Migraine Prophylaxis: General Considerations

When Should Migraine Prophylaxis Be Considered?

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, acetylsalicylic acid [ASA], non-steroidal anti-inflammatory drugs [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?

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 reevaluation 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

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 Prophylactic Treatment Strategies

First Time Strategies

Beta-Blocker Strategy (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.

Tricyclic Strategy (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, nortriptyline in similar doses may be better tolerated and possibly effective.

Low Side Effect Strategies

Low Side Effect Drug Strategy (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.

Low Side Effect Herbal/Vitamin/Mineral Strategy (Expert Consensus)

i. Butterbur, riboflavin, magnesium, and coenzyme 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.

Increased Body Mass Index Strategy (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 (i.e., 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.

**Hypertension Strategy (Expert Consensus)**

i. For patients with hypertension and migraine, refer to the Canadian Hypertension Education Program (CHEP) clinical practice recommendations which are updated annually and can be found at [www.hypertension.ca](http://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 (Angiotensin-converting-enzyme [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 nondihydropyridine 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.

**Depression/Anxiety Strategy (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 selective serotonin re-uptake inhibitors [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 migraine prophylactic drugs should 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.

**Additional Monotherapy Drug Strategies (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.

**Refractory Patient Strategy (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.

**Migraine during Pregnancy Strategy (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 nortriptyline.

**Migraine during Lactation Strategy (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.
Table. Summary of Recommendations*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation Strength</th>
<th>Quality of Evidence</th>
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</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>Strong</td>
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<tr>
<td>Propranolol</td>
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<td>Magnesium citrate</td>
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<td>Divalproex</td>
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<tr>
<td>Lisinopril</td>
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Not Recommended for Use in Episodic Migraine** (Do not use)

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</tr>
<tr>
<td>Feverfew</td>
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<td>Moderate</td>
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*Utilizing Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria; **Migraine with headache on less than 15 days a month.