**Migraine : Prophylactic Treatment**

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**Abstract**

Prophylactic treatment constitutes an important aspect of migraine management and includes avoidance of trigger factors and lifestyle advice followed by consideration of medications. The drugs of first choice are beta-blockers, flunarizine, topiramate, valproate and amitriptyline. Drugs of second choice with less efficacy and evidence are venlafaxine, gabapentin, naproxen, butterbur root, riboflavin and magnesium. Botulinum toxin type A has not yet been shown to be effective. The choice of prophylactic drugs would depend on efficacy, co-morbidity, side effects, availability and cost. Non-pharmacological treatments such as relaxation techniques, bio-feedback, cognitive behavioral therapy and acupuncture are supported by some evidence but require far more specialist time or technical devices. All the drugs used in migraine prophylaxis have been detected by serendipity. Drugs developed, in the future, on the basis of the current knowledge of pathophysiology will hopefully be more effective.

**Introduction**

Migraine is the most common headache diagnosis in neurological services in Asia and is among the top 10 most disabling disorders worldwide. However, it still remains under diagnosed and undertreated. Many patients require management of individual migraine episodes as well as prophylactic treatment to prevent future episodes. Migraine prophylaxis involves avoidance of trigger factors, lifestyle advice followed by consideration of medications. Adequate prophylaxis is necessary to reduce the frequency and severity of migraine attacks and thereby improve the quality of life and prevent medication overuse headache.

**Goals of prophylaxis**

The goals of long-term migraine treatment would be to:

- Reduce the attack frequency, severity, and disability.
- Avoid acute headache medication overuse.
- Improve the quality of life.
- Reduce headache-related distress and psychological symptoms.

**Indications for Prophylaxis**

Preventive treatment can be either preemptive, short term or chronic. Preemptive treatment is used when there is a known headache trigger, such as exercise or high altitude excursion or sexual intercourse. Patients can be advised to pre-treat before the activity. A single dose of indomethacin may abort exercise-induced migraine. Short term prevention is used when the patient is likely to have exposure for a certain period of time, e.g. menstrual migraine. These patients can be treated with daily medication just before and during exposure. Chronic prophylaxis is used for patients with migraine frequency and severity significant enough to interfere with their daily activities.

Recommendations for migraine prevention have in the past focused on patients who had two or more attacks per month. These recommendations did not account for the need of the individual patient or other migraine characteristics. Recent recommendations for starting preventive therapy are:

- Recurring migraines that, in the patients’ opinion, significantly interfere with their daily routines, despite acute treatment
- Contraindication to or failure or overuse of acute therapies

- Overwhelming costs of repetitive acute therapy
- Uncommon migraine conditions, such as hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction.

**Principles of Prophylaxis**

Patients should be advised to maintain a regular lifestyle, with adequate sleep, meals, exercise, and manage stress. Any identifiable trigger should be avoided. If this regimen does not adequately control their migraine attacks, prophylactic drug treatment is indicated. Adherence to the following principles will enhance the success of therapy:

A. Medication use

- Therapy should be initiated with medications that have the highest level of evidence-based efficacy.
- The lowest effective dose of the drug should be used and increased slowly until clinical benefits are achieved without any adverse events.
- An adequate trial of two to three months should be given to each drug.
- Use of a long-acting formulation may improve compliance.
- If sequential monotherapies are ineffective, combination of first line drugs should be tried before advancing to drugs of second choice.
- Medication overuse should be suspected if there is a lack of response to several prophylactic drugs.

B. Evaluation

- The patient’s headache frequency and severity should be monitored through a headache diary.
- Therapy should be re-evaluated after 3 to 6 months, and tapered or discontinued, if headaches are well controlled.

C. Coexisting conditions

Co-morbidity should be taken into account and a drug that will treat both should be selected.

D. Pregnancy

Most medications with proven benefit in migraine prophylaxis are not safe in pregnancy. The severity of the migraine episodes, frequency, response to acute medications, patient preferences and the stage of pregnancy should be considered while choosing a drug. If treatment is absolutely necessary, a drug with the lowest risk of adverse
effects on the foetus should be tried first.

E. Withdrawal
After 6 to 12 months of effective prophylaxis, gradual withdrawal should be considered.

**Drugs for Migraine Prophylaxis**

**Drugs used for migraine prophylaxis act in two ways:**

1. **By inhibition of cortical spreading depression (CSD)** - The antiepileptic drugs (topiramate, valproate, gabapentin), calcium channel blockers (flunarizine, verapamil), propranolol, amitriptyline, and tonabersat are some examples of drugs that reduce neuronal hyperexcitability and inhibit CSD.

2. **By restoration of nociceptive dysmodulation** - Modulators of serotonergic and adrenergic systems and cholinergic enhancing drugs may restore descending nociceptive inhibition and play a role in migraine prevention.

**Beta blockers**

Propranolol 40-160 mg per day is effective in reducing the frequency of migraine and in providing moderate reduction in headache intensity and/or duration (Level A). Propranolol is comparable in efficacy to flunarizine, amitriptyline, naproxen sodium, divalproex sodium, and methysergide.

Other beta blockers such as metoprolol, atenolol, timolol, and nadolol are likely to have similar benefits. Beta-blockers with intrinsic sympathomimetic activity (acebutolol, alpenolol, oxprenolol, pindolol) are ineffective for migraine prophylaxis.

When propranolol is prescribed to a patient using rizatriptan, the patient should be advised to reduce the dose of rizatriptan by half and to maintain a gap of two hours between intake of rizatriptan and propranolol. Adverse events most commonly reported with beta-blockers are fatigue, depression, nausea, dizziness, and insomnia. These symptoms are fairly well tolerated and are seldom the cause of premature withdrawal.

**Antiepileptics**

**Topiramate**

Topiramate blocks voltage-sensitive sodium channels and voltage-activated calcium channels, inhibits glutamate release, and increases GABA levels. It significantly reduces the mean monthly frequency of migraine in patients receiving 50-100 mg per day. Patients receiving 200 mg per day of topiramate tend to have frequent adverse effects. The most common adverse effect with topiramate is paresthesia, followed by fatigue, weight loss, somnolence, psychomotor slowing, language problems, renal calculi, and rarely secondary angle closure glaucoma. Topiramate is started at a dose of 25 mg at bedtime. The dose is increased by 12.5-25 mg per week to reach a target of 50 mg given twice a day. Usually these paresthesias are transient and if the patient isexplained about it prior to starting the drug, they are able to tolerate it and drug withdrawal is seldom required. If paresthesia develops, the dose should be decreased to the least tolerable dose and then increased to a lower target dose more slowly. Topiramate is similar in efficacy to propranolol and valproate.

**Divalproex/ sodium valproate**

Valproate at high concentrations increases GABA levels in synaptosomes, perhaps by inhibiting its degradation, by facilitating the postsynaptic responses to GABA, by increasing potassium conductance at lower concentrations and by producing membrane hyperpolarization. In patients with episodic migraine, divalproex 250-750 mg/day is recommended (Level A). Divalproex and sodium valproate are comparable in efficacy to propranolol, flunarizine and topiramate.

**Other antiepileptic drugs**

Gabapentin, levetiracetam and zonisamide are less effective than topiramate and valproate for migraine prophylaxis. Lamotrigine is not efficacious in the treatment of migraine.

**Antidepressants**

 Amitriptyline is the only antidepressant with fairly consistent support for efficacy in migraine prevention. It downregulates serotonin receptors, increases the levels of synaptic norepinephrine and enhances endogenous opioid receptor actions. Amitriptyline is effective in the prophylaxis of migraine at a dose of 10-75 mg per day (Level A). It is more efficacious than propranolol for patients with mixed migraine and tension-type headache. Selective serotonin reuptake inhibitors (SSRIs) have not shown significant benefits in migraine prophylaxis.

**Calcium channel antagonists**

The mechanism of action of the calcium channel antagonists in migraine prophylaxis is uncertain. They prevent contraction of vascular smooth muscles and inhibition of Ca++ dependent enzymes involved in prostaglandin formation. Flunarizine in doses of 5-10 mg per day has been found to be comparable to propranolol, topiramate, and valproic acid for migraine prophylaxis. Nimodipine, verapamil and nicardipine have been less thoroughly studied than flunarizine.

**Alpha-2 agonists**

Clonidine and guanfacine have been shown to be better than placebo but inferior to beta blockers at reducing headache frequency. Most commonly reported adverse events with clonidine are drowsiness and tiredness.

**Nonsteroidal anti-inflammatory drugs (NSAIDs)**

Many NSAIDs have been tried over the years for migraine prophylaxis. Naproxen (750 to 1500 mg) has been extensively investigated so far. It is especially useful in menstrual migraine. Recent interest has been focused on aspirin (75 to 150 mg) particularly in patients who need platelet inhibitors for other medical conditions.

**Other agents**

Pizotifen, buspirone, acetazolamide, montelukast, and methysergide are of limited value in prophylaxis of migraine. Methysergide is associated with retroperitoneal and retropleural fibrosis after prolonged use. Feverfew (Tanacetum parthenium), butterbur extract (Petasites hybridus), magnesium, riboflavin and coenzyme Q 10 have not been proven to be conclusively effective. Lisinopril and candesartan have been shown to be effective in isolated trials and are to be preferred in patients with hypertension.

**Botulinum toxin A**

Botulinum toxin type A (BoNT-A) is a focially acting protein that inhibits the release of acetylcholine from presynaptic nerve endings and blocks the release of pain mediators, such as substance P, glutamate, and calcitonin gene related peptide. The biologic effects of BoNT-A are reversible and last for approximately 3 to 6 months. A meta-analysis of eight randomized, double-blind, placebo-controlled trials concluded that BoNT-A was not significantly different from placebo, both from a clinical and statistical perspective. Therefore, Botulinum toxin A is not recommended for the prophylactic treatment of migraine.
Indian Literature on Migraine Prophylaxis

There are several small, single center, open label and double blind published Indian studies on drugs for migraine prophylaxis. Clonidine did not show a statistically significant difference as compared to placebo. Propranolol and flunarizine were superior to placebo in reducing the frequency of migraine attacks. Nifedipine significantly reduced the frequency and severity of pain in migraine. Low dose topiramate was efficacious in migraine prophylaxis as compared to both placebo and lamotrigine. A combination of cyproheptadine and propranolol provided significantly greater relief as compared to individual drug treated groups and placebo. Acupuncture provided more than 50% relief in a significant number of patients. Biofeedback and systematic relaxation were very useful in migraine and had significantly better long-term prophylactic effect than propranolol in migraine. The doses of various prophylactic drugs required by our patients is lesser as compared to Western data.

Recommendations

The US Headache Consortium has classified drugs into various groups based on their established clinical efficacy, significant adverse events, safety profile, and clinical experience of participants of drug trials:

Group 1. Medications with proven high efficacy and mild to moderate adverse events, on the basis of multiple Class-I randomized controlled trials. They should be considered as first line drugs for migraine prophylaxis (Level A).

Group 2. Medications with probable efficacy and mild to moderate adverse events, on the basis of at least one Class I or two Class II studies. They should be considered as second line drugs for migraine prophylaxis (Level B).

Group 3. Medications with possible efficacy based on one class II or two Class III studies. Drugs in this group may be considered for the migraine prophylaxis (Level C).

Group 4. Medications with inadequate or conflicting evidence to support their use for migraine prevention. Drugs in this group have no recommendation (Level U).

Group 5. Medications proven to have limited or no efficacy. Drugs in this group should not be considered for the migraine prophylaxis (Level B).

The drugs in various groups are enumerated in Table 1.

Nonpharmacological Interventions

Nonpharmacological interventions such as relaxation training, biofeedback and cognitive-behavioral therapy may be considered as treatment options for prevention of migraine (Level A). Aerobic exercise has been tried, however its efficacy is uncertain. Hyperbaric oxygen may be an effective, but rarely practical prophylactic measure. These interventions are indicated in patients who show insufficient or no response to drugs, have contraindications or poor tolerance to drug treatment, pregnancy and significant stress. Acupuncture has been shown to be at least as effective as or possibly more effective than prophylactic drug treatment in a recent Cochrane review and has fewer side effects. Thus acupuncture should be considered a treatment option for patients willing to undergo this treatment.

Use of Abortive Medication Along with Preventive Treatment

Many patients of migraine can have breakthrough headaches while on prophylaxis. Such patients, particularly with headaches during menstruation, should receive abortive medications. It has been observed that preventive medications make abortive agents more effective. However, a limited use, not exceeding two times a week is recommended to prevent medication overuse headache.

Combinations of drugs

A number of conditions have been noted to be comorbid with migraine, notably psychiatric disorders (anxiety, depression, panic disorder), epilepsy, asthma, and cardiovascular diseases (stroke, angina). The presence of a comorbid disease poses significant therapeutic implications. The goal should be to treat both the conditions adequately with a single agent wherever possible (Table 2). If combining a second drug is necessary, care should be taken while choosing the second drug to avoid drug interactions and increased adverse effects (Table 3).

Limitations of Migraine Prophylaxis

According to the American Migraine Prevalence and...
Migraine preventive medications show a ceiling effect and most of the drugs provide 50% relief in approximately 50% of patients.

Future Targets

It has been well documented that mutations in the calcium channel are implicated in familial hemiplegic migraine; therefore calcium ion transporters are considered as novel targets for the development of future anti-migraine drugs. The L-calcium channel blockers (verapamil) and novel calcium channel antagonists (dorzatpine, ziconotide) are being studied for migraine prophylaxis. Newer serotonergic/noradrenergic reuptake inhibitors (SNRIs), especially mirtazapine and duloxetine may potentially prevent migraine attacks. New 5-HT7 modulators and 5-HT4 agonists appear promising for migraine prophylaxis.18,19

Cortical spreading depression may be inhibited through the use of sigma receptor agonists (dextromethorphan, carbetapentane), non-NMDA (AMPA-kainate) ionotropic receptor blockers, potassium current modulators, and glycine site modulators. The chloride channel enhancers and metabotropic glutamate receptor modulators are also of interest. Tonabersat, a novel gap junction inhibitor, may have potential value in migraine prophylaxis.16,19

Conclusion

One-third of patients suffering from migraine require prophylactic therapy. The preventive drugs with the best documented effectiveness are the beta blockers, flunarizine, divalproex, topiramate, and amitriptyline. Choice of drugs should be made on the basis of efficacy of drug, adverse events, patient preference, headache profile, and the presence or absence of coexisting disorders.

Salient Features

- Migraine prophylaxis includes avoidance of trigger factors and lifestyle advice, followed by consideration of medications.
- Medications having the highest level of evidence-based efficacy should be started first.
- Lowest effective dose of the drug should be used and increased slowly.
- After 6 to 12 months of effective prophylaxis, gradual withdrawal should be considered.
- Propranolol 40-160 mg/day or flunarizine 5-10 mg/day is recommended as first line therapy for prophylaxis in patients with migraine (Level A).
- In patients with episodic and chronic migraine, topiramate 50-100 mg/day is recommended (Level A).
- In patients with episodic migraine divalproex 250-750 mg/day is recommended (Level A).
- Amitriptyline 10-75 mg/day is better for patients with mixed migraine and tension-type headache (Level A).

Table 3: Drug combinations

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<tr>
<th>Combinations preferred</th>
<th>First agent</th>
<th>Second agent</th>
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<tbody>
<tr>
<td>Beta blocker and flunarizine</td>
<td>Beta blocker, divalproex, flunarizine</td>
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References