Preventive Management of Migraine
PREVENTIVE MANAGEMENT OF MIGRAINE

Objectives

- Review the principles of preventive treatment
- Identify and assess effectiveness of therapeutic interventions
- Evaluate options for treatment of refractory headache patients
- Identify refractory patients and refer to specialist
GENERAL PRINCIPLES OF PREVENTIVE TREATMENT

- Start low and increase dose slowly
  - Use long-acting formulation if compliance an issue
- Adequate trial (2 to 3 months) at an appropriate dosage
- Avoid interfering, overused, and contraindicated medications
- Evaluate therapy
  - Use headache calendar (diary)
  - Attempt to taper and discontinue treatment when headaches well controlled

Therapy should be initiated with the lowest effective dose of the chosen pharmacologic agent. Increase the dose slowly until clinical benefits are achieved in the absence of adverse events or until limited by adverse events. Give each treatment an adequate trial. Monitor compliance. A clinical benefit may take as long as 2 to 3 months to become apparent. Patients commonly take new treatments for 1 to 2 weeks without seeing an effect and then discontinue prematurely, with both the physician and patient believing the medication was not effective. Long-acting formulations may improve compliance. Avoid interfering medications (i.e., overuse of certain acute medications, such as ergotamine and caffeine).

Maximize compliance by discussing the following with the patient:
- Rationale for the particular treatment
- When and how to use the treatment
- Adverse effects that may be likely

Address and establish patient expectations:
- Discuss the expected benefits of therapy and how long it will take to achieve them
- Create a formal management plan based on patient preferences

Monitor the patient’s headache by having them keep a user-friendly diary to measure attack frequency, severity, duration, disability, response to type of treatment, and adverse medication effects. After a period of stability, consider tapering or discontinuing treatment.


GENERAL PRINCIPLES OF PREVENTIVE TREATMENT

Assess Coexisting Conditions

Select drug to treat both disorders
Do not use migraine drug if contraindicated for other condition
Do not use drug for other condition that exacerbates migraine
Be aware of drug interactions
Special concern for women of childbearing potential

Take into account the presence of coexisting diseases. Some comorbid conditions are more common in persons with migraine. These conditions include
- Stroke
- Myocardial infarction
- Raynaud’s phenomenon
- Epilepsy
- Affective disorders
- Anxiety disorders

Coexisting diseases present both treatment opportunities and limitations. Once the coexistent condition has been identified, select a pharmacologic agent that will treat both disorders. Establish that the coexistent disease is not a contraindication for the selected migraine therapies (e.g., β-blockers are contraindicated in patients with asthma). Ensure that treatments being used for coexistent conditions do not exacerbate migraine. Beware of interactions between pharmacologic agents used for migraine and those used for other conditions.

Special attention should be directed to women who are pregnant or want to become pregnant. Preventive migraine medications may have teratogenic effects. If treatment is absolutely necessary, select a treatment with the lowest risk of adverse effects to the fetus.

The goals of treatment are to:
- Relieve or prevent the pain and associated symptoms of migraine
- Optimize the patient’s ability to function normally

Preventive medications are taken whether or not headache is present in an attempt to reduce the frequency and perhaps the severity and duration of anticipated attacks. A preventive migraine drug could raise the threshold to activation of the migraine process either centrally or peripherally.

Drugs conceivably could:
- Decrease activation of the migraine generator
- Enhance central antinociception
- Raise the threshold for spreading depression
- Stabilize the more sensitive migrainous nervous system by changing sympathetic or serotonergic tone

Preventive drugs most likely work by more than one mechanism. The drugs could, in part, have a peripheral mechanism of action similar to specific acute medications.


WHEN TO USE PREVENTIVE MANAGEMENT

- Migraine significantly interferes with patient’s daily routine, despite acute Rx
- Acute medications contraindicated, ineffective, intolerable AEs, or overused
- Frequent headache (≥2 attacks per week)
- Uncommon migraine conditions
- Patient preference

Previously accepted recommendations for migraine prevention have focused on patients who have two or more attacks per month. Some patients with up to four to eight attacks per month do well on symptomatic treatment alone. This suggests that recommendations are arbitrary and that preventive treatment should be tailored to account for individual patient needs or other migraine characteristics.

Preventive therapy may be more appropriately guided by one or more of the following circumstances:

- Recurring migraines that, in the patient’s opinion, significantly interfere with their daily routine, despite receiving acute treatment
- Contraindication to, ineffectiveness, or overuse of acute therapies
- Adverse events with acute therapies
- Frequent headaches
- Cost of both acute and preventive therapies
- The presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, and migrainous infarction
- Patient preference

Use of acute treatment more than twice per week also may warrant initiation of preventive therapy.


The major medication groups for preventive migraine treatment include:

- Anticonvulsants
- Antidepressants
- β-Adrenergic blockers
- Calcium channel antagonists
- NSAIDs
- Serotonin antagonists
- Others (including riboflavin, minerals, herbs, and botulinum toxin A)

If preventive medication is indicated, the agent preferentially should be chosen from one of the first-line categories, based on the drug’s side effect profile and the patient’s coexistent and comorbid conditions.
Therapeutic opportunities
- Treat two disorders with a single drug
  - Hypertension or angina—use β-blocker
  - Depression—use TCAs or SSRIs
  - Epilepsy or mania—use divalproex or topiramate

Therapeutic limitations
- Avoid β-blockers with depression, asthma, or hypotension

When initiating preventive treatment, choose a drug with the most efficacy, based on the patient’s preference and the presence of any coexistent or comorbid diseases. Coexistent and comorbid diseases have important implications for treatment.

The presence of secondary illness provides therapeutic opportunities, but also imposes therapeutic limitations. In some instances, two or more conditions may be treated with a single drug.

When treating migraine and hypertension or angina, β-blockers or calcium channel blockers may be effective for all conditions. For the patient with migraine and depression, TCAs or SSRIs may be especially useful. For the patient with migraine and epilepsy or mania, sodium valproate or topiramate is useful.
ASSESSING IMPROVEMENTS WITH MIGRAINE PREVENTION

Common endpoints used in preventive studies
- Reduction in attack frequency
- Reduction in attack intensity/severity
- Decrease in migraine-induced disability
- % of patients with >50% reduction in attack frequency

Improvements in overall migraine status using preventive treatments usually take several weeks to months. Over this time, slow decreases in migraine frequency, severity and disability may be difficult to assess if not specifically tracked using diary cards. The most common ways to assess improvements in migraine status are to track attack frequency, attack severity and overall disability (MIDAS or HIT-6 tests). Treatment efficacy trials use these endpoints in addition to others. One common endpoint used in clinical trials is the percent of patients who demonstrate a 50% or greater reduction in attack frequency during the course of the clinical study.
### Preventive Treatment: Drug Choice

<table>
<thead>
<tr>
<th>COMORBID CONDITION</th>
<th>DRUG</th>
<th>EFFICACY*</th>
<th>SIDE EFFECTS*</th>
<th>RELATIVE CONTRAINDICATION</th>
<th>RELATIVE INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Divalproex**</td>
<td>4+</td>
<td>2+</td>
<td>Liver disease, bleeding disorders</td>
<td>Mania, epilepsy, impulse control</td>
</tr>
<tr>
<td></td>
<td>Topiramate**</td>
<td>4+</td>
<td>2+</td>
<td>Renal disease</td>
<td>Epilepsy, mania, neuropathic pain</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>2+</td>
<td>2+</td>
<td></td>
<td>Epilepsy, neuropathic pain</td>
</tr>
<tr>
<td></td>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCAs**</td>
<td>4+</td>
<td>2+</td>
<td>Mania, urinary retention, heart block</td>
<td>Other pain disorders, depression, anxiety disorders, insomnia</td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
<td>2+</td>
<td>1+</td>
<td>Mania</td>
<td>Depression, OCD</td>
</tr>
</tbody>
</table>

*On a scale of 0 to 4; **assessed as effective based on 2 or more double-blind controlled trials


As discussed earlier, other disorders are more common in persons with migraine. If present, select a drug to treat both disorders. Look at the side effect profile of the drug and balance it against its efficacy. Establish that the coexistent disease is not a contraindication for the selected migraine therapy.

For the patient with migraine and epilepsy or migraine and manic depressive illness, divalproex sodium and topiramate should be considered. Gabapentin is an alternative of less proven efficacy. Older patients with cardiac disease may not be candidates for TCAs, calcium channel or β-blockers, but they could easily use divalproex sodium, gabapentin, or topiramate. Monoamine oxidase inhibitors (MAOIs) are drugs reserved for patients with refractory depression.

### Preventive Treatment: Drug Choice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Side Effects*</th>
<th>Relative Contraindication</th>
<th>Relative Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiserotonin</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Methysergide **</td>
<td>4+</td>
<td>4+</td>
<td>Angina, PVD</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td><strong>β-Blockers</strong> **</td>
<td>4+</td>
<td>2+</td>
<td>Asthma, depression, CHF,</td>
<td>HTN, angina</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>2+</td>
<td>1+</td>
<td>Constipation, hypotension</td>
<td>Migraine with aura, HTN,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>angina, asthma</td>
</tr>
</tbody>
</table>

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Methysergide is effective but is not a first-line drug because of the risk of fibrosis with long-term use. When migraine and hypertension and/or angina occur together, β-blockers or calcium channel blockers are useful. In the asthmatic, depressed, or insulin-dependent diabetic patient, β-blockers should be used with caution. Verapamil often is used, although without scientific evidence, to treat migraine with aura and hemiplegic migraine.

### Preventive Treatment: Drug Choice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Side Effects*</th>
<th>Relative Contraindication</th>
<th>Relative Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen**</td>
<td>2+</td>
<td>2+</td>
<td>Ulcer disease, gastritis</td>
<td>Arthritis, other pain disorders</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td>Preference for natural products</td>
</tr>
<tr>
<td>Feverfew</td>
<td>2+</td>
<td>2+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>2+</td>
<td>1+</td>
<td>Myasthenia gravis</td>
<td>Dystonia or Spasticity</td>
</tr>
<tr>
<td>Petasites</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candasartan</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Lisinopro</td>
<td>2+</td>
<td>1+</td>
<td></td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

*On a scale of 0 to 4; **assessed as effective based on two double-blind, randomized controlled trials


NSAIDs often are used for menstrual migraine or in the presence of other pain disorders, but would not be used in the presence of ulcerative disease.

Riboflavin and feverfew often are used by patients with a preference for natural products.

Headache experts often use two preventive medications in combination and believe it may produce synergistic benefit.


Clinical evidence is building that supports the clinical efficacy of antiepileptic medications in the treatment of migraine prevention. Randomized, double-blind, placebo-controlled trials establish divalproex sodium, topiramate, gabapentin, and carbamazepine as effective treatments for prevention of migraine.
This double-blind, randomized, placebo-controlled study assessed the efficacy of gabapentin for the prevention of migraine (n=143). The study included a 4-week, single-blind, placebo baseline period and was followed by a 12-week, double-blind, treatment period. During the treatment phase, gabapentin was titrated up (900 mg/day (end of week 1) to 2400 mg/day (end of week 4) during the first 4 weeks (900 mg/day (end of week 1) to 2400 mg/day (end of week 4), followed by an 8-week stable treatment phase, and must have been receiving a stable dose of study medication by the end of the titration period.

- 46.4% (26/56 patients) in the gabapentin group and 16.1% (5/31) patients receiving placebo showed at least a 50% reduction in the 4-week migraine rate (P=.008)
- At the end of study, the median 4-week migraine rate was 2.7 for the gabapentin-treated patients and 3.5 for the placebo-treated patients (P =.006), compared with 4.2 and 4.1, respectively, during the baseline period
- 33 patients (24.1%) withdrew from the study: 24 (24.5%) of 98 gabapentin-treated patients; 9 (20.0%) of 45 placebo-treated patients
- 16 [16.3%] of 98 gabapentin-treated patients withdrew due to adverse events; 4 [8.9%] of 45 placebo-treated patients withdrew due to adverse events

This multicenter, randomized, double-blind study compared the efficacy of divalproex sodium (concentration levels between 70 to 120 mg/L) and placebo in the prophylaxis of migraine headache. Patients (n=170) participated in a 4-week, single-blind placebo baseline phase and a 12-week treatment phase (4-week dose adjustment, 8-week maintenance).

- 48% percent of divalproex-treated patients and 14% of placebo-treated patients showed a ≥50% reduction in migraine headache frequency from the baseline phase (P<.001).

- The mean migraine headache frequency per 4 weeks was 3.5 in the divalproex group and 5.7 in the placebo group (p < or = .001), vs. 6.0 and 6.4, during the baseline phase, respectively

- 13% of divalproex-treated patients and 5% of placebo-treated patients withdrew due to treatment intolerance/adverse events

Similar results were observed with divalproex sodium given in doses ranging between 500 to 1500 mg/d.


This was a 26-week, double-blind, randomized, placebo-controlled study that assessed the efficacy and safety of topiramate for migraine prevention. Treatment groups: topiramate (50, 100, or 200 mg/d) or placebo. **Topiramate was titrated by 25 mg/wk for 8 weeks to until the maximum tolerated dose for that treatment group, whichever was less and treatment dose was maintained for 18 weeks.**

- 483 patients were randomized and 468 provided at least 1 postbaseline efficacy assessment
- Primary endpoint: mean monthly migraine frequency was significantly lower for patients receiving topiramate at 100 mg/d (-2.1, P =.008) and topiramate at 200 mg/d (-2.4, P<.001) vs. placebo (-1.1) vs. placebo (p<0.05; within the first month)
- The percent of patients with a 50% or greater reduction in monthly headache frequency was significantly greater with topiramate at 50 mg/d (39%, P =.01), 100 mg/d (49%, P<.001), and 200 mg/d (47%, P<.001) vs. placebo (23%)
- Reasons for patients withdrawing due to adverse events were primarily due to paresthesia, fatigue, and nausea


Patients treated with preventive medication may continue to have attacks of episodic migraine. Menstrual migraine attacks often persist to a greater extent than nonmenstrual attacks. Preventive medication also may decrease the intensity and duration of the attacks, and may make acute medications more effective. Using preventive and acute medication together presents a new set of complexities.

The amount of acute medication must be limited to prevent the development of drug-induced daily rebound headache and loss of efficacy of the preventive medication. This is one of the causes of secondary failure of preventive medication.
Certain acute medications should be used with caution in the presence of some preventive medications. Ergotamine, DHE, and sumatriptan potentially could have enhanced vasospastic properties in the presence of methysergide. However, many authorities have found that the ergots are more effective in patients being treated with methysergide. MAOIs increase the half-life and the area under the curve of oral sumatriptan. Therefore, the dose of oral sumatriptan should be reduced and used cautiously, if at all, in patients taking MAOIs. Meperidine and sympathomimetics are potentially lethal additions to MAOIs and may result in serotonin syndrome or hypertensive crisis.
MIGRAINE PREVENTION IN SPECIAL POPULATIONS

To date, there are no randomized, double-blind, placebo-controlled evidence. These suggestions are based on clinical experience. Nonpharmacological therapies often prove helpful in these populations.

- Elderly: neurontin; TCAs; Beta-blockers
- Pregnancy: nonpharmacological, magnesium, B₁₂
- Pediatrics / adolescents:
  - Topiramate (2-6 mg/kg/d up to 200 mg)
  - Ciproheptadine (2-10 mg/day)
  - Amitriptyline.

To date, there are no randomized, double-blind, placebo-controlled evidence for prevention of migraine in the elderly, in pregnancy, or in children and adolescents. There are several things that can be tried, but these are based solely on clinical experience. Often, nonpharmacological therapies may prove helpful in these special populations.
All patients need nonpharmacologic treatment—the extent and type is dependent on the individual patient. Nonpharmacologic approaches for migraine are an adjunct to preventive therapies, but they also work alone for migraine prevention.

Certain factors steer the clinician to use behavioral techniques. Many patients will express a preference for nonpharmacologic intervention, which may be a good indicator of potential success. Because motivation is essential for effective behavioral techniques, these patients may have a greater likelihood of success with the nonpharmacologic techniques.

For those patients who are intolerant of medication, those for whom abortive and preventative agents are contraindicated, and those who have failed to respond to drug therapy, nonpharmacologic treatments may play a particularly important role. Pregnant women are appropriate candidates for nonpharmacologic treatment because medication raises concerns of injury to the fetus. Analgesic overusers may benefit from alternative strategies to control medication intake. Behavioral techniques may supplement stress coping skills in patients for whom life stress exacerbates headache.

NONPHARMACOLOGIC TREATMENTS

Effective: GRADE A
- Relaxation training
- Thermal biofeedback with relaxation training
- EMG biofeedback
- Cognitive behavioral therapy

Insufficient evidence to recommend: GRADE C
- Acupuncture
- TENS
- Cervical manipulation
- Occlusal adjustment
- Hyperbaric oxygen
- Hypnosis

The benefits of behavioral therapy (e.g., biofeedback, relaxation) are in addition to preventive drug therapy (e.g., propranolol, amitriptyline): GRADE B


Grade A biofeedback interventions, including relaxation training, thermal biofeedback with relaxation training, EMG, and cognitive behavioral training, are all considered effective.

Physical treatments of acupuncture, TENS, cervical manipulation, occlusal adjustment, hyperbaric oxygen, and hypnosis, either are ineffective or have been inadequately studied to establish their efficacy.

The benefits of behavioral therapy appear to be additive with pharmacotherapy.

Migraine prevention can be difficult to initiate. Patients may be hesitant to take daily medication for headache. Often, education and patients are key to successful treatment with preventive medications. It may take some patients up to 3 months to see an improvement in headache patterns, especially if they are not keeping a diary, where headaches slowly become less frequent and less severe. Until successful preventive medication is underway, regulating acute medications can be problematic. Coexisting conditions (depression, anxiety) also may need to be monitored and possibly treated. This will help influence which preventive therapy might be best for each patient.
PREVENTIVE CASE DISCUSSION

Dr. Allan Purdy
Division of Neurology
QEI Health Sciences Centre
CASE PRESENTATION

49 year old female; headaches since teenager

Last 10 years changed to mild almost daily headaches with some bad headaches ~4 per month (severe, pounding, one-sided); daily headache is usually dull and bilateral

Some worse with light, sound, alcohol, or hormone fluctuations; no nausea or vomiting

Tried triptans with some heaviness in left arm and throat tightness

Neurological examination normal

This patient happens to be perimenopausal and is a professional secretary. She does not take daily analgesics. She was on sumatriptan, and it was felt that her symptoms in her left arm were not cardiac, but this needed to be further investigated. She also experienced some throat tightness.

Sumatriptan worked well, but she found she was taking 10 to 12 doses a month.

Has headache history revealed that she had migraine headache without aura when younger. Here headaches appear to have progressed and with almost mild headache on a daily basis and “bad” headaches, which resemble her previous migraines.

Diagnosis: This patient is developing chronic daily headache. She is not on analgesics at this time, therefore, her headaches cannot be attributed to medication overuse. She tried rizatriptan without any benefit over sumatriptan and still reported similar arm and throat symptoms. Her history and work-up were unrevealing for cardiac symptoms. Her history with previous preventive therapy included: amitriptyline and propranolol. She reported having no change in headache status and objected to the weight gain associated with amitriptyline. Propranolol was not tolerated due increased fatigue/lethargy.

Case presented by Dr. Allan Purdy, Division of Neurology; QEII Health Sciences Centre, April 19th, 2004.
CASE DISCUSSION

What is best therapy at this time
First-line triptans working but with some side effects
Should she try other abortive medications? If so, what?
What about the chest / arm discomfort?
Should she be on prophylactic medication, and if so which one?

This patient is still a good candidate for prophylactic medication, but another medication should be tried, one without the associated side effects previously reported. She was tried on a starting dose of topiramate, which was gradually increased to 75 mg/d.

Approximately 6 weeks after treatment was started, her daily headache was reduced, and only occasional month migraines are reported. These migraines are severe in intensity and respond to zolmitriptan 2.5 mg without any major side effects.

Discussion points:

• She might have benefited from continued use of sumatriptan, and a lower dose could have been tried / different delivery (50 mg; 25 mg; or the nasal spray)
• The weight loss (25 pounds in 10 months) may also help with psychosocial and behavioral parts of lifestyle change (exercise, depression, etc.)
• Due to being perimenopausal, ongoing cardiac monitoring should be done, in this case, she had no further evidence of heart disease

Case presented by Dr. Allan Purdy, Division of Neurology; QEII Health Sciences Centre, April 19th, 2004.