic tension type headache or transformed and chronic migraine were not included.

Due to the large number of different pharmacological agents assessed over the past 60 years for the prophylaxis of migraine, we limited our search to those agents commonly used in clinical practice. The list of target drugs included (1) Antiepileptics: valproic acid / divalproex sodium / sodium valproate, gabapentin, topiramate, (2) Antidepressants: amitriptyline, venlafaxine, (3) Antihypertensives and other calcium channel antagonists: propranolol, nadolol, metoprolol, flunarizine, verapamil, candesartan, lisinopril, (4) Vitamins/minerals/herbals: riboflavin, coenzyme Q10, butterbur, magnesium, feverfew, (5) Botulinum toxin type A, (6) Serotonin antagonists: pizotifen.

For the efficacy analysis, the main outcome considered was headache frequency. Among headache frequency measures, the preferred measures were the number of migraine attacks or migraine days per four week period, and the responder rate (proportion of patients achieving a 50% decrease in the frequency of migraine attacks in comparison to baseline).

Search Methods for Identification of Studies

For the identification of studies included or considered for this guideline, a detailed search strategy was developed for Ovid MEDLINE (1950 to April 2008) and EMBASE (1980 to April 2008). The search strategy combined the subject search with a highly sensitive search strategy for randomized controlled trials. The subject search used a combination of controlled vocabulary and free-text terms. Search terms used were: i) migraine disorders/pc or migraine with aura/pc or migraine without aura/pc (1283); ii) limit 1 to (humans and (controlled clinical trial or meta analysis or randomized controlled trial)) (282). More details on the literature search are given in Appendix 2, Section 8. A review article based on this systematic review has been published previously[3]. A second literature search was carried out in June, 2011, using the same search terms, in order to update the literature review.

In addition, the Cochrane Collaboration Library was searched for systematic reviews of agents used for migraine prophylaxis. Cochrane systematic reviews were used to summarize trial data if similar inclusion criteria and methodology were used in the review.

Methods of the Review

Titles and abstracts of studies identified by the literature search were screened for eligibility by two independent reviewers (TP and WJB). Papers that could not be excluded with certainty on the basis of the information contained in the title or abstract were retrieved in full for screening. Papers passing the initial screening process were retrieved and the full text was reviewed independently by two reviewers (TP and WJD). For the literature update search done in June 2011, full text articles were again reviewed independently by two reviewers (WJB and LD) (See acknowledgement).

Assessment of Individual Clinical Trials

Studies were graded with respect to methodological quality using criteria developed by the US Preventive Services Task Force[4]. Studies are rated "good" if all of the following criteria are met: assembly of comparable groups, adequate randomization, allocation concealment, confounders distributed equally, maintenance of comparable groups, absence of overall high or important differential loss to follow-up, measurement instruments are acceptable and applied equally, masking of outcome assessment, clear definition of interventions, all important outcomes considered and intention to treat analysis performed. A "fair" study does not meet all criteria but has no fatal flaw that invalidates its results. A "poor" study contains a fatal flaw. Fatal flaws include the assembly of non-comparable groups, the use of unacceptable or unequally applied measurements, lack of blinding of outcome assessment, failure to address key confounders, and lack of intention to treat analysis.

Grading of Recommendations and Assessment of Overall Quality of Evidence

The recommendations were graded based on the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Using the GRADE system, the strength of a recommendation reflects the extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects[5]. The strength of a recommendation in the GRADE system is based on several factors including[6]:

1. The balance between the desirable and undesirable consequences of a therapy, for example, the balance between the benefits and the side effects of a drug.
2. The quality of the evidence on which judgements of the magnitude of the benefit and the potential harm of an intervention are based.

We graded the strength of the recommendations in this section of the guideline based on the above, using an expert consensus group (see Appendix 2). Uncertainty about or variability in patient values and preferences, also part of the GRADE process,

Table 1: Levels of evidence: GRADE System (7)

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.

was considered. We did not specifically consider treatment cost. The quality of evidence for or against the use of a drug was placed into one of four categories: high, moderate, low, and very low[7]. Importantly, these categories were used to classify the body of evidence related to a medication rather than individual research studies or clinical trials. Definitions for the categories used for evidence quality are given in Table 1.

The GRADE system was chosen to classify the recommendations in this guideline because it appeared to allow for the best characterization of a recommendation, given that drug efficacy, drug side effects, and the degree of evidence available in the literature were all considered in grading a recommendation. There is some evidence that it is among the best recommendation grading system in terms of influencing the decisions of clinicians[8].

The GRADE recommendations are made in two categories. A strong recommendation means that the intervention could be used for most patients, and that the benefits of therapy outweigh the potential risks. A weak recommendation indicates that the intervention could still be applied to a majority of patients, but it would not be appropriate for many. With a weak recommendation, the balance between risks and benefits is closer or more uncertain. In other words, whether the intervention is suitable for a patient depends a great deal on the clinical situation and the nature of the patient. For this reason, weak recommendations are sometimes called "conditional' recommendations, as whether they are appropriate depends (or is conditional) on the details of the clinical situation much more so than for a strong recommendation[9]. The quality of evidence supporting the recommendation indicates how much confidence we have in that recommendation. The meaning of the various recommendation categories and their clinical implications are given in Table 2[6,7,9]. As shown in Table 2, it is important to recognize that the recommendations as formulated in GRADE are somewhat dichotomous. If the benefits clearly outweigh the risks and burdens, a medication gets a strong recommendation, even though the evidence that the drug is effective may be poor. Thus, for a drug with very few side effects, it is possible to have a strong recommendation coupled with low quality evidence (eg riboflavin). Both features of the recommendation are however, clearly stated in, for example, "Strong – low quality evidence".

Table 2: Recommendation grades: meaning and clinical implications*

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

*Only categories used in this guideline are shown

Statistical Methods

Meta-analysis was performed by treatment type where appropriate if more than one trial was identified. Odds ratios (ORs) were calculated for the responder rate (proportion of study subjects with a decrease in their migraine attack frequency of at least 50%) relative to placebo. ORs from multiple studies were tested for homogeneity using the chi-squared test and by calculating the I^2 statistic. If study estimates were homogenous, they were combined using a fixed-effects model. When studies with heterogeneous results were clinically similar, the study estimates were combined using a random-effects model. Clinical heterogeneity was assessed by looking at trial and patient characteristics, and outcome measures. Clinically heterogeneous studies were not statistically combined.

Characteristics of Included Studies

The initial search strategy yielded 883 abstracts and 3 Cochrane systematic reviews. After analysis of the abstracts and systematic reviews, only 59 studies and one Cochrane systematic review met our inclusion criteria and were included. The updated literature search in June 2011 resulted in the inclusion of an additional eight publications reporting relevant clinical trials, and two additional published meta-analyses.

The vast majority of studies used the International Classification of Headache Disorders[1] or Ad Hoc[2] criteria for the diagnosis of migraine. The majority of study participants were women. Pregnant or lactating women were excluded. Most studies specifically excluded patients with chronic daily headache, or medication use on more than 10 to 15 days per month. Patients were usually required to have between two and eight migraine attacks per month for study inclusion, and were not permitted to take any other migraine prophylactic treatment

Table 3: Antiepileptics

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Freitag, Divalproex sodium extended release, 2002	237	Good	4 wk baseline, randomization to divalproex sodium extended release 500 to 1000 mg or placebo for 12 wks	4 wk migraine rate reduction from baseline	Migraine rate reduction Placebo -0.6 Divalproex sodium -1.2 Responder rate Placebo 28% Divalproex sodium 41%	 0.006 0.024	
Mathew, Divalproex sodium, 1995	107	Fair	4 wk baseline, randomization to placebo or divalproex sodium or placebo for 12 wks (mean dose 1087 mg)	4 wk migraine rate	4 week migraine rate Placebo 5.7 Divalproex sodium 3.5 Responder rate Placebo 14% Divalproex sodium 48%	<0.001 <0.001	Randomization method not stated. Allocation concealment unclear.
Klapper, Divalproex sodium, 1997	171	Fair	4 wk baseline, randomization to valproate 500 mg, 1000 mg, 1500 mg or placebo for 12 wks	4 wk migraine frequency	Mean reduction in 4 week attack frequency Placebo 0.5 500 mg 1.7 1000 mg 2.0 1500 mg 1.7 Responder rate Placebo 21% Divalproex 44%	 0.05 0.05	Randomization method not stated. Allocation concealment unclear.
Jensen, Sodium Valproate 1994	43	Poor	4 wk run-in, randomization to valproate (1000 to 1500 mg) or placebo for 12 wks, washout 4 wks, then crossover to alternate Rx for 12 wks	Mean # of days with migraine per 4 wks	Mean # of migraine days per 4 wks Baseline 6.1 Placebo 6.1 Valproate 3.5 Responder rate Placebo 21% Valproate 65%	0.0003 0.0018	Intention to treat analysis is lacking. Allocation concealment unclear.
Hering, Sodium Valproate 1992	32	Fair	Randomization to 400 mg valproate or placebo for 8 wks, followed by crossover to alternate Rx for 8 wks	Mean # of attacks over 8 wk treatment phase	Valproate 8.826 Placebo 15.586	<0.001	Randomization method not stated. Allocation concealment unclear.
Di Trapani, Gabapentin 2000	63	Fair	One month baseline period, randomization to gabapentin 1200 mg or placebo for 12 wks	Frequency of migraine attacks in 3rd month of Rx vs baseline and placebo	Frequency of migraine Placebo: Baseline 5.41 3rd month 4.70 Gabapentin: Baseline 5.08 3rd month 3.13	<0.001	Generally comparable groups (little data given). Not all important confounders accounted for. Method of randomization not stated. Allocation concealment unclear.
Mathew, Gabapentin 2001	145	Poor	4 wk baseline, randomization to gabapentin up to 2400 mg per day or placebo for 12 wks	4 wk migraine rate during last 4 wks of Rx period	4 wk migraine rate median change from baseline Placebo: -0.8 Gabapentin:-2.0 Responder rate Placebo 16.1% Gabapentin 46.4%	0.013 0.008	Minor problems with follow up. Intention to treat analysis is lacking.
Brandes, Topiramate, 2004	483	Good	28 day prospective baseline, randomization to placebo, topiramate 50, 100 or 200 mg per day for 26 wks	Mean monthly migraine frequency	Mean monthly migraine frequency Placebo Baseline 5.6 Rx phase 4.5 50 mg Baseline 5.4 Rx phase 4.1 100 mg Baseline 5.8 Rx phase 3.5 200 mg Baseline 5.1 Rx phase 3.0 Responder rate Placebo 23% 50 mg 39% 100 mg 49% 200 mg 47%	ns ns 0.008 <0.001 <0.01 <0.001 <0.001	
Silberstein, Topiramate 2004	487	Good	28 day prospective baseline, randomization to placebo, topiramate 50, 100 or 200 mg per day for 26 wks	Mean monthly migraine frequency	Mean monthly migraine frequency Placebo Baseline 5.6 Rx phase 4.6 50 mg Baseline 5.6 Rx phase 4.1 100 mg Baseline 5.4 Rx phase 3.3 200 mg Baseline 5.6 Rx phase 3.3 Responder rate Placebo 23% 50 mg 36% 100 mg 54% 200 mg 52%	ns ns <0.001 <0.001 0.04 <0.001 <0.001	
Mei, Topiramate 2004	115	Poor	28 day prospective baseline, followed by randomization to placebo or topiramate 100 mg per day for 16 wks	Mean monthly migraine frequency	Mean monthly migraine frequency Placebo Baseline 5.76 Final 4 weeks 4.57 Topiramate Baseline 5.26 Final 4 weeks 2.6 Responder rate Placebo 21% Topiramate 63%	0.1 <0.001 <0.01	Intention to treat analysis is lacking.
Storey, Topiramate 2001	40	Fair	4 week baseline, followed by randomization to topiramate up to 200 mg or placebo for 16 wks	28 day migraine rate	28 day migraine rate Placebo Baseline 4.37 Rx phase 3.83 Topiramate Baseline 5.14 Rx phase 3.31 Responder rate	 0.003 0.226	Method of randomization not stated in Methods. Allocation concealment unclear.

Table 3: Antiepileptics continued

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Silberstein, Topiramate 2006	211	Fair	28 day prospective baseline, randomization to topiramate 200 mg per day or placebo for 20 wks	Change in mean monthly migraine frequency	Change in mean monthly migraine Placebo -1.04 Topiramate -1.43 Responder rate Placebo 34% Topiramate 40%	 ns ns	Method of randomization not stated in Methods. Allocation concealment unclear.
Diener, Topiramate 2004	575	Fair	28 day prospective baseline, randomization to topiramate 100 mg, 200 mg, propranolol 160 mg or placebo for 26 wks	Change in mean monthly migraine frequency	Change in mean monthly migraine Placebo -0.8 100 mg -1.6 Topiramate 200 mg -1.1 Propranolol 160 mg -1.6 Responder rate Placebo 22% 100 mg 37% Topiramate 200 mg 35% Propranolol 160 mg 43%	 0.011 0.459 0.01 0.028	Method of randomization not stated in Methods. Allocation concealment unclear.
Shaygannejad, Topiramate 2006	64	Fair	1 month prospective baseline, randomization to topiramate 50 mg or sodium valproate 400 mg for 2 months, washout for 2 months, then crossover to alternate Rx for 2 months	Mean monthly difference in migraine frequency from baseline	Change in mean monthly migraine Sodium valproate Baseline 5.4 Rx period 3.6 Topiramate Baseline 5.4 Rx period 2.4	 <0.001 <0.001	Method of randomization not stated in Methods. Allocation concealment unclear. Some but not all important outcomes are considered.
Gupta, Topiramate 2007	57	Good	28 day prospective baseline, then randomization to lamotrigine 50 mg, topiramate 50 mg or placebo for 4 weeks, washout for 7 days, then crossover to alternate Rx	Responder rate for frequency of migraine attacks per month (more than 50% reduction from baseline)	Responder rate Topiramate 63% Placebo 30% Lamotrigine 46% Placebo 34% Topiramate vs Lamotrigine p=0.019	 <0.001 0.093	
Dodick, Topiramate 2009	347	Good	28 day prospective baseline, then randomization to amitriptyline or topiramate with a 4 week titration phase followed by a 22 week maintenance period. Mean daily dose achieved: topiramate 91 mg, amitriptyline 89 mg.	Change from the prospective baseline period in the mean monthly rate of migraine episodes (beyond 24 hours duration an attack was considered a new episode).	Change in the monthly rate of migraine episodes: Topiramate: -2.6 Amitrip -2.7. Responder rates: Top: 55.6% Amitrip: 45.9%	P = NS P = NS	
Keskinbora, Topiramate 2008	75	Poor	Patients were randomized to topiramate alone, amitriptyline alone, or a combination of the two. This was followed by an 8 week titration period and then a 4 week maintenance period.	Change in mean monthly migraine frequency, headache severity, and duration during the entire double blind phase compared to baseline.	Marked reduction in migraine frequency from baseline in all groups, but no difference between the three treatment groups	P = 0.42	Intention to treat analysis is lacking. Key confounder (very different amitrip dosage in combination group) not addressed.
Ashtari, Topiramate 2008	62	Fair	Patients were randomized to topiramate 50 mg or propranolol 80 mg for a treatment period of 8 weeks.	Monthly migraine frequency	Migraine frequency Topiramate Baseline 6.07 Treatment 1.83 Propranolol Baseline: 5.83 Treatment 2.20	P = 0.036 (favouring topiramate)	Intervention not clearly defined (nature of baseline period not clarified).
Lipton, Topiramate 2011	385	Fair	After a 4 week prospective baseline period, subjects were randomized to topiramate 100 mg or placebo. This was followed by a 6 week titration period and a 20 week maintenance period.	Whether a subject reported !15 headache days (migraine or non-migraine) per 28-day period at month 6.	Reduction in migraine days per month: Topiramate: -6.6 Placebo: -5.3	P = 0.001	High overall dropout rate: Only 63% in the topiramate group and 56 % in the placebo group completed treatment.

during the study period. The use of symptomatic therapy for migraine attacks was permitted.

Results: Specific Prophylactic Medications

Antiepileptics

(see Table 3 for summary of individual study results)

Divalproex sodium / sodium valproate

There have been three parallel group trials and two crossover studies comparing divalproex sodium to placebo. The three parallel group studies were clinically similar, allowing meta-analysis. The crossover trials will be described separately.

All three parallel group studies[10-12] involved a four week prospective baseline, followed by randomization to divalproex sodium (dose ranging from 500 to 1500 mg) or placebo for 12 weeks. One study was of "good" quality, and the other two of "fair" quality. A total of 510 participants were included. The odds of having a 50% or greater reduction in migraine attack frequency on divalproex sodium relative to placebo was 2.74 (95% CI 1.48, 5.08: p=0.001). In general, side effects were higher in the divalproex sodium treatment group, especially at higher doses, and included nausea, somnolence, tremor and dizziness. The highest drop-out rate due to adverse events in all studies was 27% in patients taking the 1500 mg dose.

Hering[13] compared divalproex sodium 800 mg per day to placebo for eight weeks in a "fair" quality crossover study of 29 patients. The mean number of migraine attacks during the divalproex sodium treatment phase was significantly lower than during the placebo treatment phase, with a mean attack frequency over the eight week period of 15.6 attacks during placebo, and of 8.8 attacks during the divalproex sodium treatment phase ($p<0.001$). An additional crossover study comparing sodium valproate to placebo[14] also demonstrated a significant improvement in migraine attack frequency, but was of "poor" quality due to the lack of intention to treat analysis.

Weak recommendation, high quality evidence: While there is high quality evidence that divalproex sodium 500 to 1500 mg per day is effective for migraine prophylaxis, a weak recommendation was made based on the risk benefit profile of this medication for many patients. Divalproex sodium often promotes weight gain and may cause reversible tremor and hair loss. It is usually avoided in women with child bearing potential. When considered for this patient group, it should be given with folic acid, and caution should be exercised with careful consideration of birth control status due to the potential risk for teratogenicity.

Gabapentin

There have been two studies evaluating gabapentin in the prophylaxis of migraine, one of "fair" and one of "poor" quality. In the "fair" study by Di Trapani et al[15], after a one month baseline period, 63 patients were randomized to placebo or gabapentin 1200 mg per day for 12 weeks. The frequency of migraine headaches in the third month of treatment was compared to baseline and to placebo. Gabapentin resulted in significantly fewer migraine attacks (3.13 attacks per month) compared to baseline (5.08 attacks per month, $p<0.001$), and compared to placebo (4.7 attacks per month: $p<0.001$). Gabapentin was well tolerated; no patients withdrew because of side effects which were generally mild and transient, consisting of somnolence, dizziness, tremor and ataxia.

The second study randomized 145 patients and compared gabapentin to placebo[16]. It also showed a significant benefit of gabapentin therapy for migraine prophylaxis. This study was rated as "poor", as an intention to treat analysis was lacking.

Strong recommendation, moderate quality evidence: We recommend that clinicians offer gabapentin at a target dose of at least 1200 mg per day to eligible patients for migraine prophylaxis.

Topiramate

In our initial literature review, six parallel group trials comparing topiramate to placebo, two of "good" quality, three of "fair" quality, and one of "poor" quality were found. Meta-analysis of these studies was possible, with study data combined according to the dose of topiramate received in each trial.

Topiramate 50 mg was compared to placebo in two studies[17,18] in a total of 462 patients. These two studies were nearly identical in design, with patients randomized to placebo or topiramate 50, 100 or 200 mg per day for 26 weeks, after a 28 day prospective baseline. For the 50 mg dose, the odds of having a 50% or greater reduction in migraine attack frequency on topiramate versus placebo was 2.03 (95% CI 1.35, 3.05: $p=0.0007$).

Topiramate 100 mg was compared to placebo in four studies[17-20] of similar clinical design, in a total of 828 patients. The odds of a 50% or greater reduction in migraine attack frequency on topiramate 100 mg relative to placebo was 3.27 (95% CI 2.21, 4.85: $p<0.00001$).

Topiramate 200 mg was compared to placebo in five clinically similar studies[17-19,21,22] including a total of 864 patients. The odds of a 50% or greater reduction in migraine attack frequency on topiramate 200 mg versus placebo was 2.44 (95% CI 1.81, 3.28: $p<0.00001$).

Side effects were common in studies of topiramate, particularly in the 200 mg dose group, and leading to premature withdrawal from the trial in approximately 30% of participants. The most commonly reported side effects were paraesthesias, weight loss, altered taste, anorexia, fatigue, and memory impairment. Other special considerations when prescribing topiramate include its interaction with oral contraceptives (decreasing effectiveness of contraception), potential to predispose to renal calculi and rarely, acute angle closure glaucoma.

One study comparing topiramate to placebo also had an arm comparing topiramate to propranolol 160 mg[19]. The topiramate 100 mg per day group was similar to propranolol 160 mg with respect to migraine frequency reduction, responder rate, and reduction in migraine days. Treatment limiting adverse events occurred in 28% of the topiramate 100 mg group, compared to 20% of the propranolol group.

Two crossover studies comparing topiramate to other antiepileptic drugs were also found in our initial literature review. Shaygannejad[23] compared the efficacy of topiramate and sodium valproate for migraine prophylaxis in a study of "fair" quality. After a one month baseline period, patients were randomized to topiramate 50 mg or valproate 400 mg for two months, followed by a two month washout, and cross over to the alternate treatment for two months. Both treatments led to significant improvements in migraine frequency compared to baseline, with no difference in efficacy between treatments. Both treatments were well tolerated, with only mild transient side effects that did not lead to premature cessation of therapy (likely as a result of low medication dosages used in the study).

Gupta[24] compared the efficacy of topiramate to placebo and lamotrigine in the prophylaxis of migraine in a crossover study of "good" quality. After a 28-day prospective baseline, patients were randomized to topiramate 50 mg, lamotrigine 50 mg, or placebo for four weeks, followed by a washout period of seven days, then crossover to each of the alternate treatments in succession. Treatment with topiramate had a significantly greater responder rate than the placebo or lamotrigine treatment phases. There was no significant difference in the occurrence of side effects between treatment arms.

In our literature review update, four additional studies comparing topiramate to other prophylactic drugs or placebo were found, and are summarized below. They confirm topiramate to be an effective migraine prophylactic drug.

Dodick et al[25] compared topiramate 100 mg with amitriptyline 100 mg (or maximum tolerated dose) in a "good" randomized, double blind non-inferiority trial. The intent to treat population included 172 patients in the topiramate group and 159 in the amitriptyline group. The mean reduction in monthly migraine

episodes was not significantly different between topiramate (-2.6) and amitriptyline (-2.7). Subjects receiving topiramate had a mean weight loss of 2.4 kg, versus a mean weight gain of 2.4 kg on amitriptyline. There was no significant difference between the two groups in terms of discontinuations due to adverse events.

Keskinbora et al[26] compared topiramate, amitriptyline, and a combination of both drugs without placebo control in a "poor" trial. Seventy five patients were randomized in total, and no difference in outcome measurements were found between the three groups. Mean daily dose in the amitriptyline only group was 102 mg, in the topiramate only group 42 mg, and in the combination drug group 17 mg for amitriptyline and 34 mg for topiramate. With a total N of 75 (only 63 patients completed the study), the study would appear to have limited power to detect differences between groups. All groups showed substantial improvement from baseline.

Ashtari et al[27] in a fair study randomized 62 patients in a parallel group trial to topiramate 50 mg or propranolol 80 mg. Sixty patients completed the study, with topiramate slightly superior to propranolol in terms of reduction of monthly headache frequency (P = 0.036). Both drugs produced substantial headache frequency reduction from baseline.

Lipton et al[28] randomized 385 patients 1: 1 to topiramate or placebo with a 26 week follow up. This study was done primarily to determine whether topiramate prophylaxis could reduce the progression of high frequency migraine to chronic migraine. The study was negative for this primary endpoint, but secondary end points included the mean change in migraine days per month from baseline. This study once again showed a significant effect for topiramate in reducing migraine days per month as compared to placebo.

Two additional studies also found in our literature review update are not summarized here in detail, and not included in the tables. These included a study (rated "poor" quality) by Lo et al[29] which randomized 40 patients to four different doses of topiramate without placebo control in an Asian population, and a study (rated "poor" quality) by Millán-Guerrero et al[30] which randomized 90 patients to topiramate or subcutaneous injection of histamine for migraine prophylaxis without placebo control.

In comparison to other drugs, topiramate appears to have similar efficacy to propranolol, amitriptyline, and sodium valproate, and superior efficacy to lamotrigine for migraine prophylaxis.

Strong recommendation, high quality evidence: We recommend that clinicians offer topiramate to eligible patients for migraine prophylaxis. We found high quality evidence that topiramate provides a reduction in migraine frequency, though side effects from treatment are common. Due to the high number of adverse events and withdrawals on the 200 mg dose of topiramate, and the high quality evidence for a therapeutic benefit on the 100 mg dose, the recommended target dosage of topiramate for migraine prophylaxis is 100 mg per day. As was done in the clinical trials, the dosage should be increased gradually (see Section 3).

Antidepressants

(see Table 4 for summary of individual study results)

Amitriptyline

Our initial literature review found four trials of amitriptyline for migraine prophylaxis, two crossover studies comparing amitriptyline to placebo or propranolol, and two parallel group studies comparing amitriptyline to placebo or fluvoxamine. Of these studies, one was of "fair"[31] quality, and three were of "poor" quality[32-34] due to the lack of an intention to treat analysis. All placebo-controlled studies found a beneficial effect of amitriptyline for migraine prevention relative to placebo.

In the "fair" quality study by Gomersall[31], participants were randomized to amitriptyline 10 to 60 mg per day or placebo for 27 weeks, followed by crossover to the alternate treatment. The total number of attacks during the amitriptyline treatment phase of the study was 207, compared to 356 migraine attacks during the placebo phase ($p<0.001$). The main side effects observed during the amitriptyline treatment phase were dry mouth and drowsiness.

Two recent trials, already discussed in the section on topiramate above, have compared amitriptyline to topiramate without placebo control. A "good" quality large trial[25] found no difference in efficacy between topiramate (mean dose 91 mg) and amitriptyline (mean dose 89 mg). A smaller "poor" quality study[26] also found no difference in efficacy between topiramate (mean dose 42 mg) and amitriptyline (mean dose 102 mg).

A recent systematic review[35] which examined all published randomized controlled prophylactic trials involving tricyclics, most of which compared amitriptyline to placebo or another drug (not all trials were double blind) concluded that tricyclics were effective in migraine prophylaxis. In this meta-analysis, the likelihood of obtaining at least a 50% reduction in migraine was greater in patients taking a tricyclic (mainly amitriptyline) as compared to placebo: relative risk 1.53, 95% confidence intervals 1.16 – 2.01). The likelihood of experiencing a 50% clinical improvement was also greater in patients receiving a tricyclic (mainly amitriptyline) as compared to patients receiving an SSRI (fluoxetine or citalopram): relative risk 1.74, 95% confidence intervals 1.42 – 2.14). Although many of the trials analyzed in this meta-analysis were older trials and of poor quality, it provides some additional evidence for the efficacy of amitriptyline in migraine prophylaxis.

Despite the lack of well performed randomized, double-blind placebo-controlled studies of amitriptyline in migraine prevention (largely a function of when this drug came to market and the standards of trial design and reporting at that time), clinical experience with this drug is extensive among headache specialists, many of whom consider amitriptyline an effective treatment for migraine prophylaxis. A large recent "good" quality non-inferiority trial which compared amitriptyline to topiramate has further bolstered the evidence that amitriptyline is effective (reduction in monthly migraine frequency was 2.6 for topiramate and 2.7 for amitriptyline[25].

Strong recommendation, high quality evidence: We recommend that clinicians offer amitriptyline 10 to 100 mg per day to eligible patients for migraine prophylaxis, although an occasional patient may require and tolerate higher doses.

Table 4: Antidepressants

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Bank, Amitriptyline 1994	70	Poor	4 wk placebo run in period, randomization to amitriptyline 25 mg or fluvoxamine 50 mg for 12 wks	Not defined	Both Rxs resulted in improvement in headache index compared to baseline period	<0.02	Intention to treat analysis is lacking. No data given on patient groups. Not all important outcomes are considered. Method of randomization not stated. Allocation concealment unclear.
Gomersall, Amitriptyline 1973	26	Fair	Randomization to amitriptyline 10 to 60 mg per day or placebo for 27 wks, then crossover to alternate Rx	Not defined	Total number of attacks Amitriptyline phase 207 Placebo phase 356	<0.001	Method of randomization not stated. Allocation concealment unclear. Minor problems with follow-up. Not all important outcomes considered..
Couch, Amitriptyline 1979	100	Poor	4 wk baseline, randomization to amitriptyline 100 mg or placebo for 4 wks	Not defined	Responder rate Placebo 34% Amitriptyline 55%	<0.05	Intention to treat analysis is lacking Not all important confounders are accounted for. Method of randomization not stated. Allocation concealment unclear.
Ziegler, Amitriptyline 1987	30	Poor	4 wk placebo baseline, randomization to amitriptyline 50 to 150 mg, or propranolol 80 to 240 mg for 8 wks, 4 wk washout, and crossover to alternate Rx for 8 wks	Not defined	No raw data provided on headache frequency Treatment with amitriptyline and propranolol superior to placebo No significant difference between propranolol and amitriptyline	<0.05	Intention to treat analysis is lacking. Problems with follow-up. Not all important outcomes considered. Method of randomization not stated. Allocation concealment unclear.
Dodick, Amitriptyline 2009	347	Good	28 day prospective baseline, then randomization to amitriptyline or topiramate with a 4 week titration phase followed by a 22 week maintenance period. Mean daily dose achieved: topiramate 91 mg, amitriptyline 89 mg.	Change from the prospective baseline period in the mean monthly rate of migraine episodes	Change in the monthly rate of migraine episodes: Topiramate: -2.6 Amitrip -2.7. Responder rates: Top: 55.6% Amitrip: 45.9%	P = NS P = NS	
Keskinbora, Amitriptyline 2008	75	Poor	Patients were randomized to topiramate alone, amitriptyline alone, or a combination of the two. This was followed by an 8 week titration period and then a 4 week maintenance period.	Change in monthly migraine frequency: double blind phase compared to baseline.	Marked reduction in migraine frequency from baseline in all groups, but no difference between the three treatment groups	P = 0.42	Intention to treat analysis is lacking. Key confounder (very different amitrip dosage in combination group) not addressed.
Ozyalcin, Venlafaxine 2005	60	Fair	Randomization to venlafaxine 75 mg, venlafaxine 150 mg, or placebo for 10 wks	Not defined	Difference in # of days with headache (comparing 1st two weeks of treatment to final two weeks of treatment) Placebo: 1 Venlafaxine 75 mg: 2 Venlafaxine 150 mg: 4	0.006, 150 mg vs placebo	Allocation concealment unclear. Method of randomization not stated.
Bulut, Venlafaxine 2004	76	Poor	4 wk run-in period, randomization to venlafaxine 150 mg or amitriptyline 75 mg for 12 wks, 4 wk washout, crossover to alternate Rx for 12 wks	Not defined	Migraine attack frequency per month Venlafaxine Baseline: 4.15 Rx period: 1.77 Amitriptyline Baseline: 3.27 Rx period: 1.54 Venlafaxine vs Amitriptyline: nonsignificant	<0.001 <0.01	Intention to treat analysis is lacking. Method of randomization not stated in methods. Allocation concealment unclear. Problems with follow-up.

Venlafaxine

There have been two trials assessing venlafaxine in the prophylaxis of migraine, one of "fair" quality[36] comparing venlafaxine to placebo, and one of "poor" quality[37] comparing venlafaxine to amitriptyline. Ozylacin et al[36] randomized patients to venlafaxine 75 mg daily, venlafaxine 150 mg daily, or placebo for ten weeks. Patients who received venlafaxine 150 mg per day had a significantly greater reduction in the median number of days with headache (four days) compared to placebo (one day). Side effects in the treatment groups were common in the first four

Table 5: Antihypertensives and other calcium channel blockers *

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Markley, Verapamil 1984	20	Poor	4 wk prospective baseline, randomization to placebo or verapamil 80 mg TID for 8 wks, then crossover to alternate Rx	Not defined	Mean # of headaches per week Placebo 3.4 Verapamil 2.8	<0.05	Intention to treat analysis is lacking. Not all important outcomes considered. Method of randomization not stated; Allocation concealment unclear.
Soloman, Verapamil 1983	23	Poor	Randomization to verapamil 80 mg QID or placebo for 3 months, 5 day washout, then crossover to alternate treatment	Primary outcome not defined	Mean number of migraines per month Placebo 6.7 Verapamil 3.8	<0.05	Intention to treat analysis is lacking. Method of randomization not stated. Allocation concealment unclear.
Schrader, Lisinopril 2001	60	Good	Four wk placebo run in period, randomization to lisinopril 20 mg OD or placebo for 12 wks, two wk washout, crossover to alternate Rx group for 12 wks	# of hours with headache; # of days with headache, and # of days with migraine	Days with migraine over 12 weeks: Lisinopril: 14.6 Placebo: 18.7 Mean percentage reduction: 22%	95% CI: 11 to 33	
Tronvik, Candesartan 2003	60	Good	Four wk placebo run in period, randomization to candesartan 16 mg or placebo for 12 wks, four week washout period, then crossover to alternate Rx group for 12 wks	# of days with headache over 12 wk Rx period	Days with headache Candesartan: 13.6 Placebo: 18.5 Mean reduction with candesartan: 4.9 Migraine days Candesartan: 9.0 Placebo: 12.6 Mean reduction with candesartan: 3.5	0.001 <0.001	
Diener, Telmisartan 2009	95	Poor	Four week baseline followed by a 12 week double blind treatment period	Reduction in number of migraine days per month	Reduction in migraine days / month different between telmisartan and placebo only after extensive statistical adjustment: Telmisartan: 38% Placebo: 15%	0.03	Some inequality between groups at baseline in migraine days per month. Reduction in migraine days not consistent across centers. Study appeared under powered.
Frietag, Nadolol, 1984	32	Poor	8 wk placebo baseline, randomization to nadolol 80 mg, 160 mg or 240 mg or placebo for 12 wks	No primary outcome stated	Responder rate Nadolol 27% Placebo 0%	0.104	Inadequate power of study.
Ryan, Nadolol, 1982	80	Poor	2 month placebo baseline, randomization to placebo or nadolol 80 mg, 160 mg or 240 mg for 3 months	Primary outcome not stated	Number of attacks per month, difference between baseline and month 4 & 5 (average): Placebo 2.45 80 mg 2.99 160 mg 4.15 240 mg 4.31	No p values given	No data given on patient groups (cannot ensure comparability). No information given on the number of patients randomized to each group. No comment if results statistically significant; No p values given.
Louis, Flunarizine, 1980	58	Fair	Randomization to flunarizine 5 mg BID or placebo for 3 months	Primary outcome not stated	Number of attacks during three month treatment period Placebo group: 85 attacks Flunarizine group: 50 attacks	<0.0001	Some but not all important outcomes considered. No statement on allocation concealment.
Sorensen, Flunarizine, 1986	29	Fair	4 wk baseline, randomization to flunarizine 10 mg or placebo for 16 wks. 4 wk washout, then crossover to alternate treatment	Primary outcome not stated	Median number of migraines (last 4 wks of treatment period) Baseline 3.5 Placebo 3.2 Flunarizine 2.0	<0.05	No statement on allocation Concealment. Method of randomization not stated.
Frenken, Flunarizine 1984	35	Fair	Randomization to flunarizine 10 mg or Placebo for 12 wks	Primary Outcome not stated	Mean monthly migraine attacks (month 3) Flunarizine 0.8 Placebo 2.6	<0.05	No statement on allocation concealment. Inadequate reporting of study results.

Table 5: Antihypertensives and other calcium channel blockers * continued

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Mendenopoulos, Flunarizine, 1985	20	Fair	1 month medication free baseline, randomization to flunarizine 10 mg or placebo for 3 months	Primary outcome not stated	Number of migraine attacks- raw data not given. Intergroup differences in change from baseline significant after 3 months of treatment Median attack reduction in flunarizine group 50% No value given for placebo group	0.033	No statement on allocation concealment. Inadequate reporting of study results.
Al Deeb, Flunarizine, 1992	50	Poor	6 month prospective baseline, randomization to flunarizine 10 mg or placebo for 3 months	Primary outcome not stated	Migraine attack frequency Flunarizine group: Baseline 13.75 Treatment 9.9 Placebo group: Baseline 9.83 Treatment 7.86	0.08	Intention to treat analysis is Lacking. No statement on allocation concealment. Method of randomization not stated. Generally comparable groups.
Thomas, Flunarizine, 1991	29	Poor	Randomization to flunarizine 10 mg or placebo for 12 wks, 2 wk washout, then crossover	Primary outcome not stated	Results uninterpretable; authors state no significant decrease in migraine frequency between flunarizine and placebo phases of study		Intention to treat analysis is lacking. No statement on allocation concealment. Method of randomization not stated. More than 20% drop-outs.
Louis, Flunarizine, 1982	75	Poor	Randomization to flunarizine 10 mg or pizotifen 2-3 mg for 4 months	Primary outcome not stated	Mean reduction in number of attacks over the 4 month period: Flunarizine 54% Pizotifen 45%	ns	Intention to treat analysis is lacking. No statement on allocation concealment. Method of randomization not stated.
Rascol, Flunarizine, 1986	35	Fair	Randomization to flunarizine 10 mg or pizotifen 2 mg for 4 months	Primary outcome not stated	Reduction in migraine attack frequency: Flunarizine 65% Pizotifen 45%	ns	No statement on allocation concealment.
Cerbo, Flunarizine, 1986	27	Fair	1 month run-in, randomization to flunarizine 15 mg or pizotifen 1.5 mg for 2 months, 15 day washout, then crossover to alternate treatment for 2 months	Primary outcome not stated	Migraine attack frequency decreased compared to run-in period for both drugs (no raw data given)	<0.05	No statement on allocation concealment. Method of randomization not stated.

*For propranolol placebo controlled trials and propranolol comparison trials with nadolol, metoprolol, and flunarizine, see text above and Cochrane review by Linde and Rossnagel[38].

weeks of therapy, consisting mainly of nausea, vomiting and drowsiness, and caused 6 of 41 venlafaxine treated patients to discontinue therapy.

The "poor" quality study[37] which compared venlafaxine to amitriptyline in the prophylaxis of migraine also found that venlafaxine 150 mg per day resulted in a significant improvement in migraine attack frequency compared to baseline, and that this treatment was no different in efficacy to amitriptyline 75 mg per day. This study was rated as "poor" since it was lacking an intention to treat analysis.

Weak recommendation, low quality evidence: We recommend that clinicians offer venlafaxine extended release at a target dose of 150 mg per day to eligible patients for migraine prophylaxes.

Antihypertensives and Other Calcium Channel Blockers
(see Table 5 for summary of individual study results)

Propranolol

A Cochrane Systematic Review of the use of propranolol for migraine prophylaxis was published in 2004 by Linde and Rossnagel[38]. Potentially eligible studies were identified by searching Medline (1966-2003) and the Cochrane Central Register of Controlled Trials (Issue 2, 2003). Randomized, double-blind trials of at least four weeks duration comparing clinical effects of propranolol with placebo or another drug in adult migraine patients were included.

A total of 58 trials with 5072 participants met the inclusion criteria. The 58 selected trials included 26 comparisons with

Table 6: Vitamins/minerals/herbals

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Schoenen, Riboflavin 1998	55	Good	Baseline one month placebo phase, randomization to riboflavin 400 mg or placebo for 12 wks	Change in attack frequency in month 4 compared to baseline month 1	Change in attack frequency Placebo: 0 Riboflavin: -2 Responder rate Placebo: 19% Riboflavin: 56%	0.0001 0.01	
Maizels, Riboflavin 2004	52	Fair	Baseline one month run-in phase, randomization to riboflavin 25 mg or combination riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg for 3 months	Responder rate	Responder rate Riboflavin 25 mg: 44% Combination treatment: 42%	0.87	Method of randomization not stated in methods.
Sandor, Coenzyme Q10 2005	43	Fair	Baseline one month placebo phase, randomization to coenzyme Q10 100 mg three times daily or placebo for 3 months	Change in attack frequency in month 4 compared with baseline month 1	Change in attack frequency Placebo:-0.09 Coenzyme Q10: -1.19 Responder rate Placebo: 14.3% Coenzyme Q10: 47.6%	0.05 0.02	Generally comparable groups (minor differences between treatment and placebo groups present).
Peikert, Magnesium 1996	81	Fair	Baseline one month period, randomization to magnesium 600 mg or placebo for 12 wks	Reduction in attack frequency in final month of treatment compared to the baseline	Reduction in attack frequency Placebo: 0.58 Magnesium: 1.51 Responder rate Placebo 34.4% Magnesium 52.8%	0.03 0.149	Allocation concealment not stated. Randomization procedure not adequately described.
Pfaffenrath, Magnesium 1996	69	Fair	Baseline 4 wk period, randomization to magnesium 240 mg twice daily or placebo for 12 wks	% of patients with a 50% reduction in duration of migraine or intensity of migraine at the end of the 3rd month of Rx compared to baseline	Placebo: 29.4% Magnesium: 28.6%	Not given	Not all important outcomes considered. Method of randomization not adequately described. Allocation concealment not stated.
Köseoglu, Magnesium 2008	40	Poor	Baseline 4 week period. Randomized to magnesium 600 mg or placebo for 12 weeks	Not stated	Reduction in monthly attack frequency, final month of treatment compared to baseline: Placebo: -0.5 Magnesium: -1	0.005 (Post/ pre-treatment ratios of attack frequency)	Treatment groups of very unequal size (placebo group only 10 patients)
Lipton, Butterbur 2004	233	Good	Baseline 4 wk period, randomization to butterbur 50 mg twice daily, butterbur 75 mg twice daily, or placebo for 16 weeks	% change from baseline in migraine frequency	Mean percent change from baseline Placebo:-28% Butterbur 50 mg: -32% Butterbur 75 mg: -45% Responder rate (at month 4) Placebo: 49% Butterbur 50 mg: 56% Butterbur 75 mg: 68%	0.005 <0.05	
Diener, Butterbur 2004	33	Good	Baseline 4 wk period, randomization to butterbur 50 mg twice daily or placebo for 12 wks	# of migraine attacks per month	Attacks per month Butterbur: Baseline 3.4 12 wks 1.8 Placebo Baseline 2.9 12 wks 2.6 Responder rate Placebo 15% Butterbur 45%	0.0024 ns	

Table 6: Vitamins/minerals/herbals continued

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Pfaffenrath, Feverfew 2002	147	Good	4 wk baseline period, randomization to placebo, feverfew 2.08 mg, 6.25 mg or 18.75 mg TID for 12 wks	Total # of migraines during the last 28 day period of Rx compared to baseline	Mean change Placebo -0.7 2.08 mg -0.2 6.25 mg -0.9 18.75 mg -0.4 Responder rate Placebo 31% 2.08 mg 16% 6.25 mg 28% 18.75 mg 23%	ns p value not given	
Diener, Feverfew 2005	170	Poor	4 wk baseline, randomization to feverfew 6.25 mg or placebo TID for 16 wks	Average # of migraine attacks per 28 days during month 2 and 3 compared to baseline	Mean change Placebo -1.3 Feverfew -1.9 Responder rate Placebo 17% Feverfew 30%	 0.00456 0.047	Studied rated poor as 45 randomized patients were withdrawn from final analysis after completing studyprotocol for failure to fulfill IHS criteria.
Murphy, Feverfew 1988	72	Poor	One month run in, randomization to feverfew or placebo for 4 months, then crossover to alternate Rx for 4 months	Not defined	Mean # of attacks in each two month period Placebo 4.7 Feverfew 3.6	 <0.005	Intention to treat analysis is lacking. Method of randomization not stated Allocation concealment unclear; Problems with follow-up
de Weerdt, Feverfew 1996	50	Poor	One month placebo run-in period, randomization to placebo or 143 mg of feverfew daily for 2 months, then crossover to alternate Rx	Not defined	No significant difference between treatments for any outcome measured	ns	Intention to treat analysis is lacking; Allocation concealment unclear; Randomization method not stated; Not all important outcomes considered.

placebo and 47 comparisons with other drugs. The methodological quality of the majority of trials was unsatisfactory. The principal shortcomings were high dropout rates and insufficient reporting and handling of this problem in the analysis.

Overall, the 26 placebo controlled trials showed clear short term efficacy of propranolol over placebo. Meta-analysis of studies of propranolol at any dose including a total of 668 patients was performed, using parallel group and pooled crossover data. The relative risk of a 50% reduction in migraine frequency relative to placebo was 1.94 (95%CI 1.61, 2.35: p<0.00001). With respect to headache frequency, the standardized mean difference between propranolol and placebo was -0.40 (95% CI -0.56, -0.24), in favor of propranolol. Drop-outs due to adverse events were more common in subjects treated with propranolol compared to placebo, with a relative risk of 2.11 (95% CI 1.09, 4.08), but in total were low, affecting less than 5%. The main side effects of propranolol were fatigue, and reduction of heart rate and blood pressure.

Meta-analysis of studies comparing propranolol and calcium antagonists (mainly flunarizine) revealed a relative risk of 1 for the responder rate, and a standardized mean difference of -0.02 (95% CI -0.12, 0.08: p=0.7) between the two treatments. The rate of adverse events and drop-outs were similar between treatments.

Meta-analysis of studies comparing the responder rate of propranolol to nadolol for migraine prophylaxis favoured nadolol (RR 0.60, 95% CI 0.37, 0.97: p=0.04). Meta-analysis of studies comparing propranolol to metoprolol did not reveal a significant difference between treatments with respect to efficacy. There was no significant difference between propranolol and other beta-blockers with respect to adverse events and drop-outs.

Strong recommendation, high quality evidence: We recommend that clinicians offer propranolol at a target dose of 80 to 160 mg per day to eligible patients for migraine prophylaxis. Studies comparing propranolol to calcium channel blockers (mainly flunarizine), and metoprolol suggest comparative efficacy between treatments.

Metoprolol

The literature on metoprolol was not specifically reviewed for this guideline. The following recommendation is based on the Cochrane systematic review discussed above[38].

Strong recommendation, high quality evidence: We recommend that clinicians offer metoprolol (100 to 200 mg daily) to eligible patients for migraine prophylaxis.

Nadolol

There are two "poor" quality trials comparing nadolol to placebo for migraine prophylaxis[39,40], and three trials comparing nadolol to propranolol (already discussed in propranolol section, one "fair" trial, two "poor" trials). Both trials comparing nadolol to placebo reported a beneficial effect of nadolol in reducing migraine frequency, but had important methodological flaws. Meta-analysis of studies comparing the responder rate of propranolol to nadolol for migraine prophylaxis favoured nadolol (RR 0.60, 95% CI 0.37, 0.97: p=0.04)[38]. Drowsiness was the most commonly reported side effect but did not lead to discontinuation of therapy.

Strong recommendation, moderate quality evidence: We recommend that clinicians offer nadolol at a target dose of 80 to 160 mg per day to eligible patients for migraine prophylaxis.

Flunarizine

There have been six trials comparing flunarizine to placebo, four trials of "fair" quality[41-44], and two trials of "poor" quality[45,46]. Due to significant clinical heterogeneity, these trials were not combined statistically using meta-analysis. All four "fair" quality trials reported a significant decrease in migraine frequency with flunarizine 10 mg per day compared to placebo. The trial by Sorensen[41] found that the median number of migraines over a four week period using flunarizine 10 mg was 2.0, compared to 3.2 during placebo treatment ($p<0.05$), and 3.5 during the four week baseline ($p<0.05$). The most common side effects experienced from flunarizine treatment were sedation and weight gain.

Three trials have compared flunarizine to pizotifen for migraine prophylaxis (two "fair"[47,48], one "poor"[49]. All three trials reported a reduction in migraine frequency in both treatment groups, with no significant difference between groups with respect to efficacy or side effects.

Weak recommendation, high quality evidence: While there is high quality evidence that flunarizine 10 mg per day is effective for migraine prophylaxis, a weak recommendation was made because treatment is often limited by side effects, including depression and weight gain.

Verapamil

There are two small "poor" quality crossover studies comparing verapamil to placebo for migraine prophylaxis[50,51]. While both of these studies reported a significant benefit from treatment with verapamil on headache frequency, the studies had important methodological flaws. The only major side effect from therapy was constipation.

Weak recommendation, low quality evidence: Although verapamil has long been used for migraine prophylaxis and generally has few side effects, the evidence that it is effective is very limited.

Lisinopril

There is one "good" quality cross-over study[52] comparing lisinopril 20 mg daily to placebo for the prevention of migraine. Following a four-week placebo run in period, patients were randomized to 12 weeks of lisinopril or placebo. After a two-week placebo washout, study subjects were crossed over to the alternate treatment for another 12 week period. The number of days with migraine over the 12 week treatment period was significantly lower during the lisinopril treatment phase, 14.6 days, compared to the placebo phase, 18.7 days (mean reduction 22%, 95%CI 11 to 33%). Lisinopril was generally well tolerated, with only 3 of 60 randomized patients withdrawing due to side effects.

Weak recommendation, low quality evidence: Although lisinopril 20 mg daily is generally well tolerated, the evidence for effectiveness is limited and the magnitude of benefit in migraine prophylaxis appears small.

Candesartan

One "good" quality cross-over study[53] comparing candesartan 16 mg to placebo has been performed. Patients were treated with 12 weeks of candesartan or placebo, and crossed over to the alternate treatment after a four week washout period. There was a significant reduction in the number of days with migraine during the 12 week candesartan treatment period compared to the placebo period, with a mean reduction of 3.5 days during candesartan treatment phase ($p<0.001$). The responder rate was 40% during candesartan treatment, and 4% during the placebo phase. The treatment was well tolerated, with no significant difference in adverse events between groups.

A recent clinical trial with telmisartan[54] provided some additional but limited support for the use of angiotensin receptor blockers in migraine prophylaxis. This double blind placebo controlled randomized parallel group study was considered of "poor" quality because of baseline inequalities between the two groups and lack of power. Side effects of treatment were minimal, but reduction in migraine days per month was significantly different between telmisartan and placebo only after extensive statistical adjustment for baseline group inequality and inconsistency of results between centres. Even after statistical adjustment, a significant difference between the telmisartan group and the placebo group for the 50% responder rate endpoint was not demonstrated (telmisartan 40%, placebo 25%, $P = 0.07$).

Strong recommendation, moderate quality evidence: We recommend that clinicians offer candesartan 16 mg per day to eligible patients for migraine prophylaxis. Although the evidence that candesartan provides a reduction in migraine frequency is limited, one good randomized trial supports its use and side effects of treatment are minimal.

Vitamins/minerals/herbals

(see Table 6 for summary of individual study results)

Riboflavin

There have been two studies of riboflavin for migraine prophylaxis, one of "good" quality[55] comparing riboflavin 400 mg per day to placebo, and one of "fair" quality[56] comparing a combination treatment of riboflavin 400 mg, magnesium 300 mg

Table 7: Botulinum toxin type A:

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Evers, Botox, 2004	60	Good	4 week baseline, randomization to placebo injection, botulinum toxin A 16 units, or botulinum toxin A 100 units	Responder rate at month 3 compared to the baseline month	Responder rate Placebo 25% 16 units 30% 100 units 30%	0.619	
Saper, Botox, 2007	232	Fair	30 day baseline, randomization to placebo injection or one of four botulinum toxin A injection protocols	Frequency of migraine headaches per month at day 60 compared to baseline	No significant among group differences from baseline in the frequency of migraines (raw data not given)	All p>0.411	Allocation concealment unclear. Method of randomization not stated.
Relja, Botox 2007	495	Fair	30 day baseline, 30 day placebo run-in, then stratified randomization (placebo responders or nonresponders) to three treatments with botulinum toxin A 75units, 150 units, 225 units or placebo every 90 days	Mean change from baseline in the frequency of migraine episodes from day 150 to 180 of the study protocol	Mean change from baseline Placebo -1.4 75 units -1.5 150 units -1.7 225 units -1.6	0.817	Allocation concealment unclear. Method of randomization not stated in methods.
Vo, Botox 2007	32	Fair	4 week baseline, followed by randomization to botulinum toxin A 135 units or 205 units (based on body weight) or placebo	Average frequency of headache days during 30 day blocks for 3 months	No significant difference found between treatment groups for headache frequency at any time period (raw data not given)	0.63	Generally comparable groups. Problems with follow-up. Allocation concealment unclear.
Aurora, Botox 2007	369	Fair	30 day baseline, 30 day placebo run-in, stratified randomization (placebo responders or nonresponders) to three Rxs with botulinum toxin A (110 to 260 units) or placebo every 90 days	Mean change from baseline in frequency of migraine episodes from day 150 to 180	Mean change from baseline Placebo -2.2 Botulinum toxin A -2.4	0.999	Problems with follow-up.
Elkind, Botox 2006	418	Fair	Series of three sequential studies. Study 1: patients randomized to placebo or botulinum toxin A 7.5 units, 25 units, or 50 units. Study 2: patients randomized to placebo or 7.5 units in study 1 randomized to two Rxs with 25 units or 50 units. Patients receiving 25 units or 50 units in study 1 continued to receive same dosage for two more Rxs. Study 3: Patients randomized to placebo or to continue 25 units or 50 units for one Rx.	Frequency of migraine headaches per month compared to baseline.	Migraine frequency not different among treatment groups at any visit in any of the studies (assessed as change from baseline)	All p>0.201	Allocation concealment unclear. Method of randomization not stated.
Silberstein, Botox 2000	123	Fair	1 month baseline, randomization to placebo, botulinum toxin A 25 units, or botulinum toxin A 75 units	Change from baseline in the number of moderate to severe migraines per month	Mean change from baseline at month 2 Placebo: -0.37 25 units: -1.57 75 units: data not given	0.008	Allocation concealment unclear. Method of randomization not stated in methods
Anand, Botox 2006	32	Poor	Randomization to placebo or 50 units of botulinum toxin A	Frequency of attacks per four weeks	Results uninterpretable; raw data not given		Groups assembled not comparable. Key confounders not addressed. Method of randomization not stated in the methods. Allocation concealment Unclear.Not all important outcomes considered.
Petri Dysport 2009	127	Good	One month baseline, followed by randomization to 210units, 80 units, or placebo. Three month followup	Change from baseline in attack frequency	Change in attacks per month: Bot. toxin A: -0.94 Placebo: -0.54	NS	
Chankrachang Dysport 2011	128	Good	One month baseline followed by randomization to 240 units, 120 units, or placebo. Three month follow up	Change from baseline in migraine attack frequency	Change in attacks per month: Placebo: -2.23 Bot. toxin A: 240 units: -1.83 120 units: -1.95	NS	

and feverfew 100 mg to riboflavin 25 mg. These studies were not combined statistically due to clinical heterogeneity.

In the study by Schoenen[55], after a baseline one month placebo phase, patients were randomized to riboflavin 400 mg once daily or placebo for 12 weeks. The primary outcome assessed was the change in attack frequency in Month 4 compared to baseline (Month 1). A significantly greater reduction in attack frequency was found, with patients in the riboflavin treatment group having

on average two fewer attacks per month, while there was no change in the placebo group (p=0.0001). In addition, the proportion of responders in the treatment group was significantly higher, with 56% of patients in the riboflavin group achieving a 50% decrease in migraine frequency in comparison to 19% in the placebo group. The treatment was very was tolerated, with minimal side effects causing treatment discontinuation in one patient.

Maizels[56] compared a combination treatment of riboflavin, magnesium, and feverfew to low dose riboflavin. After a one-month baseline run-in, patients were randomized to three months with either treatment. The primary outcome, percentage of patients who achieved a 50% decrease in migraine frequency in Month 3 compared to baseline, was not significantly different between groups, with 44% of patients treated with riboflavin 25 mg, and 42% of patients on the combination treatment achieving this response to treatment. As this effect was felt to exceed that reported for placebo agents in previous migraine trials, it was felt that riboflavin 25 mg was an active comparator.

Despite the evidence from these trials, clinical experience with riboflavin for migraine prophylaxis has been generally disappointing, with minimal prophylactic effect observed amongst the headache specialists involved in the creation of this guideline. Side effects are minimal, but include yellow discoloration of urine.

Strong recommendation, low quality evidence: We recommend that clinicians offer riboflavin 400 mg per day to eligible patients for migraine prophylaxis. There is some evidence for benefit and side-effects are minimal.

Coenzyme Q10

There is one "fair" quality study[57] assessing coenzyme Q10 for the prophylaxis of migraine. After a one-month placebo baseline, subjects were randomized to treatment with coenzyme Q10 100 mg three times daily or placebo for three months. The primary outcome variable, the change from baseline to Month 4 in attack frequency, was significantly greater in the coenzyme Q10 group compared to placebo. In addition, the 50% responder rate for attack frequency was 47.6% in the coenzyme Q10 group, compared to 14.3% in the placebo group (p=0.02). Tolerability of the treatment was excellent, with only one patient discontinuing treatment.

Strong recommendation, low quality evidence: We recommend that clinicians offer coenzyme Q10 300 mg per day (dosed as 100 mg three times daily) to eligible patients for migraine prophylaxis.

Table 8: Serotonin antagonists

Study Reference	N	Quality Assessment	Intervention	Primary Outcome	Results	p value	Quality Criteria Unfulfilled
Bellavance, Pizotifen, 1990	176	Fair	8 wk placebo baseline, randomization to placebo, naproxen 550 mg BID or pizotifen 0.5 mg TID for 12 wks	Primary outcome not defined	Migraine frequency per wk Pizotifen: Baseline 1.53 Rx phase 0.98 Placebo: Baseline 1.64 Rx phase 1.46	<0.01 ns	Method of randomization not stated in the methods. Allocation concealment unclear
Lawrence, Pizotifen,1977	36	Poor	Randomization to pizotifen 1 mg TID or placebo for 12 wks	Primary outcome not defined	Complete migraine resolution in 6/14 in pizotifen group, 0/14 in placebo group No other detailed statistics or p values provided		Intention to treat analysis is lacking. Inadequate reporting of study results.
Ostermann, Pizotifen, 1977	30	Fair	Randomization to placebo, pizotifen 3 mg or divascan 15 mg for 8 wks, followed by crossover to each alternate treatment for 8 wks	Primary outcome not defined	Number of migraine attacks per week: Pizotifen 0.9 Placebo 1.4 Responder rate: Pizotifen 12/28 Placebo 1/28	<0.001	Method of randomization not stated in the methods. Allocation concealment unclear.
Carroll, Pizotifen, 1975	27	Poor	Randomized to 2 months of pizotifen (up to 3 mg) or placebo, 2 wk washout, then crossover to alternate treatment for 2 months	Primary outcome not defined	No summary measure of efficacy provided		Intention to treat analysis is lacking. Inadequate reporting of study results.
Sjaastad, Pizotifen, 1969	24	Fair	Randomized to placebo or pizotifen 1 mg QID for 8 wks, then crossover to alternate treatment for 8 wks	Primary outcome not defined	Responder rate: Pizotifen 9/20 Placebo (not stated) Headache days reduced by 43% during pizotifen treatment compared to placebo	<0.05	Method of randomization not stated in the methods. Allocation concealment unclear.

Magnesium

Two "fair" quality studies[58,59] have been performed comparing magnesium to placebo in the prophylaxis of migraine headache. After a one month baseline period, Peikert et al[58] randomized patients to 24 mmol elemental magnesium (600 mg elemental magnesium as trimagnesium dicitrate) or placebo daily for 12 weeks. Patients treated with magnesium had a significantly higher reduction in attack frequency in the final month of treatment compared to baseline than the placebo group. Eight (19%) of the magnesium treated patients developed soft stools or diarrhea within the first four weeks of treatment, causing treatment discontinuation in two patients. There were no other complications from therapy.

Pfaffenrath[59] compared 10 mmol elemental magnesium twice daily (243 mg elemental magnesium twice daily, contained in magnesium-L-aspartate-hydrochloride trihydrate) to placebo for 12 weeks following a four week baseline period. The percentage of patients achieving their primary outcome, a reduction of 50% in the duration of migraine (in hours) or in the intensity of migraine at the end of the third month of treatment compared to baseline, was not significantly different between groups. The main side effect experienced by patients in the treatment group was soft stools or diarrhea.

In a third "poor" study, Köseoglu[60] compared magnesium citrate (600 mg elemental magnesium daily) to a placebo control. All patients had migraine without aura. The study was rated as poor because, although 30 patients received magnesium, the placebo control group consisted of only ten patients (randomization 4:1). Migraine attack frequencies during a one month baseline period were compared to the last month of a three month treatment period. Attack frequency was reduced more in the group receiving magnesium as compared to the control group when post/pre-treatment ratios of attack frequency were compared (P = 0.005)

Strong recommendation, low quality evidence: We recommend that clinicians offer magnesium to eligible patients for migraine prophylaxis. There is some evidence for benefit and side effects are minimal. Due to the contrary evidence presented in these trials, we recommend that 24 mmol (600 mg) of elemental magnesium daily as magnesium citrate be used for migraine prophylaxis, since a positive result was only obtained with this compound.

Butterbur (*Petasites hybridus* root extract)

The efficacy of butterbur in migraine prevention has been assessed in two "good" quality trials[61,62]. Lipton[61] compared butterbur 50 mg twice daily, butterbur 75 mg twice daily and placebo in a 16 week trial following a four week baseline period. The primary outcome assessed was the change in frequency of migraine attacks per month over the entire treatment period calculated as a percentage change from baseline. The butterbur 75 mg group had a significantly greater percent change from baseline, -45%, compared to the 50 mg group (-32%), and placebo (-28%). The percentage of treatment responders was significantly higher in the 75 mg group (68%) compared to the placebo treated group (49%) ($p<0.05$). Butterbur 50 mg was not significantly better than placebo. Significant differences in the incidence of adverse events between butterbur and placebo were observed only for burping.

Table 9: Summary of recommendations*

Recommended For Use in Episodic Migraine** (Use)		
	Recommendation	
Drug	**Recommendation Strength**	**Quality of Evidence**
Topiramate	Strong	High
Propranolol	Strong	High
Metoprolol	Strong	High
Amitriptyline	Strong	High
Nadolol	Strong	Moderate
Gabapentin	Strong	Moderate
Candesartan	Strong	Moderate
Butterbur	Strong	Moderate
Riboflavin	Strong	Low
Coenzyme Q10	Strong	Low
Magnesium citrate	Strong	Low
Divalproex	Weak	High
Flunarizine	Weak	High
Pizotifen	Weak	High
Venlafaxine	Weak	Low
Verapamil	Weak	Low
Lisinopril	Weak	Low
Not Recommended for Use in Episodic Migraine (Do not use)**		
Botulinum toxin type A	Strong	High
Feverfew	Strong	Moderate

*Utilizing Grade Criteria; ** Migraine with headache on less than 15 days a month.

Diener[62] and colleagues performed an independent analysis of a trial by Grossman and Schmidramsl comparing butterbur 50 mg twice daily for 12 weeks to placebo in 33 patients. The original protocol and analysis had a number of shortcomings, and an independent reanalysis of the original data was performed to follow regulatory requirements. Compared to a four week baseline period, patients in the butterbur group had a significant decrease in the number of migraine attacks per month at Week 12 compared to placebo. Mean attack frequency decreased from 3.4 at baseline to 1.8 at week 12 ($p=0.0024$). There was no significant difference in mean attack frequency from baseline to Week 12 in the placebo group. The percentage of treatment responders was 45% in the butterbur treated group, compared to 15% in the group receiving placebo.

Meta-analysis of the two studies for the 50 mg twice-daily dose of butterbur compared to placebo gives an odds ratio of 2.24 for achieving a 50% reduction in migraine attack frequency at week 12 (95% CI 0.64, 7.81: $p=0.20$).

Strong recommendation, moderate quality evidence: We recommend that clinicians offer butterbur 75 mg twice daily to eligible patients for migraine prophylaxis. The magnitude of benefit may be small, but side effects are minimal. Due to the contrary evidence presented in these two trials for the 50 mg dose, we recommend that 75 mg of butterbur twice daily be used for migraine prophylaxis.

Caution: only commercially prepared products in which plant carcinogens and hepatotoxic alkaloids have been removed and which have been standardized to contain a minimum of

15% petasins are recommended. Patients should be cautioned against consuming the plant in any other form.

Feverfew

There have been four studies on feverfew for migraine prophylaxis, two parallel group studies of "good"[63] and "poor"[64] quality, and two crossover studies of "poor" quality[65,66].

Pfaffenrath[63] compared feverfew at doses of 2.08 mg, 6.25 mg, and 18.75 mg three times daily to placebo for 12 weeks in a parallel group study of "good" quality. There was no difference between the treatment or placebo groups in the primary or secondary outcomes in the intention to treat sample.

The three remaining studies, two of which found a beneficial effect of feverfew[64,65], and the other which found no difference between feverfew and placebo[66], were of poor quality, due to failure to include an intent to treat analysis.

There was no difference in the rate of adverse events between placebo and feverfew groups.

Clinical experience with feverfew suggests that at best, it has a minimal effect on migraine frequency.

Strong recommendation, moderate quality evidence: We recommend against offering feverfew for the prophylaxis of migraine. The evidence indicates that feverfew is no better than placebo for the prophylaxis of migraine.

Botulinum toxin type A

(see Table 7 for summary of individual study results)

Botulinum Toxin Type A

Our initial literature review found eight studies on the use of botulinum toxin type A (onabotulinumtoxinA) for the prophylaxis of migraine. Six of these trials (one of "good" quality[67], five of "fair" quality[68-72] were negative with respect to the primary outcome on migraine frequency. One "fair" quality trial[73] was positive for the primary outcome on migraine frequency in one of their treatment subgroups. One study of "poor" quality[74] did not have results which were interpretable with respect to the treatments effect on migraine frequency. Since that review, two additional small "poor" quality studies have been done, one comparing onabotulinumtoxinA to valproate (no difference found)[75], and another which compared onabotulinumtoxinA to placebo in patients with poor prophylactic medication compliance (no difference found for headache days per month)[76]. As both these studies included significant numbers of patients with chronic migraine, they will not be considered further here and have not been included in the tables.

There have also been two recent studies comparing another type of botulinum toxin type A (Dysport) to placebo in patients with episodic migraine. In a "good" quality study, Petri[77] randomized 127 patients (210 units: 32 patients, 80 units: 32 patients, placebo: 63 patients) to botulinum toxin A or placebo. No significant reduction in migraine attacks per month as compared to placebo was found.

Chankrachang et al[78], in another "good" quality study, randomized 128 patients equally to botulinum toxin A 240 units, 120 units, or placebo. No difference in the primary endpoint (change from baseline in migraine attack frequency) was found between the three groups.

A meta-analysis[79] which examined all eight randomized double-blind placebo controlled clinical trials of botulinum toxin A published up to October 2007 concluded that botulinum toxin A for the prophylactic treatment of episodic migraine headaches was not significantly different from placebo, both from a clinical and statistical perspective.

Given these results, the evidence does not support the use of botulinum toxin type A for the prophylaxis of episodic migraine headache. This is in contradistinction to clinical trials in chronic migraine (migraine with headache on over 14 days a month) where two large randomized clinical trials have shown efficacy[80,81].

Strong recommendation, high quality evidence: We recommend against providing botulinum toxin type A for the prophylaxis of episodic migraine in patients with less than 15 headache days per month. The evidence indicates that botulinum toxin type A is no better than placebo for the prophylaxis of migraine in such patients.

Serotonin Antagonists

(see Table 8 for summary of individual study results)

Pizotifen (pizotyline)

There have been five studies comparing pizotifen to placebo for the prophylaxis of migraine, three of "fair" quality[82-84], and two of "poor" quality[85-86]. Studies could not be combined using meta-analysis due to significant clinical heterogeneity. All five studies reported a beneficial effect of pizotifen over placebo for migraine prophylaxis. Dosages of pizotifen ranged from 1.5 to 4 mg per day. Only three of the studies provided detailed report of results with statistical analysis. Ostermann[83] reported a responder rate of 43% during pizotifen treatment, compared to 4% during placebo treatment. The main side effects observed in all five studies were weight gain and sedation, which occurred in less than 20% of patients.

Weak recommendation, high quality evidence: While there is high quality evidence that pizotifen 1.5 to 4 mg per day is effective for migraine prophylaxis, a weak recommendation was made based on the side effects commonly associated with this medication. Weight gain and sedation are common with pizotifen.

How to choose between treatment options

In this systematic review, recommendations for use in migraine prophylaxis have been made for 17 medications. Eleven of these have received a strong recommendation; while six have received a weak recommendation (see Table 9 for summary of recommendations).

For those medications with a strong recommendation for use, only four have a high quality of evidence for efficacy in migraine prophylaxis (topiramate, propranolol, metoprolol, and amitriptyline), four have moderate quality of evidence (nadolol, gabapentin, candesartan, and butterbur), and three paradoxically have low quality of evidence (riboflavin, coenzyme Q10, and magnesium citrate. However, it must be kept in mind that in the Grade system of recommendations, as discussed earlier, the strength of a recommendation is based not only on the quality of the evidence available for efficacy or for the potential harm of an intervention, but also on the balance between the benefits and side

effects. Hence, those medications which were given a strong recommendation for use despite low quality evidence received this strong recommendation in part because they have minimal or no side effects.

On the other hand, three drugs with high quality evidence for efficacy received a weak recommendation primarily because of frequent and significant side effects (divalproex sodium, flunarizine, and pizotifen).

Potential side effects and evidence for efficacy both play an important role in drug choice in an individual patient. Section 3 deals in much greater detail with choosing a prophylactic medication for a specific patient. In general, because of the lack of proven differences in efficacy between different prophylactic medications, a prophylactic medication is often selected based to a significant extent on potential side effects and the presence of other disorders which may be coexistent with migraine in a given patient. Clinical experience amongst headache specialists does suggests that, in general, the antiepileptics, antihypertensives and antidepressants have greater clinical effectiveness than the vitamin/mineral/herbals which generally have limited efficacy but also very low side effect profiles.

Choice of a prophylactic medication is therefore often based on five considerations:

1. Evidence of efficacy in migraine prophylaxis.
2. Side effect profile.
3. Coexistent conditions (hypertension, depression, obesity, insomnia, etc). Some prophylactic drugs can treat both the migraine and one of these comorbid conditions. This is discussed in greater detail under "Treatment Strategies" in Section 3 of this guideline. Some prophylactic medications may also be contraindicated by certain co-existent medical conditions (for example flunarizine in depression, or a beta-blocker in asthma). The "side effects" of a prophylactic medication can be helpful for some patients with co-existent conditions. The obese patient, for example, may benefit from the weight loss often produced by topiramate, and the patient with insomnia may benefit from the sleep inducing properties of amitriptyline.
4. Patient disability and migraine severity. A patient with major migraine-related disability may do better with a drug with proven efficacy despite some risk of side effect. It may be appropriate for a patient with a lesser degree of disability to try potentially less effective medications with fewer side effects first.
5. Patient preferences. Some patients may wish to try medications with low side effect profiles first despite potential lower effectiveness, while others may be less concerned about the possibility of side effects. Patients with a strong preference for vitamins/minerals/herbals could be offered one of these preparations first.

Despite the above, finding the right prophylactic medication for a patient often involves medication trials with several medications before a successful outcome is reached. Patients need to understand that an adequate trial of a medication takes 8 to 12 weeks, and that more than one medication may need to be tried.

Drugs Not Included in the Systematic Review

The drugs listed below are sometimes considered by physicians for migraine prophylaxis, but were not included in our systematic review. We include some comments here based on a general literature review and other recently published guidelines in order to provide readers with some information regarding their use. They are not recommended for general use.

Selective serotonin reuptake inhibitors

The drugs reviewed in detail for this guideline are drugs which are available and in clinical use as migraine prophylactics in Canada. The selective serotonin reuptake inhibitors (SSRIs) were not included as they are not extensively used as migraine prophylactics in Canada, and were considered by our expert panel to not be effective. Other recent guidelines have reached similar conclusions. The Scottish Intercollegiate Guidelines Network concluded that Selective serotonin reuptake inhibitors are not recommended in the prophylaxis of migraine[87]. A recent review on antidepressants and migraine prevention concluded that studies to date on the use of SSRIs as migraine prophylactics are small, inconsistent, and not only have SSRIs not shown an efficacy comparable to that of amitriptyline, they have been associated with new-onset or exacerbation of headaches as an adverse effect[88].

EXPERT CONSENSUS

i. Selective serotonin reuptake inhibitors are not recommended for the prophylaxis of migraine.

Other tricyclic antidepressants

Koch and Juergens[88] reviewed the clinical trials data supporting the use of other tricyclic antidepressants (other than amitriptyline) in migraine prophylaxis. No controlled studies supporting efficacy in migraine prevention were found for nortiptyline, imipramine, trimipramine, or desipramine. Two small negative controlled trials provided no support for the use of clomipramine, and one small randomized double-blind crossover study with doxepin was unable to show a reduction in the number of headache days per month[88]. In summary, there is no good evidence for the use of any of the tricyclic antidepressants other than amitriptyline for migraine prophylaxis. Nortiptyline is widely used in Canada, and is felt to be effective (expert opinion only). A controlled trial of nortriptyline in episodic migraine prophylaxis is badly needed.

EXPERT CONSENSUS

i. Imipramine, trimipramine, desipramine, clomipramine, and doxepin are not recommended for routine use for migraine prophylaxis. Nortriptyline may be useful (expert opinion only).

Clonidine

Clonidine is not widely used for migraine prophylaxis in Canada, and was not felt to be effective (expert opinion). Other recent guidelines have concluded that, although older studies did suggest some efficacy in migraine prophylaxis, more recent and better designed studies did not show any efficacy[89].

EXPERT CONSENSUS

i. Clonidine is not recommended for migraine prophylaxis.

Methysergide

Methysergide is no longer available in Canada, and was not reviewed because its side effects do not allow universal use as a migraine prophylactic. Other guidelines, based on the available evidence, have considered methysergide as clearly effective, but concluded the drug could only be recommended for short term use (maximum six months) because of potentially serious side effects (retroperitoneal fibrosis and other fibrotic syndromes)[89]. The SIGN Guidelines concluded that methysergide, although effective, should only be used under specialist supervision[87].

EXPERT CONSENSUS

i. Methysergide is an effective migraine prophylactic, but because of side-effects should only be used under specialist supervision.

Oxcarbazepine

Not all antiepileptics are effective in migraine prophylaxis. A recent "good" quality randomized double-blind placebo controlled clinical trial with 85 patients found no benefit for oxcarbazepine in migraine prophylaxis[90].

Melatonin

Melatonin was recently assessed for migraine prophylaxis in a daily dose of 2 mg. This small (n = 48) placebo controlled "good" quality trial found no benefit of melatonin over placebo for migraine prophylaxis[91].

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Treatment Strategies: Pharmacological Prophylaxis - Section III

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ABSTRACT: ***Background:*** Our guideline development process resulted in recommendations for use for 17 migraine prophylactic drugs, herbals, vitamins or minerals. ***Objective:*** To organize the available prophylactic medications into migraine prophylactic strategies in order to assist the practitioner in choosing a specific prophylactic agent for an individual patient. ***Methods:*** Prophylactic strategies were developed based on the systematic literature review used for the development of this guideline, and a general literature review. Expert consensus groups were used to formulate and validate specific recommendations. ***Results:*** Our analysis resulted in the formulation of nine strategies for pharmacological migraine prophylaxis. There were based on evidence for drug efficacy, drug side effects, migraine severity, and co-existent medical and psychiatric disorders. They ranged from "first time" strategies for patients undergoing prophylaxis for the first time to "refractory patient strategies". Also included were strategies for patients with migraine associated with depression, anxiety, hypertension, and increased body mass index. ***Conclusions:*** The available migraine prophylactic medications can be organized into a series of strategies based on patient clinical features. These strategies may be useful in assisting the practitioner to make appropriate prophylactic choices for the patient with migraine.

RÉSUMÉ: Stratégies de traitement : prophylaxie pharmacologique – Section III. ***Contexte :*** Des recommandations pour l'utilisation de 17 médicaments prophylactiques, remèdes à base de plantes médicinales, vitamines ou minéraux, ont été formulées suite à l'élaboration de notre ligne directrice. ***Objectif :*** Le but de cette démarche était d'organiser les médicaments prophylactiques disponibles en stratégies prophylactiques de la migraine afin d'aider le médecin à choisir un agent prophylactique spécifique pour un patient donné. ***Méthode :*** Les stratégies prophylactiques ont été développées à partir d'une revue systématique de la littérature utilisée pour l'élaboration de cette ligne directrice et d'une revue générale de la littérature. Des recommandations spécifiques ont été formulées et validées par des groupes de consensus composés d'experts. ***Résultats :*** Les neuf stratégies élaborées pour la prophylaxie pharmacologique de la migraine résultent de notre analyse. Elles sont fondées sur des données factuelles concernant l'efficacité des médicaments, les effets secondaires, la sévérité de la migraine et les maladies médicales et psychiatriques coexistantes chez le patient. Elles vont de stratégies initiales pour des patients qui utilisent une prophylaxie pour la première fois, à des stratégies pour des patients réfractaires au traitement. Nous avons également élaboré des stratégies pour les patients qui présentent de la migraine associée à une dépression, à de l'anxiété, à de l'hypertension et à un indice de masse corporelle élevé. ***Conclusions :*** Les médications prophylactiques de la migraine qui sont disponibles peuvent être organisées en différentes stratégies, selon les caractéristiques cliniques du patient. Ces stratégies peuvent être utiles pour aider la médecin traitant à faire des choix appropriés en prophylaxie de la migraine chez un patient migraineux.

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On the basis of our analysis, 11 prophylactic drugs received a strong recommendation for use and six received a weak recommendation (see Section 2). Where head to head comparison trials between different prophylactic drugs have been done, they have generally not shown clear superiority of one drug over another. A practical approach is therefore needed for medication selection for the individual patient at a specific time.

The available drugs can be organized into a number of treatment "strategies" in order to choose the most appropriate drug for an individual patient. These strategies are listed in Table 1, and commonly used drug dosages and side-effects are summarized in Table 2. In the more detailed description of each strategy below, a conservative approach is taken, with drug dosages increased slowly over several weeks for most drugs. For some patients, these dosages can be built up more rapidly if that seems appropriate and the drug is well tolerated. However, many patients with migraine seem quite sensitive to drug side effects, and a slow dosage build up is often the best course of action. It also provides the patient with a sense of control and may help some accept the concept of daily drug intake for an intermittent disorder.

This migraine treatment guideline is focused on patients with intermittent migraine attacks who are candidates for prophylactic therapy. Patients with migraine and chronic daily headache

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(chronic migraine), including patients with medication overuse, will be the focus of another guideline. It should be noted, however, that for many patients with acute medication overuse, prophylaxis should be started early and likely at the same time that the overuse of symptomatic medications is addressed and withdrawal started[1,2].

Strategy development

It should also be noted that although the treatment strategies presented here are broadly based on evidence from clinical trials, they also include a significant component of clinical judgment and expert opinion. Therefore, some of the recommendations in this strategy section may be controversial. Drugs used for short term prophylaxis of menstrual migraine (non-steroidal anti-inflammatory drugs, hormonal therapies, and triptans) have not been evaluated in this guideline.

The systematic review that was done as part of the development of this guideline and which served as a basis for some of the discussion on treatment strategies is described in detail in Section 2. Other details regarding the overall development of this guideline including the use of consensus groups are provided in Appendix 2.

Patient preference studies have shown that the majority of individuals with migraine rate higher efficacy rates as the most important aspect of choosing a migraine prophylactic drug[3]. At the same time, patient preference studies have shown that weight gain is one of the side effects that patients reject most[4]. Weight gain is a potential side effect of many migraine prophylactic drugs, with the exception of topiramate, candesartan, lisinopril, and the mineral, vitamin, and herbal options. Memory loss is also one of the most rejected side effects[4], and this side effect may apply in particular to topiramate. As can be seen, the choice of a prophylactic medication for any given patient must be individualized, and each drug would appear to have a place in the spectrum of prophylactic therapy. The strategies listed below reflect this. It should be noted that migraine prophylaxis is an "off label" use for most of the medications listed in these migraine strategies. To date, only three of these drugs, flunarizine, topiramate, and pizotifen have received an official Health Canada indication for migraine prophylaxis.

There is a significant evidence base for the use of many drugs as monotherapy for migraine prophylaxis. Although there is much less evidence for the use of more than one drug simultaneously, this strategy is used for patients with difficult migraine by some headache experts, especially where monotherapy has failed or where specific comorbidities might indicate the use of a second drug with migraine prophylactic value. Polypharmacy is likely to increase overall medication side effects.

The strategies considered here are summarized in Table 1. A patient information sheet explaining the basic principles of migraine prophylaxis is provided as Appendix 3.

Migraine Prophylactic treatment strategies

1. ***First time strategies:*** The drugs commonly chosen for initiating prophylactic treatment for the first time remain the beta-blockers and the tricyclic antidepressants. Both are good choices for the patient who is being prescribed migraine prophylaxis for the first time, and which of these two drug classes is chosen first will depend on specific patient characteristics and preferences. If one proves unsatisfactory, the other can be tried if there are no contraindications.

Some clinicians would consider some other drugs as options for patients undergoing prophylaxis for the first time, in particular topiramate which has high quality evidence for efficacy.

Although it is not included here as a first line strategy because of its side effect profile, it can be considered in that context whether or not the patient is overweight. For details regarding its use, please see the "Increased body mass index strategy" below.

a. *Beta-blocker strategy:* For the otherwise healthy migraine sufferer without asthma, significant depression, or cardiac contraindications for beta-blockers, a beta-blocker is often considered. Patients with unusually low blood pressure may not tolerate beta-blockers well, and for these the tricyclics may be a better option. If aerobic exercise plays a major role in the patient's life, beta-blockers are best avoided and strategy 1b should be employed. The most commonly used beta-blocker is propranolol at a starting dose of 20 or 40 mg twice a day, with the daily dose increased by 20 mg twice a day every one or two weeks as necessary and tolerated. The dose may be increased if

Table 1: Prophylactic drug treatment strategies, based on the clinical setting*

1. First time strategies: (for the patient who has not had prophylaxis before)
   a. Beta-blocker strategy: propranolol, nadolol, metoprolol
   b. Tricyclic strategy: amitriptyline (nortriptyline)
2. Low side effect strategies:
   a. Drug: candesartan, lisinopril
   b. Herbal / vitamin / mineral: Magnesium citrate, riboflavin, butterbur, Coenzyme Q10
3. Increased body mass index strategy: topiramate
4. Hypertension strategy: propranolol, nadolol, metoprolol, candesartan, lisinopril
5. Depression / anxiety strategy: amitriptyline, venlafaxine, (nortriptyline) (dual therapy)
6. Additional monotherapy drug strategies: topiramate, divalproex, gabapentin, pizotifen, flunarizine, verapamil
7. Refractory patient strategy: concomitant use of two drugs
8. Migraine during pregnancy strategy: drug avoidance if possible. When necessary, magnesium, propranolol, metoprolol, amitriptyline and (nortriptyline) are considered relatively safe options (See section 3)
9. Migraine during lactation strategy: drug avoidance if possible. When necessary, magnesium, propranolol, nadolol, metoprolol, amitriptyline, (nortriptyline) and valproate** are considered compatible with breast feeding (See section 3).

*Drugs in brackets have insufficient evidence from randomized trial to routinely recommend their use. **Valproate is teratogenic, and should be avoided in women at risk for pregnancy.

Table 2: Pharmacologic agents: recommended dosages for migraine prophylaxis, adverse effects, and cautions

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Antiepileptics:					
Divalproex sodium (also valproic acid or sodium valproate)	250 mg/d for 1 week, then 250 mg BID for 1 week, then 250 mg in am & 500 mg at bedtime; ↑ weekly by 250 mg, if needed	750-1500 mg/d (divided BID)	Liver disease, bleeding disorders, alcoholism, obesity; avoid in pregnancy (human teratogen); small risk of encephalopathy when combined with topiramate	Epilepsy, mania, anxiety	Nausea/vomiting, tremor, weight gain, alopecia, ↑ hepatic enzymes, neural tube defects (if used during pregnancy)
Topiramate	15 or 25 mg/d; ↑ by 15 mg weekly or 25 mg every 1-2 weeks	100 mg/d (at bedtime) or 50 mg BID; up to 200 mg/d may be used, if needed & tolerated	Kidney stones, kidney failure, angle closure glaucoma, pregnancy; small risk of encephalopathy when combined with valproate	Epilepsy, obesity, mania, anxiety, essential tremor, alcohol dependence	GI (nausea, anorexia); renal calculi; paresthesias; acute glaucoma; CNS (dizziness, tremor, sedation, cognitive impairment, depression); weight loss; metabolic acidosis
Gabapentin	300 mg/d & ↑ by 300 mg every 3-5 days, or start with 300 mg TID & ↑ weekly by 300 mg	1200-1500 mg/d (divided TID); up to 1800 mg/day may be used, if needed & tolerated	Kidney failure	Epilepsy, mania, anxiety, insomnia	Drowsiness, dizziness
Antidepressants:					
TCAs: Amitriptyline (or nortriptyline. Note: nortriptyline has no controlled trial evidence for efficacy)	10 mg/d (bedtime or 1 h before); ↑ by 10 mg every 1-2 weeks	20-40 mg/d (bedtime); up to 100-150 mg/d may be used, if needed & tolerated	Heart block, significant CV disease, urinary retention, uncontrolled glaucoma, prostate disease, mania	Insomnia, depression, anxiety, neuropathic pain, co-morbid tension-type headache	Weight gain, drowsiness, confusion, anticholinergic effects (dry mouth, constipation), ↓ seizure threshold, sexual dysfunction cardiovascular effects
SNRIs: Venlafaxine extended release	37.5 mg once daily for 1 week; ↑ weekly by 37.5 mg (may ↑ weekly by 75 mg)	150 mg/d (once daily)	Hypertension, kidney failure	Depression, anxiety	Nausea/vomiting, sexual dysfunction, drowsiness, dizziness, blurred vision
Antihypertensives: Beta-blockers:					
Propranolol	20-40 mg BID; ↑ by 20 mg BID every 1-2 weeks	80–160 mg/d (divided BID or LA form once daily)	Asthma, heart block, CHF, hypotension, bradycardia, Raynaud's, peripheral vascular disease, insulin-dependent diabetes, depression, sexual dysfunction	Hypertension, angina	Fatigue, reduced exercise tolerance, bradycardia, CHF, hypotension, bronchospasm, impotence, sleep disturbance
Nadolol	20-40 mg/d (morning); ↑ by 20-40 mg every 1-2 weeks	80–160 mg/d once daily	See Propranolol	See Propranolol	See Propranolol; may have fewer CNS side effects
Metoprolol	50 mg BID	100-200 mg/d (divided BID or SR form once daily)	See Propranolol	See Propranolol	See Propranolol
Calcium Channel Blockers:					
Flunarizine	5-10 mg/d (at bedtime); ↑ to 10 mg/d in 1-2 weeks (if start with 5 mg/d)	10 mg/d (at bedtime)	Depression, Parkinson's	Dizziness, vertigo	Weight gain, depression, drowsiness, extrapyramidal effects
Verapamil (not recommended for routine use because of low quality evidence for efficacy)	40 mg TID; ↑ to 80 mg TID over 1-2 weeks; SR: start with 160 mg/d; ↑ to 240 mg/d (divided BID) over 1-2 weeks	240 mg/d (divided TID; SR divided BID); doses > 480 mg/d not recommended	Constipation, hypotension, severe CHF, bradycardia, heart block, arrhythmias; avoid concomitant use with beta-blockers	Hypertension, angina	Constipation, peripheral edema, AV conduction disturbances
Antihypertensives: ACEIs/ARBs:					
Candesartan	8 mg/d, ↑ to 16 mg/d in 1 week (once daily)	16 mg/d (once daily)	Hypotension, pregnancy (especially 2nd & 3rd trimesters); monitor K if used with K-sparing diuretics	Hypertension	Hypotension, dizziness
Lisinopril	10 mg/d (once daily)	20 mg/d (once daily)	Hypotension, pregnancy (especially 2nd & 3rd trimesters); monitor K if used with K-sparing diuretics	Hypertension	Hypotension, dizziness, fatigue, non-productive cough, angioedema (rare)
Serotonin antagonists:					
Pizotifen (pizotyline)	0.5 mg at bedtime for 1 week; 0.5 mg BID for 1 week; 0.5 mg TID, ↑ up to 4 mg/d, if needed	1.5- 4 mg/d (1 mg BID is good target); full dose can be given at bedtime	Obesity	Insomnia	Drowsiness, weight gain (can be significant)

Table 2: Pharmacologic agents: recommended dosages for migraine prophylaxis, adverse effects, and cautions continued

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Vitamins/minerals/herbals:					
Riboflavin	400 mg/d (or 200 mg BID)	400 mg/d (once daily or divided BID)	None	None	Yellow discolouration of urine (benign)
Coenzyme Q10	100 mg TID	300 mg/d (100 mg TID to minimize GI adverse effects)	Hypotension	Hypertension	GI upset
Magnesium citrate	300 mg (elemental magnesium) BID	300 mg (elemental magnesium) BID	Kidney failure, diarrhea	Constipation	Diarrhea, GI upset
Butterbur (*Petasites*)	75 mg BID	75 mg BID	None	Allergic rhinitis	GI (burping)

* not all inclusive; GI = gastrointestinal; CV = cardiovascular; CNS = central nervous system; CHF = congestive heart failure; AV = atrioventricular; ACEIs = angiotensin converting enzyme inhibitors: ARBs = angiotensin receptor blockers; TID = three time daily; BID = twice daily; SR = sustained release; LA = long-acting; SR = slow release; TCAs = tricyclic antidepressants; SNRIs = serotonin-norepinephrine reuptake inhibitors; GI = gastrointestinal; MI = myocardial infarction; /day = per day; BID = twice a day; TID = three times a day. Information sources for this table include references[49-53], The Compendium of Pharmaceuticals and Specialties 2009[54].

necessary to 160 mg daily, although many patients will not tolerate that dose because of fatigue and / or hypotension. Propranolol has a relatively short half life (4 hours), but is often given twice a day. The long acting form may be used instead to improve patient compliance. An alternative is to use nadolol (half life 16 hours), which allows for once daily dosing. Nadolol penetrates the CNS less than propranolol, but nevertheless clinical trials have shown superiority over placebo, and meta-analyses comparing nadolol to propranolol have suggested superiority for nadolol. Therefore, nadolol is a good choice for first line migraine prophylaxis, with once daily dosing and perhaps fewer CNS side effects than other beta blockers (i.e. vivid dreams and drowsiness). The usual daily dosage range is 80 to 160 mg, although doses up to 240 mg have been recommended. There is evidence for a dose-response curve, with 160 mg likely more effective than 80 mg. Nadolol may be started at 20 to 40 mg daily in the morning, and the daily dose increased by 20-40 mg every one or two weeks as necessary and tolerated to a maximum of 160 mg daily. The literature on the use of beta-blockers in migraine prophylaxis is complex, with many older clinical trials. Different groups interpret this literature differently, and the European Federation of Neurological Sciences Task Force has concluded that among the beta-blockers the evidence for migraine prophylactic use is best for propranolol and metoprolol[5]. The starting dose for metoprolol is usually 50 or 100 mg daily, and the target dose is 100 to 200 mg daily. It must be given twice daily, unless a long-acting form is used.

EXPERT CONSENSUS

i. Propranolol, nadolol, and metoprolol are good initial prophylactic drug choices for many patients with migraine.

ii. For propranolol the usual starting dose is 20 to 40 mg twice daily. The dose can be increased slowly (every one to two weeks) as necessary and tolerated up to a maximum of 160 mg daily. The long acting form may also be used.

iii. For nadolol, the usual starting dose is 20 to 40 mg given once daily in the morning. The dose can be increased slowly (every one to two weeks) as necessary and tolerated, up to a maximum of 160 mg daily.

iv. For metoprolol, the usual starting dose is 50 mg twice a day. The dose can be increased slowly (every one to two weeks) as necessary and tolerated to a maximum dose of 200 mg daily. The long acting form may also be used.

b. *Tricyclic strategy:* Amitriptyline is commonly used as an initial migraine prophylactic drug, and can be especially helpful in patients with sleep disturbances. Insomnia is a very frequent complaint among migraine sufferers, and sleep deprivation can be a potent migraine trigger. Amitriptyline is considered by many to be the best prophylactic drug for patients with migraine with major insomnia, or who have many associated tension-type headaches or symptomatic medication overuse. It can also be a good choice for the patient with depression, although the maximum dose of amitriptyline tolerated by many migraine sufferers for prophylactic use may not be high enough to provide significant antidepressant activity. Fifty mg per day or more is required by most patients to achieve significant antidepressant activity.

Usually patients are started on 10 mg at bedtime, although the dose can be given an hour or longer before bedtime both to achieve shorter sleep latency, and also to reduce the usual dose-limiting side effect, morning sedation. The daily dose is usually increased by 10 mg every one to two weeks, although both slower and faster increases may also be employed depending on the patient, until the patient has benefit or intolerable side effects occur. Most patients will stabilize their dose between 20 and 40 mg, and a reasonable strategy is to ask the patient to increase the dose up to 30 or 40 mg if tolerated but to go back to a lower dose if necessary because of side effects, and see the patient in follow up before increasing the dose further. Otherwise patients may

continue to increase the dose until they have intolerable side effects, and then simply discontinue the drug and be reluctant to restart it. Most patients will experience some degree of dry mouth even at low doses, but are able to tolerate this side effect. Patients differ greatly, however, in how rapidly they metabolize amitriptyline, and if a patient has no benefit but also no side effects at lower doses, they may be fast metabolizers, and higher doses should be tried.

Higher doses of amitriptyline are used by some physicians. In one recent blinded non-inferiority trial which compared topiramate and amitriptyline, the mean daily dose of amitriptyline achieved was 88.9 mg[6]. Twenty-two percent of patients exited the trial in the amitriptyline group because of adverse events. Other guidelines have recommended a dose of amitriptyline of 50 to 150 mg daily[5]. A recent review of antidepressants for migraine prevention recommended starting amitriptyline at 25 mg at bedtime, and increasing the dose to 75 – 100 mg if necessary, or higher[7]. Our experience has been that many patients with migraine will not tolerate doses of that magnitude, and a start low (10 mg) and go slow (increasing the dose by 10 mg increments) is preferable unless the patient is hospitalized, has major depression, or has demonstrated good tolerance to amitriptyline previously. Some patients will not tolerate even minimal doses of amitriptyline. For these, nortiptyline in similar dosages to those suggested above for amitriptyline can be tried. Nortriptyline is the major metabolite of amitriptyline, and clinical experience suggests that it may have similar efficacy. It produces fewer side effects than amitriptyline in virtually every category including anticholinergic side effects, drowsiness, and likely also appetite stimulation. In patients without significant insomnia, nortiptyline can be tried first in order to avoid side effects, but this is outside the realm of evidence-based medicine, as no randomized, blinded clinical trials have been done to determine the potential efficacy of nortriptyline in episodic migraine prophylaxis. Expert opinion suggests that nortriptyline is effective, and some experts utilize it in many patients because it is better tolerated than amitriptyline.

Expert consensus

i. Amitriptyline is a good initial migraine prophylactic drug. It may be particularly useful in patients with insomnia or associated tension-type headache.

ii. When starting amitriptyline prophylaxis for migraine, a low initial dose should be used in most patients (10 mg) and the dose should be built up slowly (10 mg every week or every two weeks).

iii. In patients without insomnia or in those who cannot tolerate amitriptyline, nortiptyline in similar doses may be better tolerated and possibly effective.

2. ***Low side effect strategies:*** Unless their migraine disorder is relatively severe, patients are often reluctant to take daily medications for a disorder which produces intermittent symptoms, as it means taking medication on many days when they are asymptomatic. Concern about possible or already experienced drug side effects is a common reason for this attitude. Agents with very few side effects are often more palatable to these patients, and may be a good choice for "first time" prophylaxis in these patients, although with the reservations noted below.

a. *Low side effect drug strategy:* To date, only one good controlled trial with candesartan is available, but this evidence does indicate that it is an effective migraine prophylactic, and has few side effects. Lisinopril might also be placed in this category, although it likely has somewhat more side effects including the possibility of chronic non-productive cough. The dose of candesartan used in the clinical trial was 16 mg daily as a single daily dose. Based on the clinical trial, common practice is to use 8 mg daily for one week, and then increase to 16 mg once daily. Slower dosage increments are also used.

Expert consensus

i. Candesartan and lisinopril have evidence for efficacy in migraine prophylaxis, and generally have few side effects, although each has only one controlled trial to date supporting its use. The target dose for candesartan is 16 mg daily, for lisinopril 20 mg daily. Candesartan is preferred because of fewer side effects, and because clinical experience with lisinopril is more limited. Given the limited data for efficacy and the limited clinical experience with both these drugs at this time, they should not be considered as substitutes for the more established drugs in the "First time strategy" under most circumstances.

b. *Low side effect herbal / vitamin / mineral strategy:* Although these strategies may be attractive to many patients, many experts believe that despite the evidence for efficacy from randomized controlled trials, the benefit from these compounds is only modest at best. This strategy could employ butterbur, magnesium, riboflavin, or co-enzyme Q10, either singly or in combination. Feverfew, because of lack of efficacy in clinical trials, likely should not be part of this strategy. Among the above, the best evidence for efficacy is for butterbur: a dose of 75 mg twice a day should be used. If magnesium is used, magnesium citrate in a dose of 300 mg (elemental magnesium) twice daily is preferable because it has relatively good absorption from the gastrointestinal tract. The single randomized placebo controlled trial with riboflavin utilized 400 mg per day, far above the usual nutritional requirements (but with no significant side effects). Co-enzyme Q10 (100 mg three times daily) is also an option, although only one "fair" randomized trial supports its use.

Expert consensus

i. Butterbur, riboflavin, magnesium, and co-enzyme Q have very few side effects, and are evidence based options for migraine prophylaxis. These compounds are felt to have only modest efficacy, and should not be considered substitutes for "First time" strategy drugs under most circumstances.

3. ***Increased body mass index strategy:*** Weight gain is a major issue for a significant proportion of patients with many of the drug-based migraine prophylactic strategies. Topiramate is an exception since it promotes weight loss in most patients. Topiramate produces less weight gain and less deterioration in cardiovascular disease risk markers than some other commonly used migraine prophylactic drugs like amitriptyline[6,8]. Therefore, it is a useful migraine prophylactic medication in patients who are overweight, or who have major concerns regarding weight gain. In these patients, it may be considered a good "first time" strategy. The dose is best built up slowly to avoid side effects.

Most clinical trials started the patient on 25 mg once daily for a week, then 25 mg twice daily for a week, and then increased the daily dose by 25 mg every week until a dose of 50 mg twice a day was reached. Topiramate has a long half life (21 hours), and once daily dosing seems logical for reasons of compliance. If once daily dosing is used, the dose is usually given at bedtime. A slower dose build up can also be used, either through increasing the daily dose by 25 mg every two weeks, or by using the 15 mg capsule and increasing the daily dose weekly by 15 mg increments. The usual target dose for topiramate is 100 mg daily, although it is possible that some patients may experience additional benefit at higher doses. In general, if 100 mg daily has provided no significant benefit after two months, the drug should be stopped and a different prophylactic tried.

Topiramate should be avoided or used with caution in patients with a history of renal calculi. The maintenance of good hydration should be recommended for all patients on topiramate. Patients frequently experience numbness in the hands and feet, due to topiramate-induced carbonic anhydrase inhibition. They should be warned of this side effect, and reassured that it is harmless. It may lessen with time. If it persists, potassium supplementation, either through ingestion of high potassium foods or through potassium tablets is sometimes used based on anecdotal evidence. Approximately one-quarter of patients stop topiramate because of side effects, with central nervous system side effects of sedation, word finding difficulty, or slowed cognition being prominent offenders. A rare but serious side effect is acute secondary angle closure glaucoma, which usually presents with abrupt severe visual blurring (myopia) and eye pain. When it does occur, it usually occurs early in therapy. Although it is very rare, patients should be warned of this side effect, and instructed to stop the drug immediately if it occurs. Stopping the drug is usually sufficient therapy. It is also helpful if patients are told that topiramate makes carbonated drinks taste "flat", a harmless side effect that is very common. Topiramate is an enzyme-inducing anticonvulsant. Although it therefore has the potential to reduce the effectiveness of estrogen containing oral contraceptives, this effect is dose dependant and appears to not be significant at doses of 100 mg per day.

Expert consensus

i. *Topiramate is a migraine prophylactic drug which, because of its propensity to promote weight loss, is particularly useful in patients who are overweight, in patients who are particularly concerned about weight gain, and in patients with co-existent illnesses which might be exacerbated by weight gain (ie diabetes).*
ii. *Topiramate should be started at a low dose (15 or 25 mg daily), and the daily dose should be increased slowly (by 15 every week or 25 mg every two weeks in order to improve drug tolerability.*
iii. *The usual target dose for topiramate in migraine prophylaxis is 100 mg daily.*

4. ***Hypertension strategy:*** Nadolol, propranolol, metoprolol, candesartan, or lisinopril should be considered for migraine prophylaxis in patients who also require medication treatment for hypertension. Dosage regimens for these have been discussed in prior strategies, except for lisinopril which is usually used in a dose of 20 mg daily. While monotherapy has advantages, it may be advantageous in some patients to treat the migraine and the hypertension independently, utilizing what the clinician considers to be the best treatment for each disorder in that particular patient.

Expert consensus

i. *For patients with hypertension and migraine, refer to the Canadian Hypertension Education Program's (CHEP) clinical practice recommendations which are updated annually and can be found at www.hypertension.ca. The following recommendations for managing patients with both migraine and hypertension have been reviewed with CHEP and are consistent with those evidence based recommendations. The specific angiotensin receptor blockers and angiotensin converting enzyme inhibitors listed below are those with evidence for efficacy in migraine prophylaxis.*
ii. *Simplification of medical regimens is known to improve adherence, and the use of the same medication for both migraine and hypertension may reduce the potential for drug side effects and interactions. Recommended options are:*

    a. *Propranolol, nadolol, or metoprolol* (for patients under age 60). (Some other beta-blockers may also be effective, but have not been reviewed in this guideline.)
    b. *Candesartan* (Candesartan has also demonstrated efficacy for patients with isolated systolic hypertension)
    c. *Lisinopril* (ACE inhibitors have been found to be less effective for lowering blood pressure as monotherapy in patients of African (black) origin).

iii. *Combination therapy is often required to achieve blood pressure targets. For patients requiring additional medication for blood pressure control, adding a thiazide diuretic and / or a calcium channel blocker to one of the above medications is indicated (combinations of beta blockers and non-dihydropyridine calcium channel blockers like verapamil should be avoided due to the risk of heart block).*
iv. *If adequate migraine prophylaxis is not achieved and the blood pressure is at target, other migraine prophylactic medications may be added.*

5. ***Depression / anxiety strategy:*** Depression is common in patients with migraine in Canada, both in the general population[9] and in patients referred to headache specialists in Canada[10]. In a population based study, migraine was associated with major depressive disorder, bipolar disorder, panic disorder, and social phobia, all of which occurred more than twice as often in those with migraines compared with those without[9]. In 310 patients with migraine referred to headache specialists in Canada, 17% had moderate or severe depression as measured by the Beck Depression Inventory II[10]. In the general population, migraine is also comorbid with generalized anxiety disorder (Odds Ratio [OR] 3.5 to 5.3), as well as panic disorder (OR 3.7), and bipolar disorder (OR 2.9 to 7.3)[11]. Migraine prophylaxis in these populations poses special therapeutic problems.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the management of major depressive disorder in adults include the selective serotonin reuptake inhibitors (SSRIs) and the serotonin and noradrenaline reuptake inhibitors (SNRIs) (ie venlafaxine and duloxetine) among the first-line antidepressant medications. The older

tricyclic antidepressants like amitriptyline are considered second line because of tolerability and safety issues in the setting of overdose (not because of efficacy)[12]. However, the SSRIs have little value as migraine prophylactics, and may exacerbate migraine[7]. On the other hand, amitriptyline is a migraine prophylactic drug with proven effectiveness[6,13].

Monotherapy has the potential to improve treatment adherence and reduce the potential for drug interactions. Traditionally amitriptyline has been used in migraine patients with depression, and has been recommended in a recent review as the drug of first choice for patients with migraine and depression[7]. It is important to note that the doses used for migraine prophylaxis are often lower than those considered necessary for treatment of either depression or anxiety. A recent Cochrane review has investigated the tolerability and efficacy of amitriptyline in comparison with the other tricyclic/heterocyclic antidepressants and with the selective serotonin reuptake inhibitors. This systematic review concluded that amitriptyline is at least as efficacious for depression as other tricyclics or newer compounds. However, the burden of side-effects in patients receiving it was greater. In comparison with the selective serotonin reuptake inhibitors amitriptyline was less well tolerated[14]. An appropriate strategy in the patient with migraine and depression might therefore be to increase the dose of amitriptyline gradually. If the patient can tolerate a dose adequate for depression management, than monotherapy can be employed; if the patient cannot, then dual therapy needs to be considered.

An alternative to amitriptyline for migraine and depression / anxiety monotherapy is venlafaxine, but the experience with this medication in migraine prophylaxis remains limited, despite some evidence for efficacy.

Nortriptyline is often used in migraine prophylaxis despite lack of randomized controlled trial evidence for efficacy[15]. The primary reason for this is its better tolerability compared to amitriptyline. Nortriptyline in equivalent doses is a much less potent antagonist than amitriptyline at the receptor types which cause the major side effects of amitriptyline. These include the H1 receptor responsible for sedation, the alpha 1 receptor responsible for hypotension, and the muscarinic receptor responsible for anticholinergic effects like dry mouth and tachycardia. Because nortriptyline is a major metabolite of amitriptyline, it is often assumed that it is efficacious in migraine prophylaxis, and clinical experience does seem to confirm this. There is randomized controlled trial evidence that nortriptyline is as effective as amitriptyline in post-herpetic neuralgia[16]. More research into the efficacy of nortriptyline as a migraine prophylactic is badly needed.

Clinical practice guidelines for the management of anxiety disorders published in the Canadian Journal of Psychiatry[17] indicate that the SSRIs and the SNRIs are generally preferred to the tricyclics for the treatment of anxiety as they are safer and better tolerated. Among the SSRIs, paroxetine and sertraline have Health Canada approved indication for treatment of several of the anxiety disorder subtypes, as does venlafaxine[17]. For generalized anxiety disorder, sertraline and venlafaxine are among the recommended first line treatments. Imipramine is the only tricyclic listed as a second line treatment, while propranolol is not recommended[17]. Reviews on the treatment of anxiety disorders do list the tricyclic category as a second line treatment for anxiety, and sedating tricyclics are felt to be useful in the presence of insomnia[18]. Based on anecdotal evidence, physicians treating migraine have long used amitriptyline in that setting.

Dual therapy, in which migraine and depression and / or anxiety are treated separately, has been advocated to ensure that both disorders are treated optimally[19]. If dual therapy is chosen, care should be taken to avoid migraine prophylactic drugs which clearly aggravate depression, (flunarizine) and to avoid or use with caution other prophylactic drugs which may predispose to depression (topiramate)[20]. Although beta-blockers have been felt to contribute to depression in the past, this has been challenged. A meta-analysis which examined 15 randomized, controlled studies involving 35,000 subjects taking beta-blockers for the treatment of cardiovascular conditions demonstrated no statistical difference between beta-blockers and placebo with respect to depression, although beta-blockers were associated with increased incidence of fatigue and sexual dysfunction[21]. A study involving the Harvard Community Health Plan population found that depression occurred no more frequently in beta-blocker users than in individuals using angiotensin converting enzyme inhibitors, calcium channel blockers, or thiazide diuretics[22]. It would appear, therefore, that beta-blockers do not predispose to depression, although they may produce symptoms including fatigue and sexual dysfunction which may be suggestive of depression.

Drug interactions also need to be considered, particularly when tricyclic drugs and SSRIs are combined. Amitriptyline is metabolized through multiple cytochrome P450 enzymes, including CYP2D6. Nortriptyline is metabolized exclusively through CYP2D6. Nortriptyline is also a major metabolite of amitriptyline. Fluoxetine and paroxetine are particularly powerful inhibitors of 2D6, citalopram and escitalopram are intermediate, and sertraline has the least 2D6 inhibition. Venlafaxine also has relatively modest 2D6 inhibition, while duloxetine is intermediate[23]. If SSRI – amitriptyline or nortriptyline co-therapy is planned, sertraline is the SSRI least likely to cause problems with drug interactions[23].

Some SSRIs, particularly fluoxetine, and fluvoxamine, are potent inhibitors of many CYP450 isoenzymes. These drugs, along with paroxetine which is a particularly powerful inhibitor of the P450 2D6 isoenzyme, are therefore best avoided in tricyclic-SSRI combinations. In addition to its much more favourable profile of CYP450 inhibition (it inhibits only the 2D6 isoenzyme and only to a modest degree)[23] sertraline is also better tolerated than many other SSRIs[12], and may be one of the most efficacious SSRIs for treatment of depression[24].

It has been suggested that all SSRIs with the exception of sertraline and possibly citalopram and escitalopram are unsuitable for combination with tricyclics[23], however if the dose of the tricyclic is kept low perhaps other combinations are likely feasible. If such combinations are used the patient should be followed carefully for potential side effects related to high tricyclic levels and for serotonin syndrome. Ultimately the risk of clinically significant drug interactions are a function of the doses of the drugs in question, the affinity for the receptor of interest, the local concentrations of the drugs at the receptor(s), and the biologic / genetic makeup of the patient. The P450-2D6 isozyme is polymorphic and under genetic influence as to its expression, and thus the extent of any stated interaction may be highly

variable. Patient follow-up is important for optimization of these therapies. Amitriptyline and nortriptyline serum levels can be obtained if there is clinical concern about a possible drug interaction when one of these tricyclics is combined with another P450-2D6 inhibiting antidepressant.

In summary, because of the advantages of monotherapy (less potential for drug interactions and side effects), monotherapy with one of amitriptyline or venlafaxine should be considered in patients with anxiety and /or depression who require migraine prophylaxis. Experience with venlafaxine in migraine prophylaxis is limited. Nortriptyline may be an additional although less evidence-based choice.

The dose of amitriptyline can be gradually increased to antidepressant doses in the range of 50 - 100 mg daily or higher. Many patients with migraine are unable to tolerate higher doses (over 75 mg daily) of amitriptyline, and venlafaxine may be a suitable alternative. Venlafaxine extended release should be increased gradually by 37.5 mg every week, using once daily dosing, with a target dose of 150 mg daily. The role of venlafaxine in migraine prophylaxis has yet to be determined, but has been recognized by other published guidelines. The Scottish Intercollegiate Guidelines Network for example states that venlafaxine 75 – 150 mg per day is an effective alternative to tricyclic antidepressants for the prophylaxis of migraine[25]. If nortiptyline is used, the doses are similar to amitriptyline.

In some patients, particularly if good control is not achieved with monotherapy or if the patient is unable to tolerate adequate doses of the tricyclic, clinicians may need to treat the migraine and the anxiety and / or depression with separate medications.

Possible disadvantages of this approach are more drug side-effects, and the potential for drug interactions.

EXPERT CONSENSUS

i. *Because of the advantages of monotherapy (less potential for drug interactions and side effects), monotherapy with one of amitriptyline or venlafaxine should be considered in patients with anxiety and /or depression who require migraine prophylaxis. Experience with venlafaxine in migraine prophylaxis is limited. Nortriptyline may be an alternative although less evidence-based choice.*
ii. *In some patients, particularly if good control is not achieved with monotherapy or if the patient is unable to tolerate adequate doses of the tricyclic, clinicians may need to treat the migraine and the anxiety and / or depression with separate medications.*
iii. *If SSRI – tricyclic co-therapy is planned, sertraline should be considered because of less potential for drug interactions. Most other SSRIs, in particular fluoxetine, fluvoxamine, and paroxetine, have a greater potential for significant drug interactions with amitriptyline and nortriptyline.*
iv. *Should be typically be avoided (flunarizine), or used with caution (topiramate) in patients with depression. Although traditionally beta-blockers have been considered to predispose to depression, more recent studies suggest that this is not the case.*

6. ***Additional monotherapy drug strategies:*** These strategies are often used for patients who have failed other prophylactic strategies. However, some are used in patients prescribed prophylaxis for the first time (for example topiramate and gabapentin).

a. *Topiramate:* This is a good medication choice for patients who have failed the first time strategies. Because of strong evidence for efficacy, and because it does not cause weight gain, topiramate is used early in prophylaxis including as a first time strategy by many clinicians, even in patients who are not overweight. Side effects do cause many patients to discontinue topiramate, and for this reason it has not been listed as a first time strategy in this guideline, although some clinicians would consider it to belong in that category. Details of how to use topiramate are given above in the increased body mass index strategy.

b. *Divalproex sodium:* Divalproex sodium is usually started in a dose of 250 mg daily, increased to 250 mg twice a day after a week, and then increased on a weekly basis to 250 mg in the morning and 500 mg at bedtime, and then to 500 mg in the morning and 500 mg at bedtime. Clinical trials have shown efficacy at 750 mg daily, at 1000 mg daily, and at 1500 mg daily. An enteric-coated tablet of divalproex sodium is usually used. Divalproex tends to promote weight gain in many patients. The use of divalproex in women of childbearing potential is problematic given its teratogenicity, and requires a careful assessment of the risk / benefit ratio for that patient. As many pregnancies are unplanned, most clinicians avoid divalproex in women of childbearing potential where possible. When divalproex is used in females with child bearing potential, effective contraception should be in place. Folic acid can be given as a precaution in doses of 4 to 5 mg daily, but it is not known how much this reduces the risk of teratogenicity.

c. *Gabapentin:* Gabapentin has less evidence for efficacy than divalproex, but does tend to have fewer side effects, and can be a good choice in patients on multiple other medications as it has few drug interactions. Gabapentin can promote weight gain. It has a short plasma half life (five to nine hours), and ideally requires dosing three times a day, which can be a problem for patient compliance. The usual starting dose is 300 mg three times a day, and the daily dose can be increased by 300 mg on a weekly basis. Some physicians utilize a more gradual initiation of gabapentin therapy to improve tolerability, starting with 300 mg daily, and increasing the daily dose by 300 mg every three to five days. For most patients, the target dose is 1200 to 1500 mg per day in divided doses, although the dose can be increased to 1800 mg daily, if necessary and tolerated.

d. *Pizotifen (pizotyline):* This older drug is a serotonin antagonist. Weight gain and sedation are common side effects. It is usually started in a dose of 0.5 mg at bedtime for a week, then 0.5 mg twice a day for a week, and then 0.5 mg three times a day. A good target dose is 1 mg twice a day, although the dose can be increased further up to 4 mg per day if necessary and tolerated. To minimize sedation and improve tolerance, once daily dosing at bedtime is frequently used.

e. *Flunarizine:* This older drug (a calcium channel blocker) can be started at 10 mg at bedtime, which is also the usual maintenance dose. Alternatively, a dose of 5 mg at bedtime is started and increased to 10 mg in one to two weeks. It should not be given to patients with a significant history of depression, and patients should be warned about the drugs ability to precipitate depression. It can promote weight gain in some patients and with prolonged use may rarely cause symptoms of parkinsonism.

f. *Verapamil:* Although the quality of evidence for its efficacy is low, this older drug has been used for many years based on

clinical experience. If other drugs have failed, verapamil can be tried, starting at a dose of 40 mg three a day, and increasing the daily dose over one to two weeks until a dose of 80 mg three times a day is reached if tolerated. Divided doses are necessary because of the short half life (three to seven hours), and slow release preparations may not be reliable in terms of allowing for reduced frequency of dosing. In contrast to cluster headache, given the low quality of evidence for efficacy in migraine and other drug choices that are available, doses higher than 480 mg per day are not recommended.

g. *Botulinum toxin type A (onabotulinumtoxinA):* Although recent clinical trials have shown efficacy for onabotulinumtoxinA in patients with chronic migraine (migraine with more than 14 headache days a month), clinical trials in patients with migraine of lesser frequency have not shown efficacy superior to placebo. It is therefore not recommended for episodic migraine with headache frequency under 15 days a month.

EXPERT CONSENSUS

i. *Topiramate is a useful migraine prophylactic drug. Although used for first time prophylaxis by some clinicians, it is not included here in the "First time" strategies because of its side effect profile. An exception is when it is used as part of the increased body mass index strategy.*
ii. *Divalproex sodium is a useful migraine prophylactic drug in patients when other prophylactic drugs have failed. Given its teratogenicity, it should generally be avoided in women with child bearing potential and if used, should only be used when the benefits are felt to outweigh the risks, and with appropriate contraception in place.*
iii. *Gabapentin can be considered in patients when other prophylactics have failed. It has the advantage of few drug interactions. Evidence for efficacy is less strong than for some other prophylactics.*
iv. *Flunarizine can be a useful prophylactic when other prophylactics have failed, but should be avoided in patients with a significant history of depression. Patients on flunarizine should be monitored for onset of depression.*
v. *Pizotifen is an option for migraine prophylaxis when other drugs have failed.*
vi. *Verapamil can be considered for migraine prophylaxis when other drugs have failed, but the quality of evidence for efficacy of verapamil is low.*
vii. *Although onabotulinumtoxinA is useful in chronic migraine, on the basis of clinical trial results it is not recommended for patients with episodic migraine (14 headache days per month or less).*
viii. *Based on their proven efficacy in episodic migraine, many of the prophylactic drugs listed in this guideline are also utilized in chronic migraine. However, with the exception of topiramate and onabotulinumtoxinA, the evidence for most migraine prophylactic drugs for efficacy in chronic migraine is very limited.*

7. ***Refractory patient strategy:*** Refractory migraine has been defined as migraine causing significant interference with function or quality of life despite optimal management of triggers and lifestyle factors, and adequate trials of acute and prophylactic medications. Failure of prophylactic medications is defined as failure of adequate trials of medications from at least two of the four main classes of prophylactic medications: beta-blockers, anticonvulsants, tricyclics, and calcium channel blockers. An adequate trial has been defined as a trial of two months at optimum dosage or maximum tolerated dose, unless the medication must be discontinued earlier because of side effects[26].

Patients who are refractory to multiple trials of prophylactic monotherapy need a careful reassessment to determine if there is definable reason for this. Possible explanations which can potentially be addressed include acute medication overuse, incorrect diagnosis, and psychological or social factors which are exacerbating the patient's migraine tendency[27].

In refractory migraine, several prophylactic drugs are often tried in combination, although there is little scientific evidence for this practice. Prophylactic polypharmacy is based on the hypothesis that different prophylactic drugs may work by somewhat different mechanisms, and therefore the effects of two different drugs in reducing migraine frequency may be additive[28].

In general, polypharmacy with the use of two or more prophylactic drugs simultaneously should be tried only once several prophylactic drugs used alone have failed, as adding a second prophylactic drug to an already established one has the potential to increase drug side effects and produce drug interactions. It has been suggested that patients should have failed at least two adequate trials of two of the "major" prophylactics (β-blockers and neuromodulators – topiramate or valproate) before prophylactic polypharmacy is used[28]. An exception to these rules might be the use of vitamin B2 and / or magnesium in combination with another prophylactic drug; as such combinations are unlikely to lead to problems with tolerability. Whether these combinations lead to additive benefits has not been established. Prophylactic polypharmacy is also used in patients with comorbidities. For example, if a patient whose migraine is not fully controlled on the hypertension strategy also has insomnia, amitriptyline might be added as a second prophylactic.

Headache specialists have used rational prophylactic combination therapy to treat refractory migraine for many years, and many different drug combinations have been suggested[29]. A combination of a β-blocker and amitriptyline has been recommended as an option for migraine patients experiencing interictal tension-type-like headaches. For migraine patients without tension-type headache a β-blocker in a single morning dose to maximize compliance (eg, nadolol, or long-acting propranolol) plus a neuromodulator (topiramate or valproate) has been recommended[28]. In order to reduce side effects, one or more of the combined drugs is often used in reduced doses. The addition of behavioural treatment modalities should also be considered in refractory patients.

Evidence from open label clinical trials does suggest that prophylactic drug combinations can be effective where monotherapy has failed. These trials have found that beta-blockers (propranolol or nadolol) in combination with topiramate were more effective than either drug alone[30]. In another trial, topiramate appeared to provide additional benefit when added to either a beta-blockers or flunarizine[31]. Increased efficacy has also been reported in an open label study for a combination of valproate and a beta-blocker (propranolol or nadolol) compared to either drug alone[32]. A small double-blind randomized trial without placebo control found that the combination of amitriptyline and topiramate resulted in better patient satisfaction

than either drug alone, although headache endpoints (frequency, severity, and duration) showed no differences between patient groups[33].

EXPERT CONSENSUS

i. The simultaneous use of more than one prophylactic drug may be of benefit in patients with migraine refractory to prophylactic monotherapy.
ii. The following drug combinations may be useful in patients with refractory migraine, based primarily on non-randomized trials and clinical experience: beta-blockers and topiramate, beta-blockers and divalproex sodium, beta-blockers and amitriptyline, and amitriptyline and topiramate.
iii. Patients requiring prophylactic polypharmacy should be considered for specialist referral.

8. ***Migraine during pregnancy strategy:*** Migraine prophylactic drugs should be avoided in pregnancy where possible, and particularly during the first trimester. It has been pointed out that since the probability of spontaneous remission of migraine in the second and third trimester is greater than the typical response to most prophylactic drugs; it is irrational to commence prophylactic therapy during the first trimester except under exceptional circumstances[34]. Non-pharmacological methods to reduce headache frequency including lifestyle changes should be maximized as much as possible before drug prophylaxis is resorted to. If prophylaxis becomes necessary later in pregnancy because of frequent headache or migraine associated vomiting and dehydration, there are no randomized controlled trials to guide the clinician in drug choice, and the complicated medical literature is interpreted differently by different authors.

The guidelines of the European Federation of Neurological Societies (EFNS) state that if prophylaxis is needed, only magnesium and metoprolol are recommended during pregnancy[5]. Consistent with this, it has been pointed out that oral magnesium is considered safe and one of the few agents approved by the FDA for migraine prophylaxis during pregnancy[35]. On its website (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/multi_vitmin_suppl-eng.php#53), Health Canada lists 355 mg of magnesium daily as an adequate intake for a pregnant adult, but does not comment on the higher doses used for migraine prophylaxis. Menon et al[35] concluded with regard to beta blockers, that there is no evidence for teratogenicity, but cautioned that foetal toxicity may occur as a result of complications such as intrauterine growth retardation, hypoglycaemia, bradycardia, and respiratory depression. Similarly, Silberstein pointed out that if a prophylactic becomes necessary during pregnancy, beta-adrenergic blockers such as propranolol have been used under these circumstances, although adverse effects, including intrauterine growth retardation, have been reported[36]. Both Goadsby et al and Fox et al concluded that propranolol was the drug of choice if drug prophylaxis was necessary during pregnancy[34,37]. Pfaffenrath et al concluded that metoprolol and propranolol have the greatest weight of data assessing their safety during pregnancy[38].

With regard to the safety of the tricyclics antidepressants during pregnancy, according to recent acute pain management guidelines produced by the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, the Australian Drug Evaluation Committee (ADEC) has classified amitriptyline and nortriptyline as category C drugs, that is, as drugs that, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Specifically, with prolonged maternal use during pregnancy these drugs have been reported to cause withdrawal symptoms in newborn infants[39]. This transient neonatal withdrawal-like syndrome is characterized by jitteriness, self-limiting respiratory difficulties, and problems with feeding, and has been reported to occur occasionally with third trimester antidepressant use including the tricyclic antidepressants.

Similarly, Payne et al concluded with regard to nortiptyline and several other tricyclics, that there was no confirmed evidence of birth defects in first trimester exposure, but that these drugs could produce a withdrawal syndrome with third trimester exposure. This syndrome was in most cases very mild, self-limited, and did not seem to be associated with lasting repercussions[40]. Studies have also shown that in utero exposure to tricyclic antidepressant drugs does not affect global IQ, language development, or behavioural development in preschool children[41], and that indeed exposure to tricyclic antidepressants throughout gestation does not appear to adversely affect cognition, language development, or the temperament of preschool and early-school age children[42]. A recent review by MacGregor also classified propranolol, metoprolol, and amitriptyline as drugs with data suggesting they were unlikely to cause harm. It was recommended that propranolol and metoprolol be stopped two to three days before delivery in order to reduce the likelihood of fetal bradycardia and a reduction in uterine contraction, and that infants exposed to propranolol in utero should be monitored for hypoglycemia. It was also recommended that amitriptyline be tapered where possible three to four weeks before delivery[43].

Anti-epileptic drugs are widely used in migraine prophylaxis, but unfortunately valproate, topiramate, and gabapentin, are not established as safe in pregnancy; valproate is a known teratogen[37]. A recent health care professional letter from the manufacturer of topiramate stated that for the indication of migraine prophylaxis, topiramate is contraindicated in pregnancy and in women of childbearing potential who are not using an effective method of contraception[44]. The safety of the high doses of riboflavin used in migraine prophylaxis has also not been established[35].

EXPERT CONSENSUS

i. Migraine drug prophylaxis is best avoided during pregnancy if at all possible. Strategies involving trigger management, maintenance of good hydration, regular meals, regular sleep and attention to other lifestyle factors should be considered.
ii. Magnesium is considered the safest migraine prophylactic during pregnancy.
iii. If migraine drug prophylaxis is necessary during pregnancy, the best choice is a beta-blocker (propranolol or metoprolol) or if these are contraindicated or ineffective, amitriptyline or nortiptyline.

9. ***Migraine during lactation strategy:*** Migraine prophylactic drugs are best avoided during lactation if possible. If prophylaxis is necessary, propranolol, nadolol, and metoprolol are all considered compatible with breast feeding[37]. Propanolol, which is

highly protein bound in maternal plasma, is present in relatively low concentrations in breast milk and a good choice[45]. Propranolol does not result in significant measurable drug levels in the nursing infant, while metoprolol does[45]. Amitriptyline is also highly protein bound in maternal plasma and does not produce measurable blood levels in the nursing infant[45]. Nortriptyline is found in relatively low concentrations in breast milk and there is minimal detection of the drug in infant serum[40]. Both tricyclic antidepressants and propranolol are listed as drugs of choice for use while breastfeeding by Ito[46]. Nortriptyline has been considered to have particularly strong evidence for low infant serum drug levels and safety[47]. Among the anticonvulsants, valproate is considered compatible with breast feeding[37], but given the possibility of pregnancy in this patient population, it is probably best avoided. There is insufficient evidence to assure safety of the newer anticonvulsants, and caution is recommended. Topiramate, for example, does result in measurable blood levels in the nursing infant[45]. A recent review concluded that there was no evidence of harm (highest recommendation) for the use of propranolol, metoprolol, valproate, and verapamil during breast feeding. Amitriptyline was categorized in the second highest rating (data suggests unlikely to cause harm)[43]. The American Academy of Pediatrics has classified magnesium, propranolol, nadolol, metoprolol and divalproex sodium as compatible with breast feeding[48].

Expert consensus

i. *Migraine prophylaxis should be avoided during breast feeding, if possible.*
ii. *Magnesium and the beta-blockers (propranolol, metoprolol, and nadolol) are the preferred choices if migraine prophylaxis is necessary during lactation.*
iii. *Amitriptyline and nortriptyline may be considered for prophylaxis during lactation if magnesium and beta-blockers are contraindicated or ineffective.*
iv. *Although divalproex sodium is considered compatible with breastfeeding, it may be best avoided due to the possibility of pregnancy in this population.*

Summary

Migraine prophylaxis is likely underutilized. There is good evidence from randomized controlled trials to support the efficacy of a number of different prophylactic drugs in patients with frequent migraine headaches. Choosing between evidence based regimens should be based on clinical considerations.

Among the beta-blockers, propranolol has the most evidence for efficacy, and has been used extensively in clinical practice. Nadolol and metoprolol have comparable efficacy to propranolol. The other beta-blockers have not been specifically evaluated for this guideline. Among antidepressants, amitriptyline (a tricyclic) has the best evidence for efficacy. Although nortiptyline may be better tolerated than amitriptyline, there is a lack of clinical trials evaluating its efficacy for migraine prophylaxis. Venlafaxine extended release has shown efficacy. Selective serotonin reuptake inhibitors (of questionable benefit, and may aggravate migraine), and the monoamine oxidase inhibitors (rarely used in clinical practice) have not been included in our systematic review.

Among the antieplileptics, topiramate and divalproex sodium have the best evidence for efficacy. Gabapentin has less evidence but may be better tolerated. Among the calcium channel blockers, flunarizine has the best evidence for efficacy. Verapamil has only low-quality evidence to support its use. For angiotensin-related drugs, lisinopril and candesartan have shown evidence for efficacy, although data is limited to one trial for each drug. Both are generally well tolerated, although lisinopril may cause chronic cough in some patients. Among the vitamins/mineral/herbs, butterbur, riboflavin (high dose), coenzyme Q10, and magnesium have some randomized controlled trial evidence for efficacy and all have good tolerability. Feverfew is not recommended for migraine prophylaxis.

For information on drug doses and side effects, see Table 2.

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Migraine Prophylactic Guideline Summary for Primary Care Physicians - Section IV

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Introduction

Many of the recommendations in this guideline are summarized here to provide a compact source of information for the primary care physician. More detailed discussion can be found in the main guideline document. Section 3, Table 2 can be consulted for more detailed information on drug dosages, precautions, and side effects. The evidence for efficacy of individual drugs is based on a systematic review. Statements regarding other aspects of migraine prophylaxis are based on a general literature review and expert opinion (Expert consensus).

All patients for whom migraine drug prophylaxis is being considered should be educated regarding the common migraine triggers and the important lifestyle factors which may potentially influence their headache frequency.

Objective

To assist the physician in choosing an appropriate prophylactic medication for an individual with intermittent migraine headaches (headache on ≤ 14 days a month).

Who should receive prophylaxis?

i. *Migraine prophylactic therapy should be considered in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management / lifestyle modification strategies.*
ii. *Migraine prophylactic therapy should be considered when the frequency of migraine attacks is such that reliance on acute medications alone puts patients at risk for medication overuse (rebound) headache. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, ASA, NSAIDs) on 15 days a month or more,*
iii. *Migraine prophylaxis should be considered for patients with greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective because of the risk of medication overuse headache.*

What constitutes an adequate prophylactic trial?

i. *Unless side effects dictate that the drug be stopped sooner, A prophylactic medication trial should consist of at least two months at the target or optimal dose (or at the maximum tolerated dose if the usual target dose is not tolerated) before a prophylactic drug is considered ineffective.*
ii. *A daily headache diary (available for download from www.headachenetwork.ca) is useful for assessing response to therapy.*

When should prophylactic therapy be considered effective?

i. *A prophylactic medication is usually considered effective if headache frequency is reduced by 50% or more, although lesser reductions in headache frequency may be worthwhile, particularly if the drug is well tolerated.*
ii. *In addition to reduction in headache frequency, reductions in headache intensity and migraine-related disability need to be considered when judging the effectiveness of prophylactic therapy.*
iii. *Patients on migraine prophylaxis require periodic re-evaluation both to monitor potential side effects, and to assess efficacy.*

How long should successful prophylaxis be continued?

i. *After six to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the prophylactic medication in many patients, although others may benefit from a much longer duration of prophylactic therapy. If headache frequency increases as the prophylactic drug dosage is reduced, the dosage can be increased again or the drug restarted if it has been discontinued.*

What advice should be given the patient with medication overuse when prophylaxis is being considered?

i. *When prophylactic drug therapy is started, the patient should also be evaluated for the presence of medication overuse (see*

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definition above) and cessation of medication overuse should be strongly encouraged to optimize the chances for success.

Which prophylactic drug should be used?

In this section, prophylactic drugs are divided into those with a strong recommendation for use, and those with a weak recommendation. A strong recommendation means that the intervention could be used for most patients, and that the benefits of therapy outweigh the potential risks. A weak recommendation indicates that the intervention could still be applied to a majority of patients, but it would not be appropriate for many, often because of potential side effects. With a weak recommendation, the balance between risks and benefits is closer or more uncertain, and whether the intervention is suitable for a patient depends a great deal on the clinical situation and the nature of the patient. The medication may still be very useful for selected patients. For more details, please consult Section 2 of the main guideline document.

All of the following medications are recommended for migraine prophylaxis:

- Strong recommendation:

i. High quality evidence for efficacy: Topiramate, propranolol, metoprolol, amitriptyline

ii. Moderate quality evidence: nadolol, gabapentin, candesartan, butterbur

iii. Low quality evidence: riboflavin, coenzyme Q10, magnesium citrate

- Weak recommendation:

i. High quality evidence for efficacy: divalproex sodium, flunarizine, pizotifen

ii. Low quality evidence: venlafaxine, verapamil, lisinopril.

A prophylactic drug should be chosen for an individual patient based on evidence for drug efficacy, side-effect profile, and the presence of any co-existing medical and psychiatric disorders.

Prophylactic strategies: The prophylactic drugs can be organized into treatment strategies which are based on patient clinical features. These strategies are listed below. Note that drugs in brackets have insufficient evidence from randomized trials to recommend them for routine use. For more information on dosages, precautions, and side effects, see Section 3, Table 2.

1. **First time strategy** (for the patient who has not had prophylaxis before). Although other drugs may be used for the initiation of prophylaxis in a patient for the first time (ie topiramate, gabapentin, low side effect strategies), the following appear particularly suited for first time prophylaxis.

a. ***Beta-blocker strategy:*** propranolol, nadolol, and metoprolol

EXPERT CONSENSUS

i. Propranolol, nadolol, and metoprolol are good initial prophylactic drug choices for many patients with migraine. Some other beta blockers may also be useful, but have not been reviewed for this guideline.

ii. For propranolol the usual starting dose is 20 to 40 mg twice daily. The dose can be increased slowly (every one to two weeks) as necessary and tolerated up to a maximum of 160 mg daily. The long acting form may also be used.

iii. For nadolol, the usual starting dose is 20 to 40 mg given once daily in the morning. The dose can be increased slowly (every one to two weeks) as necessary and tolerated, up to a maximum of 160 mg daily.

iv. For metoprolol, the usual starting dose is 50 mg twice a day. The dose can be increased slowly (every one to two weeks) as necessary and tolerated to a maximum dose of 200 mg daily. The long acting form may also be used.

b. ***Tricyclic strategy:*** amitriptyline (nortriptyline)

i. Amitriptyline is a good initial migraine prophylactic drug. It may be particularly useful in patients with insomnia or associated tension-type headache.

ii. When starting amitriptyline prophylaxis for migraine, a low initial dose should be used in most patients (10 mg) and the dose should be built up slowly (10 mg every week or every two weeks).

iii. In patients without insomnia or in those who cannot tolerate amitriptyline, nortiptyline in similar doses may be better tolerated and possibly effective.

2. **Low side effect strategy**

a. ***Drug:*** candesartan, lisinopril

i. Candesarten and lisinopril have evidence for efficacy in migraine prophylaxis, and generally have few side effects, although each has only one controlled trial to date supporting its use. The target dose for candesartan is 16 mg daily, for lisinopril 20 mg daily. Candesarten is preferred because of fewer side effects, and because clinical experience with lisinopril is more limited. Given the limited data for efficacy and the limited clinical experience with both these drugs at this time, they should not be considered as substitutes for the more established drugs in the "first time strategy" under most circumstances.

b. ***Herbal / vitamin / mineral:*** Mg citrate, riboflavin, butterbur, Coenzyme Q10

ii. Butterbur, riboflavin, magnesium, and co-enzyme Q have very few side effects, and are evidence based options for migraine prophylaxis. These compounds are felt to have only modest efficacy, and should not be considered substitutes for "First time" strategy drugs under most circumstances.

iii. Target doses are: butterbur 75 mg twice a day; riboflavin 400 mg daily; magnesium 300 mg (elemental magnesium) of magnesium citrate twice a day; co-enzyme Q10 100 mg three times a day.

3. **Increased body mass index strategy:** topiramate

i. Topiramate is a migraine prophylactic drug which, because of its propensity to promote weight loss, is particularly useful in patients who are overweight, in patients who are particularly concerned about weight gain, and in patients with co-existent illnesses which might be exacerbated by weight gain (ie diabetes).

ii. Topiramate should be started at a low dose (15 or 25 mg daily), and the daily dose should be increased slowly (by 15 every week or 25 mg every two weeks in order to improve drug tolerability.

iii. The usual target dose for topiramate in migraine prophylaxis is 100 mg daily.

4. **Hypertension strategy:** propranolol, nadolol, metoprolol, candesarten, lisinopril

i. For patients with hypertension and migraine, refer to the Canadian Hypertension Education Program's (CHEP) clinical practice recommendations which are updated annually and can be found at www.hypertension.ca . The following recommendations for managing patients with both migraine and hypertension have been reviewed with CHEP and are consistent with those evidence based recommendations. The specific angiotensin receptor blockers and angiotensin converting enzyme inhibitors listed below are those with evidence for efficacy in migraine prophylaxis.

ii. Simplification of medical regimens is known to improve adherence, and the use of the same medication for both migraine and hypertension may reduce the potential for drug side effects and interactions. Recommended options are:

a. *Propranolol, nadolol, or metoprolol* (for patients under age 60). (Some other beta-blockers may also be effective, but have not been reviewed in this guideline.)
b. *Candesartan* (Candesartan has also demonstrated efficacy for patients with isolated systolic hypertension)
c. *Lisinopril* (ACE inhibitors have been found to be less effective for lowering blood pressure as monotherapy in patients of African (black) origin).

iii. Combination therapy is often required to achieve blood pressure targets. For patients requiring additional medication for blood pressure control, adding a thiazide diuretic and / or a calcium channel blocker to one of the above medications is indicated (combinations of beta blockers and non-dihydropyridine calcium channel blockers like verapamil should be avoided due to the risk of heart block).

iv. If adequate migraine prophylaxis is not achieved and the blood pressure is at target, other migraine prophylactic medications may be added.

5. **Depression / anxiety strategy:** amitriptyline, venlafaxine, (nortriptyline) (dual therapy)

i. Because of the advantages of monotherapy (less potential for drug interactions and side effects), monotherapy with one of amitriptyline (individualize dose, build up slowly) or venlafaxine (target dose 150 mg daily) should be considered in patients with anxiety and /or depression who require migraine prophylaxis. Experience with venlafaxine in migraine prophylaxis is limited. Nortriptyline may be an alternative although less evidence-based choice.

ii. In some patients, particularly if good control is not achieved with monotherapy or if the patient is unable to tolerate adequate doses of the tricyclic, clinicians may need to treat the migraine and the anxiety and / or depression with separate medications.

iii. If SSRI – tricyclic co-therapy is planned, sertraline should be considered because of less potential for drug interactions. Most other SSRIs, in particular fluoxetine, fluvoxamine, and paroxetine, have a greater potential for significant drug interactions with amitriptyline and nortriptyline.

iv. Certain prophylactic drugs can precipitate or exacerbate depression, and should be typically be avoided (flunarizine), or used with caution (topiramate) in patients with depression. Although traditionally beta-blockers have been considered to predispose to depression, more recent studies suggest that this is not the case.

6. **Additional monotherapy drug strategies:** topiramate, divalproex, gabapentin, pizotifen, flunarizine, (verapamil).

i. Topiramate is a useful migraine prophylactic drug. Although used for first time prophylaxis by some clinicians, it is not included here in the "First time" strategies because of its potential side effect profile. An exception is when it is used as part of the increased body mass index strategy. For dosages, see increased body mass index strategy (Strategy 3).

ii. Divalproex sodium (500 to 1500 mg daily) is a useful migraine prophylactic drug in patients when other prophylactic drugs have failed. Given its teratogenicity, it should generally be avoided in women with child bearing potential and if used, should only be used when the benefits are felt to outweigh the risks, and with appropriate contraception in place.

iii. Gabapentin (1200 to 1800 mg daily) can be considered in patients when other prophylactics have failed. It has the advantage of few drug interactions. Evidence for efficacy is less strong than for some other prophylactics.

iv. Flunarizine (10 mg daily) can be a useful prophylactic when other prophylactics have failed, but should be avoided in patients with a significant history of depression. Patients on flunarizine should be monitored for onset of depression.

v. Pizotifen (1.5 to 4 mg daily) is an option for migraine prophylaxis when other drugs have failed.

vi. Verapamil (240 to 480 mg daily) can be considered for migraine prophylaxis when other drugs have failed, but the quality of evidence for efficacy of verapamil is low.

7. **Refractory patient strategy:** multiple drugs (lower doses than those usually used are often used in combination therapy for at least one of the drugs to reduce side effects).

i. The simultaneous use of more than one prophylactic drug may be of benefit in patients with migraine refractory to prophylactic monotherapy.

ii. The following drug combinations may be useful in patients with refractory migraine, based primarily on non-randomized trials and clinical experience: beta-blockers and topiramate, beta-blockers and divalproex sodium, beta-blockers and amitriptyline, and amitriptyline and topiramate.

iii. Patients requiring prophylactic polypharmacy should be considered for specialist referral.

8. **Migraine during pregnancy strategy:**

i. Migraine drug prophylaxis is best avoided during pregnancy if at all possible. Strategies involving trigger management, maintenance of good hydration, regular meals, regular sleep and attention to other lifestyle factors should be considered.

ii. Magnesium is considered the safest migraine prophylactic during pregnancy.

iii. If migraine drug prophylaxis is necessary during pregnancy, the best choice is a beta-blocker (propranolol or metoprolol) or if these are contraindicated or ineffective, amitriptyline or nortiptyline.

9. **Migraine during lactation strategy:**

i. Migraine prophylaxis should be avoided during breast feeding, if possible.

ii. Magnesium and the beta-blockers (propranolol, metoprolol, and nadolol) are the preferred choices if migraine prophylaxis is necessary during lactation.

iii. Amitriptyline and nortriptyline may be considered for prophylaxis during lactation if magnesium and beta-blockers are contraindicated or ineffective.

iv. Although divalproex sodium is considered compatible with breastfeeding, it may be best avoided due to the possibility of pregnancy in this population.

Other Drugs

1. Methysergide is an effective migraine prophylactic, but because of side-effects is not recommended for routine use. When methysergide is used, specialist supervision is recommended.
2. Imipramine, trimipramine, desipramine, clomipramine, and doxepin are not recommended for routine use for migraine prophylaxis.
3. Although there is good evidence for efficacy in chronic migraine, botulinum toxin type A is not recommended for prophylaxis of episodic migraine in patients with less than 15 headache days per month. We found high quality evidence that botulinum toxin type A is no better than placebo for the prophylaxis of migraine in such patients.
4. Feverfew is not recommended for the prophylaxis of migraine. We found moderate quality evidence that feverfew is no better than placebo for the prophylaxis of migraine.
5. Selective serotonin reuptake inhibitors and clonidine are not recommended for the prophylaxis of migraine.

Conclusion

Prophylactic migraine therapy is generally underutilized. If attention to life style factors, trigger management, and acute drug therapy does not provide sufficient relief from symptoms, prophylactic drug therapy should be strongly considered.