Guidelines for the prevention of migraine

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ABSTRACT

Treatment of migraine has traditionally been divided into managing acute attacks and prophylactic treatment. Treatment of acute migraine has been the subject of many research papers and review articles in recent literature partly at the cost of prophylactic treatment, which is the focus of this review. The objective of prophylactic therapy is to reduce frequency, duration and severity of attacks in addition to optimize the patient’s ability to function normally. Preventive therapy is usually undertaken in patients who have more than two migraine episodes per month or when less frequent have severely disabling headaches resistant to usual treatment. Beta-blocking drugs without intrinsic sympathomimetic activity (e.g. propranolol) are usually the first drugs of choice followed by tricyclic antidepressant agents (e.g. amitriptyline), non-steroidal anti-inflammatory drugs (e.g. naproxen), calcium antagonists (e.g. flunarizine) or valproate. The use of serotonin antagonists (e.g. methysergide) is limited because of their potential serious side effects. Migraine refractory to standard prophylactic therapy is very often the result of overuse of abortive antimigraine drugs. The choice of medication clearly depends on the patient’s profile (age, co-morbid medical conditions) and the contraindication and side effect profile of the drug.

Keywords: Migraine, prophylaxis, beta-blocking drugs, tricyclic antidepressants, non-steroidal anti-inflammatory drugs, valproate, flunarizine, serotonin antagonists.

Neurosciences 2000; Vol. 5 (1): 7-12

Migraine is a chronic intermittent disorder characterized by paroxysmal, moderate-to-severe attacks of unilateral, throbbing headache exacerbated by physical activity and accompanied by anorexia, nausea, vomiting, photophobia and phonophobia. It is ubiquitous with variable geographical prevalence. Prevalence rates range from 1.5% in Hong Kong to 14% in the Western world. The prevalence rate on the Arabian Peninsula was reported 2.6%. Migraine is much more common in females than in males; 11-18% and 3-8%, respectively. Furthermore, there is a clear racial difference in genetic vulnerability to migraine and the disorder is known to be age (most common between 25-55 years) and income-dependent (affecting mostly lower socio-economic groups). Since migraine is a common illness, which reduces health-related quality of life both during and between acute attacks, the disease has a substantial socio-economic impact on both patient and society, resulting from limitations in daily function, reduced quality of life and loss of productivity. Indirect costs, particularly loss of productivity in the workplace, represent the largest proportion of total costs of migraine. There is now substantial evidence that the pathophysiology of migraine is based on the constriction of intracranial (pial and dural) blood vessels. The ophthalmic branch of the fifth cranial nerve transmits nociceptive information from the intracranial structures to the trigeminal nucleus from where neurons project to the midbrain (lateral geniculate body, superior colliculus), cerebral cortex (visual cortex) and retina. Depolarization of these trigeminovascular neuron results in the release of vasoactive neuropeptides (e.g. calcitonin gene-related peptide (CGRP) from the dense trigeminal...
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perivascular network into the vessel wall. This, in its turn, results in neurogenic mediated vasodilation and plasma protein extravasation. This inflammatory response is transmitted to adjacent tissues. Furthermore, this noxious response can be conveyed to the trigeminal nucleus caudalis and higher brain centers for the registration of pain.

Activation of presynaptic serotonin (5-HT\textsubscript{1B}) receptors identified on trigeminal perivascular neurons inhibits both the releases of these proinflammatory mediators and neurogenic inflammation. While 5-HT\textsubscript{1B} receptor activation, expressed on vascular smooth muscle cells, mediate vasoconstriction.

**Non-pharmacological measures.** Rational prophylactic management of migraine necessitates the accurate identification and elimination of potential trigger factors (e.g. stress, emotions, fatigue, certain foods and beverages, hormonal factors and drugs e.g. oral contraceptives, vasodilators). Consequently, regular sleep and meals, and relaxation techniques for coping with family-or-work-related stress and emotional problems may constitute part of the non-pharmacological prophylactic management.

**Pharmacological measures.** The objective in prophylactic treatment of migraine is to reduce the frequency, severity and duration of attacks whilst keeping side effects to a minimum. Prophylactic treatment is particularly recommended for patients with more than two migraine attacks per month or if the response to treatment of the acute attack is disappointing. Patients with infrequent migraine attacks are unlikely to sufficiently benefit to justify the inconvenience and side effects of prophylactic agents and, last but not least, the cost of the treatment. Other considerations include severity or disability from pain or associated symptoms.

Most prophylactic therapy needs to be given on a daily basis for months or years. However, periodical therapy can be considered in e.g. exercise-triggered migraine attacks. Similarly, menses-related migraine can be effectively managed with prophylactic therapy starting one week before the menstrual period is due. When prophylactic medication is indicated, it is advised to begin with a low dosage and titrate gradually upward until the agent is given at full therapeutic dosage or the migraine attacks are properly controlled. Treatment should be given for 3 months before reassessment, and continued for 6 months or longer if beneficial. If attack frequency and severity have been reduced to such a level that preventive medication is not longer indicated (e.g. less than two attacks per month without significant clinical disability) prophylactic therapy can be gradually withdrawn. Although monotherapy is preferable because it improves compliance, combination of propranolol and amitriptyline is effective especially with associated co-morbid conditions such as tension headache and depression or both.

In the following paragraphs the pharmacological characteristics of the agents used in the prophylactic treatment of migraine in adults will be discussed. Our evaluation of the clinical efficacy of drugs is based on double blind, controlled clinical trials with a significant number of patients (at least 50 patients per study arm), unless otherwise stated. Finally, prophylactic agents are at most 60% better than placebo and less than 10% of patients will become completely free of headache. Therefore, it needs to be considered whether this 30-60% reduction in headache frequency or severity will provide meaningful improvement in the patient’s quality of life.

Table 1 gives an overview of all drugs, which are and have been used, either successfully or non-successfully, in migraine prophylaxis. No single prophylactic drug is superior when potential side effects are also considered. Finally, it is important to recognize that migraine refractory to standard prophylactic therapy is very often the result of overuse of abortive antimigraine drugs. Gradual withdrawal from any overused drug followed by prophylactic therapy is cornerstones of the treatment of analgesic rebound headache.

**Beta-blocking drugs.** The mechanism by which β-blocking drugs prevent migraine is unclear. Most likely their effect can be explained by an interaction between the adrenergic and serotoninergic systems in the central nervous system, or by a direct 5-HT\textsubscript{2} antagonistic effect.

β-Blocking drugs without intrinsic sympathomimetic activity are the only class of β-blockers with proven effect in migraine prophylaxis. The beneficial effect is usually seen within 4 weeks, but seems to increase with time. This class of agents is particularly useful in patients whose attacks are triggered by stress. Propranolol has been the most extensively studied and has proved to be effective in 19 of 21 controlled trials. The standard dose long-acting formulation of propranolol (Inderal-LA, 160 mg o.d.) is more effective in reducing the frequency of migraine attacks compared to the lower dose long-acting formulation (Half-Inderal LA, 80 mg bid). Bisoprolol, metoprolol and timolol are useful alternatives, resulting in 22-49% reduction in the number of migraine attacks. Propranolol is highly liposoluble, which explains the higher rate of central nervous system side effects compared to metoprolol and timolol. Furthermore, because of lack of selectivity, it causes β\textsubscript{2}-induced bronchoconstriction. The choice of β-blocking drug might, therefore be dictated by its side effects. None of the β-blockers is safe during pregnancy.

Other β-blocking drugs, like atenolol and nadolol, have also been evaluated for their prophylactic effect, but the trials included a small number of
patients or had methodological flaws (e.g. lack of proper statistical evaluation) and are, therefore, inconclusive. Similarly, comparison between β-blocking drugs and other class agents is not useful since most trials lack statistical power to draw valid conclusions.

**Tricyclic antidepressants.** These agents are potent monoamine re-uptake blockers within the central nervous system. However, their effect in migraine prophylaxis is most likely due to the 5-HT$_2$-receptor and calcium channel blocking potential on cerebral blood vessels, and its inhibitory effect on dorsal raphe nuclei. Amitriptyline, the prototype tricyclic antidepressant, is superior to placebo, is more effective than propranolol in reducing the severity of attacks, and has a favorable effect on the frequency and duration of attacks. Amitriptyline is particularly useful in migraine patient with associated tension headache. In general, the antimigraine effect can be achieved with lower dosages (e.g. 50 mg per day) than are required to achieve an antidepressant effect. However, the antimuscarinic side effects (drowsiness, dry mouth and blurred vision) together with increase in appetite and weight gain could be a drawback in using this drug.

**Non-steroidal anti-inflammatory drugs.** Non-steroidal anti-inflammatory drugs (NSAIDs) have an inhibitory effect on prostaglandin and leukotriene synthesis, which probably explains their effectiveness in migraine prophylaxis, and prevention of neurogenic mediated inflammation in the trigeminovascular system. In addition, their analgesic and prophylactic effect is probably explained through their effect on serotoninergic receptors.

Non-steroidal anti-inflammatory drugs (NSAIDs) could be considered as the first drug of choice for young healthy patients with migraine. Daily dosing with NSAIDs (e.g. naproxen) during the week before, through and one week after menses is particularly effective for menstrual migraine. Low-dose aspirin proves to be superior to placebo in migraine prophylaxis. Similarly, naproxen proved to be 33% more effective than placebo (52% vs. 19%). Naproxen reduced the duration and severity of attacks.

### Table 1 - Agents used in migraine prophylaxis (all are orally administered).

<table>
<thead>
<tr>
<th>Class Drug</th>
<th>Dosage (mg/day)</th>
<th>Cost # (£/month)</th>
<th>Adverse effects (Relative Contraindications)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-100</td>
<td>1.13-1.61</td>
<td>Fatigue, depression, bradycardia, hypotension, bronchospasm, vivid dreams (Bradyarrhythmia, AB blok, congestive heart failure, asthma, diabetes)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5</td>
<td>8.60</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50-200</td>
<td>1.00-3.70</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>80-240</td>
<td>5.50-16.50</td>
<td></td>
</tr>
<tr>
<td>Propranolol*</td>
<td>80-160</td>
<td>5.40-6.70</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>10-20</td>
<td>2.60-5.20</td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>50</td>
<td>2.40</td>
<td>Sedation, weight gain, dry mouth, blurred vision, cardiac arrhythmias, urinary retention (Cardiac conduction block, urinary retention, closed-angle glaucoma, epilepsy)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin*</td>
<td>300qpd-300od</td>
<td>0.07-0.14</td>
<td>Dyspepsia, gastritis, GI hemorrhage, diarrhoea (Hypersensitivity to other NSAIDs, active peptic ulcer disease, renal impairment, liver cirrhosis, coagulopathy)</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>1,500</td>
<td>6.60</td>
<td></td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>1,000-1,100</td>
<td>8.74</td>
<td></td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>300</td>
<td>67.00</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil*</td>
<td>240-320</td>
<td>10.64-16.00</td>
<td>Bradycardia, weight gain, constipation, depression (Left heart failure, AV blok)</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>10</td>
<td>5.70</td>
<td>Depression, parkinsonism, weight gain</td>
</tr>
<tr>
<td><strong>Serotonin receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methysergide</td>
<td>1</td>
<td>2.68</td>
<td>Gastric irritation, muscle cramps, insomnia, tissue fibrosis (Peripheral vascular or coronary ischemia, hypertension, impaired liver or renal function, peptic ulcer)</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>1.5</td>
<td>7.78</td>
<td>Weight gain, sedation</td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td>500-1,500</td>
<td>4.40-13.20</td>
<td>Hair loss, weight gain, hepatic dysfunction, spina bifida</td>
</tr>
</tbody>
</table>

*Modified-release; AV, atrioventricular, NSAIDs, non-steroidal anti-inflammatory drugs; GI, gastrointestinal; qod, every other day; od once daily.

# Based on British National Formulary No. 36 (September 1998).
of headaches, frequency of associated symptoms like nausea and vomiting, and the use of analgesics.23,24

Naproxen is completely absorbed after oral or rectal administration. The salt form, naproxen sodium, is much faster absorbed after oral administration that naproxen (Tmax 1 hour for naproxen sodium vs. 2 hours for naproxen).25 The half-life of the drug is 12-15 hours, which justifies its twice daily administration.

Naproxen, in comparison with other NSAIDs, has the advantage that dosage adjustments are usually not required in the elderly or those with mild renal or hepatic impairment.23 However, in view of the potential risk of gastrointestinal ulceration prolonged prophylactic treatment in elderly patients does not seem to be justified.

Mefenamic acid is as effective as propranolol in preventing migraine.26 Another fenamate, tolfenamic acid, also proved to be more effective than placebo27 and as effective as propranolol in the prophylaxis of migraine with no statistical differences in adverse effects.28 A down side to tolfenamic acid will be certainly its high cost. Since the therapeutic response to NSAIDs is idiosyncratic, it would be justified to change from one NSAID to another if no response is obtained with the initial choice. However, no reliable data is available on the use of other NSAIDs in the prophylaxis of migraine.

Serotonin receptor antagonists. A number of prophylactic antimigrainous agents display a relatively high affinity for both 5-HT1 and 5-HT1c receptors in certain cranial blood vessels and human brain. These receptors appear to mediate neuronal depolarization at the cellular level. Moreover, 5-HT1c receptors play a crucial role in the development of perivascular inflammation, which may account for the prophylactic effect in the treatment of migraine.6 Pizotifen, structurally related to cyproheptadine, also acts as a potent H1 receptor antagonist.29

Methysgeride, an amine ergot alkaloid, is one of the oldest but most effective prophylactic agents in migraine therapy.30 In our experience, about 20-30% of patients are unable to tolerate the drug because of side effects mainly gastric discomfort, muscle cramps or cardiovascular effects (tachycardia, coronary ischemia, postural hypotension). Although devoid of α-adrenergic activity, chronic use may result in fibrotic syndromes and peripheral vascular complications. Despite this, the drug is considered safe if the patient is clinical monitored and if 3-4 week drug-free intervals are included every 6 months.

The use of pizotifen (pizotyline) in migraine prophylaxis is largely based on the results of uncontrolled studies. The few reported placebo-controlled trials were performed on small number of patients who were treated for a short time.26 In one of the larger placebo-controlled studies, pizotifen was superior to placebo in only 3 out of 9 indices of efficacy, and only at certain time periods during the 3-month trial23. A recent multicenter study31 revealed that pizotifen was only marginally better than placebo in reducing headache frequency but this at the expense of the adverse events associated with the drug, particularly drowsiness and increased appetite with weight gain. Hence, the beneficial effect of pizotifen in the prevention of migraine still remains to be proven. In view of its associated antimuscarnic side effects, the drug is contraindicated in glaucoma, prostate hypertrophy, epilepsy and cardiac arrhythmias.

Cyproheptadine shows structural similarity with phenothiazine antihistaminic agents, which explains its potent H1 antagonistic effect. In addition, the agent shows potent calcium channel blocking properties and 5-HT2 antagonistic activity, which might explain its empirical use in migraine prophylaxis since the drug has never been studied in controlled clinical trials. The side effects are identical to pizotifen.

Valproate. Valproate is the most recent drug approved by the FDA for migraine prophylaxis. Valproate is a γ-aminobutyric acid (GABA) transaminase inhibitor and activator of glutamic acid decarboxylase. Its pharmacological effect in migraine could be explained in several ways: firstly, valproate decrease plasma extravasation following substance P administration.32 Secondly, valproate inhibits the firing rate of serotonergic cells on the dorsal raphe nuclei33 and thirdly, it acts at voltage dependent calcium and sodium channels. Valproate is marketed as a sodium salt but is also available as a mixture of sodium valproate and valproic acid (divalproex sodium).

In double-blind controlled clinical trials, valproate was effective in reducing migraine frequency in at least 48-65% of patients vs. 14-18% with placebo and unlike other prophylactic agents, it also reduced the duration and severity of migraine attacks.34,35

The most common dose-related side effects of valproate are nausea, tremor, and transient hair loss and weight gain. However, side effects are less likely to occur since the therapeutic efficacy is achieved with serum concentrations less than the usual therapeutic range for seizure control. Idiosyncratic reactions are extremely rare and are largely limited to hepatotoxicity, which occurs predominantly in children under 2 years of age. Since most fatalities occur within 4-6 months after starting therapy, it is recommended to monitor the patient clinically. In addition, laboratory monitoring of liver function, complete blood count with differential and serum chemistries can be useful during the initial stages of treatment. Women of childbearing potential should additionally be warned of the increased risk of spina bifida. Although still debatable, it is recommended to start folic acid administration before conception.
Calcium antagonists. The exact mechanism of action of calcium antagonists in migraine prophylaxis is uncertain. Calcium is an important mediator of vascular smooth muscle contraction, neurotransmitter release and neuronal receptor function. Calcium antagonists may act by altering the calcium flux across arterial smooth muscle preventing vasoconstriction ad release of substance P, or by a direct effect at the 5HT site. Some of them like flunarizine have additional H1-receptor and dopamine antagonistic effects.

In general, the results of calcium antagonists in migraine prevention have been disappointing and some of them like the dihydropyridine derivatives (nifedipine and nimodipine) can actually cause headaches. The limited number of controlled crossover studies, which compared verapamil (a phenylalkylamine) with placebo were conducted on a small patient population and had poorly documented baseline values for headache severity, duration and frequency. The drug might be indicated for patients who have been refractory to previous prophylactic therapy although study limitations make it difficult to draw valid conclusions about its effectiveness.

The ability of flunarizine, a piperazine derivative, to reduce the frequency of migraine attacks is well documented. Like all prophylactically used drugs, its effect on the intensity and duration of the attack is less well established. Flunarizine has been found to be as effective as propranolol in the reduction of frequency, intensity of migraine attacks and use of rescue analgesics, while in another study flunarizine was found to be superior.

Selective serotonin reuptake inhibitors. The implication of 5-HT dysregulation in migraine pathogenesis has prompted many investigators to explore the usefulness of selective serotonin reuptake inhibitors (SSRIs) in migraine. Particularly, their low potential for side effects seems to attract a lot of attention resulting in widespread empirical use. However, the potential mechanism of action, if any, of SSRIs in migraine prophylaxis remains to be established. The few clinical studies available in the prophylaxis of migraine include a small number of patients and do not provide convincing results. In a recent double-blind trial fluoxetine-treated patients proved to have only 25% less attacks compared to place-treated patients. Selective serotonin reuptake inhibitors (SSRIs) are, therefore, unlikely to play an important role in the prophylactic treatment of migraine.

In conclusion, prophylactic treatment of migraine should be tailored to each patient, taking into account individual priorities and preferences. Multiple treatment strategies are available. Beta-blocking drugs (atenolol, nadolol, metoprolol, propranolol and timolol) have an established role in the prophylaxis of migraine. Generally, the effect appears within 4 weeks after starting treatment. Propranolol is inexpensive and frequently the best choice among β-blockers. Amitriptyline is an effective prophylactic agent in migraine, and is particularly useful for patients with concomitant depression or tension headache. While the prophylactic effect of flunarizine is well-documented and in the same order as beta-blocking drugs, the ability of diltiazem, nifedipine and verapamil to reduce the frequency of migraine attacks is unclear. Alternatively, valproate has also proven to be effective in migraine prophylaxis. Methysergide is usually relegated to last-resort use because of its potentially serious side effects. Finally, women suffering from menstrual migraine may benefit from naproxen, amitriptyline or propranolol, limited to the time of their menses, but the major strategy is aimed at preventing a decrease or fluctuation in estrogen levels. Those patients favoring herbal therapy might benefit from a treatment with feverfew (tanacetum parthenium), a plant rich in parthenolide has proven to be more effective than placebo in the prophylaxis of migraine.

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