CHAPTER

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Prevention of Migraine

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Introduction

Headache is a universal experience with 1 year prevalence of about 90% and life time prevalence of about 99%. The differential diagnosis of headache is one of the largest in medicine with about 300 types of headache described. Migraine is the most common primary headache.

Epidemiology

There is scarcity of Indian data on the epidemiology of migraine. The prevalence of migraine is 17.6% in females and 6% in males in the US.[1] In an urban headache clinic 47% of the patients were found to have migraine without aura and 4% migraine with aura; Indian data for the incidence of migraine with aura seem to be lower when compared with data from other parts or the world.[2]

Impact of migraine

Migraine is underrecognized and undertreated in spite of the fact that it is the most common primary headache. More than 85% of women and more than 82% of men with severe headache had some health-related disability. About 1/3rd of the patients were severely disabled or needed bed rest during the attack.[3] Unlike in many developed countries, figures for the economic burden due to unpredictable absenteeism, frequent consultations, extensive investigations, repeated prescriptions, and ineffective over-the-counter medications are unfortunately not available for India.[4]

Pathophysiology of migraine

The pathogenesis of pain in migraine has 3 components: intracranial vasodilatation, neurogenic inflammation in perivascular area and activation of central trigeminal system- mainly, the trigeminal nucleus caudalis and its central connections. Activation of trigeminal nerve and the vessels it supplies, especially intracranial and dural vessels, is due to release of various transmitters like serotonin, norepinephrine, endorphin and gamma amino butyric acid (GABA). As there are connections between trigeminal nucleus caudalis and upper cervical nerves, neck pain may become a part of migraine process. The aura, which is seen in some cases before the actual headache phase, is related to a cortical phenomenon similar to cortical spreading of depression. The concept of brainstem migraine generator has been studied and it has been shown by some sophisticated investigation, like positron emission tomography, that perturbation in these areas of complex neurophysiologic interaction is thought to trigger a migraine attack.

Goal of Prophylaxis of migraine

Goals of prophylaxis are: (1) reduction of frequency, duration and severity of migraine attacks, (2)

Table 1 : United States evidence-based guidelines for migraine- Preventive treatment

1.	Recurring migraines that, in the patients' opinion, significantly interfere with their daily routines, despite acute treatment (e.g., two or more attacks a month that produce disability that lasts 3 or more days, or headache attacks that are infrequent but produce profound disability)
2.	Frequent headaches (more than 2 a week) or a pattern of increasing attacks over time, with the risk of developing medications overuse headache)
3.	Contraindication to, failure of, or overuse of acute therapies
4.	Adverse events with acute therapies
5.	Cost of both acute and preventive therapies
6.	Patient preference and
7.	Presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarctions (to prevent neurologic damage- as based on expert consensus).

increase responsiveness of acute attacks to abortive therapy and (3) improve quality of life and reducing disability. The indications[5] of prophylactic therapy in migraine are given in Table 1. Abortive drug treatment is largely for symptomatic relief and has no benefit beyond single attack. In many patients who have infrequent attacks, an effective abortive agent is sufficient. However, the frequent use of abortive agent may rapidly become part of the problem once a patient has slipped into the insidious cycle of analgesic rebound, prophylactic therapy may be futile and the headache just keep getting worse. Adding a preventive medication to migraine management reduces the use of other migraine medications, as well as visits to physician offices (51.1%) and emergency departments (81.8%). In addition, both acute and preventive medications were associated with lower utilization of computed tomography (75%) and magnetic resonance imaging scans (81.8%). Migraine preventive drug therapy was effective in reducing resource consumption when added to therapy consisting only of an acute medication[6].

Drugs used to prevent migraine

Prophylactic medications are empiric treatment and to date their exact mechanism of action is not known. Most of the drugs were originally used for other indications and their anti-migraine effect was found incidentally. It is likely that in many cases their effect in migraine is unrelated to the action for which they were originally prescribed. Central neuronal hyperexcitability is critical in the pathogenesis of migraine. Potential mechanism of migraine preventive medications include raising threshold of neuronal excitability, enhancing antinociception, preventing cortical spread of depression, inhibiting peripheral and central sensitization, decreasing neurogenic inflammation and modulating serotonergic, sympathetic or parasympathetic tone. The drugs used in prophylaxis are shown in Table 2. The first and second line drugs for migraine prophylaxis[7] are shown in Table 3.

Table 2 : Drugs used in prophylaxis of migraine

Angiotensin converting enzyme inhibitors/angiotensin receptor antagonists
Anticonvulsants
Antidepressants
Beta adrenergic blockers
Calcium channel antagonists
Neurotoxins
Serotonin antagonists
NSAIDs
Others- riboflavin, magnesium, feverfew, butterbur, botulinum toxin type A

Beta-blockers

The site of action of beta-blockers is central and it acts by inhibiting central[2] receptors, thereby inhibiting neuronal hyperexcitability, interaction with 5-HT receptors and cross-modulation of serotonin system.

Propranolol has been compared with placebo in 60 trials and it has been found to be consistently effective.[8] Timolol has been compared with placebo in three trials and found to be equally efficacious like propranolol[9]. There is limited evidence to support the use of atenolol, metoprolol and β-blockers with intrinsic sympathomimetic activity (acebutolol, pindolol, etc.).

The β-blockers are well-tolerated. Propranolol is the only drug which is used for prophylaxis in children. The contraindications are: asthma, heart

Table 3 : The first and second line drugs for migraine prophylaxis

First line drugs: propranolol, timolol, amitriptyline, divalproex, sodium valproate, topiramate
Second line drugs: gabapentin, naproxen, timed-release dihydroergotamine mesylate, candesartan, lisinopril, atenolol, nadolol, metoprolol, fluoxetine, verapamil, magnesium, riboflavin, coenzyme Q10, estradiol topical gel, botulinum toxin type A, phenelzine

block, diabetes mellitus, peripheral vascular disease and hypotension.

Antidepressants

Amitriptyline[10] is the only first-line antidepressant. In studies, it has been found that Amitriptyline is less efficacious compared to propranolol in general; but more effective in mixed migraine and migraine with tension features and also with co morbidities like depression and insomnia. The side-effects of amitriptyline are dryness of mouth, dizziness, postural hypotension, increased sleepiness, constipation and weight gain. If the side-effects are troublesome, then other tricyclic antidepressants (nortriptyline, doxepin, etc) may be used. Fluoxetine was not found to be effective in a large trial[9].

Anticonvulsants

Divalproex, sodium valproate[11] and topiramate[12] are first-line drug for migraine prophylaxis. Valproate and divalproex have similar mode of action. Valproate acts both centrally and peripherally. Central actions include elevation in brain GABA level, reduction in the firing rate of serotonergic cells in the dorsal raphe and reduction of C-Fos activation in the trigeminal nucleus caudalis. The peripheral effects include reduction of neurogenic inflammation in the vascular system. Divalproex and sodium valproate are relatively toxic and associated with hepatotoxicity, weight gain, tremor and teratogenicity. The side effects of gabapentin are dizziness and somnolence. Topiramate causes nausea, paresthesia and fatigue.

Nonsteroidal anti-inflammatory drugs

Naproxen is useful for prevention of menstruation-associated migraine. It is started a few days before onset of menstruation and continued for first few days of menstruation.[13]

Angiotensin converting enzyme inhibitor and angiotensin receptor blocker

Lisinopril[14] and candesartan[15] are effective in migraine. They are well tolerated except for dry cough.

Calcium channel blockers (CCB)

There is weak evidence to suggest verapamil as a first-line agent[9]. Nifedipine is not effective in migraine prevention. Flunarizine has been tried in some trials with modest results. Mechanism of action of CCB is uncertain. However, they may have the ability to block 5HT release, interfere with neurovascular inflammation, or interfere with the initiation and propagation of spreading depression that is critical. The common side effects of flunarizine, which is available in our country, are weight gain, somnolence, dry mouth and occasional exacerbation of depression.

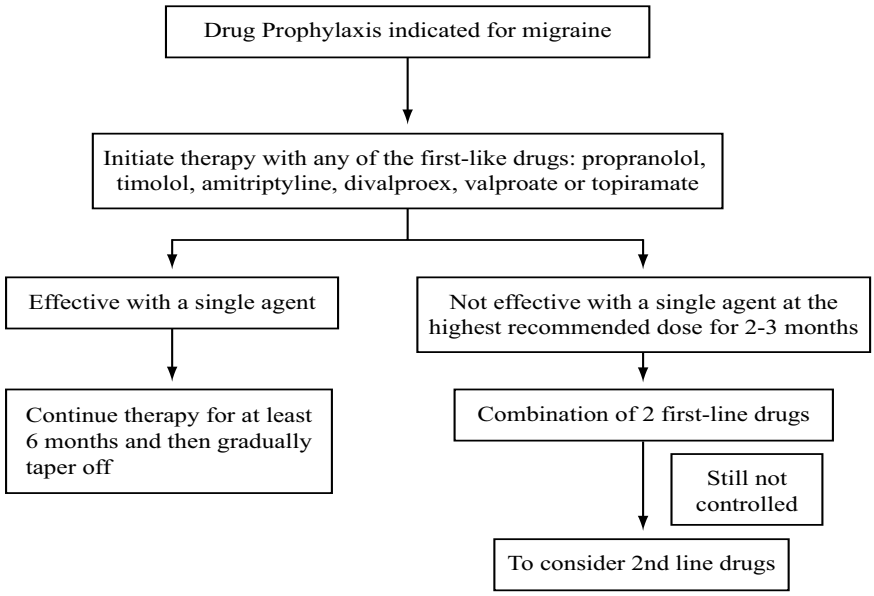
Other agents

Many other agents like magnesium[5] riboflavin[16], conezyme Q10,[17] estradiol topical gel and botulinum toxin type A[18] have been used in migraine and found to be effective. However, the data is limited. Injection of botulinum toxin type A is well tolerated and benefit typically lasts for approximately 3 months. Repeated injections are required. Transient neck discomfort may occur depending upon the site of injection. Because the toxin is not absorbed systemically, there are no systemic side effects or drug interaction. However, the cost can be prohibitive and many patients may not be able to afford it. Phenelzine is another agent used for prophylaxis. It is a monoamine oxidase inhibitor and indicated when migraine becomes refractory to other therapy. Side effects include hypertensive crisis after concomitant intake of tyramine containing diet.

Non-pharmacological therapy

It is important to note that combination of pharmacotherapy with non-pharmacologic

Flow chart 1 : Suggested flow chart showing pharmacologic prophylaxis of migraine



approaches go a long way for a successful outcome in migraine prophylaxis. Physical exercise, hygienic diet, avoidance of triggering factors, relaxation using biofeedback techniques, behavioral counseling, etc are an integral part of prophylactic protocol.

General principles of management (Flow chart 1)

- Initiate therapy with the lowest effective dose and gradually increase the dose until benefit is seen or side effects occur (Table 4).
- Patient should be treated for at least 2-3 months with full recommend dose to say that the drug has failed.
- Patient should be treated with an effective drug for at least 6 months, then the drug may be withdrawn slowly.

Table 4 : Doses of first-line medications in adults

Drugs	Dose in adults (mg/d)
Amitryptyline	10-150
Divalproex	500-1000
Propranolol	80-240
Timololol	20-30
Topiramate	50-100
Valproate	500-1000

Table 5 : Management of migraine patients with co-morbidities

Co-morbidity	Drug
Hypertension	β blockers
Angina	Calcium channel blockers
Depression	Tricyclic antidepressants
Insomnia	Tricyclic antidepressants
Under weight	Tricyclic antidepressants
Epilepsy	Sodium valproate
Mania	Sodium valproate

- Use of longer active formulations may increase compliance.
- Patients with migraine may suffer from co-morbidities (Table 5 & 6) like asthma, obesity, depression, anxiety disorder, etc. Beta-blockers are contraindicated in asthma. Drugs used for treating co-morbidities may exacerbate migraine.
- Drug interaction is another problem which should be taken into consideration.

Table 6 : Co-morbidities and drugs to be avoided

Co-morbidity	Drugs to be avoided
Epilepsy	Tricyclic antidepressants
Depression	β blockers
Obesity	Tricyclic antidepressants, valproate

Management of migraine in special situations

Pregnancy

Women of childbearing age should be counseled regarding the teratogenicity of the drugs before pregnancy. Category B drug like fluoxetine may be used, though there is doubt regarding its efficacy. Category C drugs like propranolol, topiramate, amitriptyline and gabapentin may be used and highly efficacious. Valproic acid, high dose riboflavin, lisinopril and candesartan should not be used in pregnancy.

Children

Propranolol is the drug which has been found to be effective in children in a Cochrane systematic review.[19] However, benefit of other agents could not be validated because of small study sample size.

Conclusion

Migraine is the most common cause of primary headache and still it is underdiagnosed and under treated. The impact of migraine in developed as well as developing countries is immense, especially in societal and economical fronts. It is important for every physician to keep the records of their headache cases so that a proper data bank can be established for estimation of disease burden in our country. Every patient of migraine should be dealt with on individual basis considering the clinical characteristics of the attack, its severity, and associated co-morbidity if any. It is also to be remembered that public awareness for this common disorder needs due emphasis through education, media and advertisement, so that the disease is diagnosed early and appropriate therapy instituted. Non-pharmacologic measures and proper counseling should always be included in the prevention of migraine.

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