



Management of Migraine

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ABSTRACT

Considerable uncertainty surrounds the diagnosis and management of migraine despite recent advances in the pathophysiology and treatment of migraine. Management of migraine must be based on an individualized patient treatment strategy that integrates patient education and effective use of pharmacological interventions. Despite self-treatment with simple analgesics, many patients continue to suffer considerable disability associated with their migraines. Triptans and specific medications which are more effective at relieving migraine symptoms and maintaining patient function than are nonspecific therapies, are used in only a minority of patients with migraine. For prophylaxis, anticonvulsant drugs emerging as effective options are being added to the armamentarium with traditional compounds such as calcium channel blockers, tricyclic antidepressants and beta-blockers. This article outlines a pragmatic approach to the management of migraine with special reference to the Indian context.

INTRODUCTION

Migraine is a common, complex, debilitating malady. Population-based studies have shown that approximately 6% of men and 18% of women suffer migraine attacks¹ and over 80% of these suffer some degree of headache-related disability.^{2,3} In spite of the high prevalence, migraine is under-recognised and under-treated.^{3,4} Long-term management of migraine is often a major challenge mainly because it is a chronic condition with recurrent episodic attacks, with varying characteristics among patients and even within attacks in the same patient.

Migraine attacks vary not only in severity but also in frequency. Women have more frequent and more severe attacks than men and three times as many women as men are affected.⁵ There are differences in migraine prevalence in different countries.⁶ Ravishankar in his study⁷ from an urban headache clinic in India found that 47% of patients were found to have migraine without aura and only 4% had migraine with aura; Indian data for the incidence of migraine with aura seem to be lower when compared with data from other parts of the world.

Most migraine patients get accustomed to living with headache as an integral part of their day-to-day life. 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.

Although there is as yet no biological marker to confirm the diagnosis, there have been a number of advances in diagnosis and treatment of migraine. Effective treatments are now available

which are changing the way migraine is managed. Yet most patients with migraine are never diagnosed by a physician or treated with prescription medications⁸ and those who do receive care are treated in so many different ways that they are eventually dissatisfied with the results and continue to suffer.

Variations in migraine management are primarily due to suboptimal application of the best available evidence. With the availability today of a wider range of pharmacologic options, it is necessary to have standard guidelines which will help uniform decision-making. It is anticipated that evidence-based guidelines for the diagnosis and treatment of migraine will provide symptomatic relief and will improve the quality of life and reduce the headache burden.

STANDARD GUIDELINES OF MIGRAINE MANAGEMENT

They aim at using evidence-based medicine

- To establish the diagnosis of migraine.
- To tailor pharmacologic and non-pharmacologic approaches to suit the symptomatology, medical history, lifestyle, and needs of the individual.
- To minimize pain, reduce disability and improve quality of life in the long-term management of patients with migraine.

Evidence-based (EBM) migraine management presents formidable challenges because

- The etiology and pathophysiology of migraine is still not completely understood.

- No diagnostic test is still available for migraine.
- All outcome measures in migraine treatment are by necessity subjective with a high placebo response in clinical trials.

Guidelines for Migraine Management in India

The guidelines outlined in this article are an adaptation of the recent US Headache Consortium practice guidelines for the treatment of migraine. The original evidence-based guidelines suggested in the Report of the Quality Standards Subcommittee of the American Academy of Neurology⁹ have been modified in this article to suit the Indian context. Details of the levels of evidence, the strength of evidence, the measures of scientific effect and clinical impression of effect can be found in Appendix 2 of the original publication. Some suggestions from the guidelines of the Canadian Headache Society¹⁰ have also been incorporated.

The need for this adaptation arises because of the fact that unlike other neurological problems, a disorder like migraine has numerous variables that may influence diagnosis and treatment viz. different genes, different geography and environment, different socio-economic problems, different literacy levels, different treatment options available within India and also different attitudes of patients and physicians towards a recurrent primary headache disorder like migraine. It is therefore essential to modify guidelines to suit our country keeping these factors in mind.¹¹

PRINCIPLES OF MIGRAINE MANAGEMENT

Management of migraine is much more than just a prescription. The following sequence is suggested as standard for the basic principles of migraine management.

- Establish the diagnosis correctly.
- Educate migraine sufferers about their condition and its treatment. Discuss the rationale for a particular treatment, how to use it, and what adverse events are likely.
- Establish realistic patient expectations by setting appropriate goals and discussing the expected benefits of therapy and how long it will take to achieve them.
- Empower the patients to be actively involved in their own management by encouraging patients to track their own progress through the use of a headache diary for tracking days of disability or missed work, school, or family activities.
- Treatment choice depends on the frequency and severity of attacks, the presence and degree of temporary disability and associated symptoms such as nausea and vomiting. Individualize management.
- Consider comorbidity /coexisting conditions. Coexisting conditions (such as heart disease, pregnancy and uncontrolled hypertension) need to be ascertained as they may limit treatment choices.
- Encourage the patient to identify and avoid triggers.
- The costs, benefits and hazards of the pharmacologic agents available should be considered as relevant factors in determining the most appropriate medication.
- The goals of acute treatment should be relief of headache and associated symptoms and a return to normal functioning.

MIGRAINE - DIAGNOSIS¹¹

The need for uniformity in diagnosis led to the publication of the IHS criteria (1988) as a diagnostic tool¹² and the new revised criteria (2003). Although it still has limitations, these criteria are accepted as useful aids to the diagnosis. It is recommended that we employ the IHS diagnostic criteria and use a semi-structured interview technique. For details of the criteria for diagnosing, migraine without aura and migraine with aura, the reader is referred to the original document.

Some additional questions while taking the headache-history, that will help in migraine diagnosis. Since correct diagnosis is the starting point for correct management of migraine, the patient should be questioned further in order to enhance the specificity and sensitivity of the above criteria, and to improve the “pattern recognition” of migraine. Additional questions concerning other typical migraine characteristics should be asked to confirm the following:

- The gradual build-up of headache after sustained exertion
- Abatement of headache with sleep
- The presence of stereotypic prodromal symptoms such as irritability or other mood variation, hyperactivity, inability to think or concentrate, food cravings and hyperosmia
- The regular or near-regular perimenstrual or periovulatory timing of attacks
- The presence of a family history of migraine
- The consistent precipitation of headaches by food, odours, weather changes, stress or other triggers such as fasting, travel, exposure to sunlight
- Triggers of migraine in the Indian setting may differ from that seen in the West
- The effects of pregnancy, childbirth and menopause on the headache
- The occurrence of headache at times of let-down, particularly after a high level of activity or stress

MIGRAINE - TREATMENT

Various acute and preventive therapies are available. Patients respond to a variety of medications and the medication of choice is often different in every individual. Once the diagnosis of migraine is established, the treating physician should decide on how to treat acute attacks and whether to use long-term preventive medications. Patient’s response to pharmacologic therapy is not always predictable. Therefore, management is never standard and most often needs to be individualized. Most of the prophylactics used in the West are available to us in India except a few such as methysergide.

Acute Therapy

Acute drug therapy is indicated if the head pain threatens to disrupt the patient’s ability to function normally. We must develop a treatment plan that meets the patient’s expectations and targets the following goals.

1. Treat attacks rapidly and consistently without recurrence.
2. Restore the patient’s ability to function.
3. Minimise the use of analgesics and rescue medications.
4. Minimise accompanying symptoms.

5. Look at achieving cost-effectivity in the overall management.
6. Minimise adverse events.

Patients must be warned that frequent use of symptomatic treatments (analgesics and ergotamine in particular) can lead to medication-induced (rebound) headache and eventually to chronic daily headache. Without appropriate treatment, patients are more likely to consume increasing amounts of less effective compounds, which increases the risk of rebound headache. Keeping a headache diary may help in preventing this situation.

Acute migraine attacks are of differing intensity and have variable effects on the patient's functioning. In mild attacks, the patient can continue his or her usual activities with only minimal disruption; in moderate attacks, the patient's activities are significantly impaired; in severe attacks, the patient is unable to continue his or her normal activities and can function only with severe discomfort and impaired efficiency; in ultra-severe attacks (including status migrainosus), there is prolonged (more than 72 hours) inability to function in any useful capacity. Therefore, for each patient, appropriate therapy for acute attacks of differing severity should be made available depending on their level of disability (stratified care). Treatment of acute severe attacks may sometimes need emergency hospitalisation.

Amongst the triptans that are available in the West, only sumatriptan and the second-generation rizatriptan are available to us in India. Sumatriptan¹⁸ is available as nasal spray and in tablet strengths of 25, 50 and 100 mg while rizatriptan is available as 5 and 10 mg tablets.

Guidelines for Acute Therapy

1. Educate migraine sufferers about their condition and its treatment.
2. Encourage them to participate in their own management (discuss treatment / medicine preferences).
3. Tailor the treatment to suit the individual's needs (e.g. based on their severity of illness, co-morbidity/co-existing conditions and prior response to medications).
4. Use migraine-specific agents (ergotamine, DHE, available triptans) in patients with severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen or caffeine.
5. Select a non-oral route of administration for migraines associated with nausea or vomiting as a significant component of the symptom complex. Antiemetics should not be restricted only to patients who are vomiting or likely to vomit. Nausea should be treated appropriately.
6. Consider a self-administered rescue medication in a patient with severe migraine that does not respond to other treatment.
7. Guard against medication overuse headache ("rebound headache"). Frequent use of acute medications like ergotamine, opiates, triptans, simple analgesics and combination analgesics containing caffeine or codeine are thought to cause rebound headache. Preventive therapy

given simultaneously will help reduce the need of repeated acute drugs.

Specific acute medications

The detailed mechanism of action in migraine and the drug dosages and side-effects are outside the scope of this article and have therefore not been discussed at length. The drug and dosage must be considered on a patient-by-patient basis.

Ergot alkaloids and derivatives

Ergotamine oral

1 mg (and caffeine combination) may be considered in the treatment of selected patients with moderate to severe migraine.¹⁵ Rectal suppositories are not available in India. Safe usage limits the consumption to between 4 to 6 mg per week.

Dihydroergotamine (DHE)

IM or SC is available to us and may be considered in patients with moderate to severe migraine.¹⁴ DHE, a nonselective 5-HT₁ receptor agonist, is effective in relieving headache when used subcutaneously, intramuscularly, intravenously in a dose of 0.5 mg to 1.0 mg at 8 or 12-hourly intervals. The dose should not exceed 3.0 mg per day. DHE IV plus antiemetics IV is an appropriate treatment choice for patients with severe migraine. DHE SC/ IV/ IM may be given to patients with prior antiemetics to prevent vomiting.

Triptans (5HT_{1B/1D} receptor agonists)

At present sumatriptan and rizatriptan are the only triptans available in India. Initial treatment with any triptan¹³ is a reasonable choice when the headache is moderate to severe. The recommended starting dose of sumatriptan is 25 mg orally. If needed one may increase the dose in increments of 50 mg to a maximum of 300 mg per day. A SC injection of 1/2 cc = 6 mg may be used for severe attacks with vomiting. Rizatriptan is available in tablet of 5mg and 10 mg and most patients respond well to 10 mg. Patients with nausea and vomiting may be given sumatriptan subcutaneously or as a nasal spray. Sumatriptan and rizatriptan are effective when taken at any stage of the attack, but in the case of migraine with aura it should not be taken during the aura phase, since the results of at least one study suggests that it is not effective at this stage. Sumatriptan or rizatriptan should not be taken within 24 hours of the administration of dihydroergotamine (DHE) or ergotamine.

Patients with cardiac risk factors, cardiac disease or uncontrolled hypertension must not take sumatriptan or rizatriptan. Sumatriptan is faster acting and is less apt to cause nausea than DHE; however, it has a higher rate of headache recurrence at 24 hours (44% versus 17% respectively).²² Patients must be forewarned about the possible side-effects of the triptans.

Nonspecific acute medications

Antiemetics

NSAIDs, nonopiate analgesics, and combination analgesics.

Other medications

The costs, benefits, and hazards of the available agents should be important factors in choosing the most appropriate medication. The ultimate aim should be to achieve the goals outlined.

Guidelines for Prophylactic Therapy

Preventive therapy should be employed in those patients in whom migraine has a substantial impact on life-style and who have not responded to acute care or where the frequency of migraine attacks is such that the reliance on acute care medications would increase the potential for drug-induced rebound headache. The goals of long-term migraine treatment are:

1. To reduce attack frequency, severity and duration.
2. To improve responsiveness to treatment of acute attacks.
3. To improve function and reduce disability.

The principle underlying a prophylactic treatment regimen is to use the least amount of the medication with minimal side-effects to gain control of the symptoms. When selecting a medication for prophylaxis, one should also take into account the presence of comorbid conditions. Initiating and maintaining appropriate prophylaxis entails a major commitment by the patient. Consider non-pharmacologic therapies in conjunction after taking the patient into confidence.

Additional Recommendations

- The patient should be helped to understand the general nature of migraine, the action of the medications prescribed and their interactions, side effects and contraindications.
- Except in resistant cases, only one preventive agent should be used at a time.
- If the initial treatment is ineffective, several medications may be tried in sequence.
- If there is no response to a combination of prophylactic agents from different groups (e.g. propranolol plus amitriptyline), additional investigations should be obtained.
- Prophylactic medications that are ineffective while patients are concurrently taking analgesics on a regular basis can become effective when the analgesics are withdrawn.
- The cost of medications should be considered in the choice of prophylactic agents.

Prophylactic Medications

The detailed mechanism of action in migraine and the drug dosages and side-effects are outside the scope of this article and have therefore not been discussed at length. The drug and dosage must be considered on individual patient-by-patient basis.

Beta-blockers

- Not all beta-blockers are effective in migraine. Those that are efficacious include atenolol, metoprolol, and propranolol, whereas those with intrinsic sympathomimetic activity (e.g. pindolol) are not.
- Exactly how beta-blockers decrease the frequency of migraine attacks is not certain, but they may affect the central catecholaminergic system and brain serotonin (5-HT₂) receptors.
- Beta-blockers are contraindicated in patients with asthma, chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, heart block or failure, or peripheral vascular disease. They are relatively contraindicated in pregnancy.

- Failure with one beta-blocker does not predict the response to another, so consecutive trials of different drugs in this class are appropriate.¹⁵
- When prescribing beta-blockers, start with a low dose and titrate upward as required. Once the attacks are controlled, the medication should be tapered.
- Sudden withdrawal of beta-blockers may cause rebound headaches and adrenergic side effects.

Calcium-channel blockers

- Of the available agents, flunarizine is most commonly used for migraine prophylaxis.^{16,17} Reduction in migraine frequency is the main benefit, and the overall efficacy of calcium-channel blockers is comparable to that of beta-blockers (i.e. a reduction of about 50% in headache frequency)
- Calcium-channel blockers most likely work by modulating neurotransmitters rather than by causing vasodilatation and cytoprotection through the prevention of hypoxia and cellular influx of calcium ions.
- Calcium-channel blockers are contraindicated in pregnant patients and in patients with hypotension, congestive heart failure or arrhythmia.

Tricyclic antidepressants

- Amitriptyline is useful in migraine, especially in patients with associated tension-type headaches.
- The mechanism of action is unrelated to its antidepressant activity. Amitriptyline modulates neurotransmitters, inhibiting both noradrenalin and serotonin reuptake and attenuating β -adrenergic and central serotonin receptor function.
- The effective dosage varies, but 10 mg orally each night should be given at first, followed by an increase of 10 mg every week, up to 50 mg/day; however, higher dosage may be required in the presence of comorbid depression.
- Contraindications include severe cardiac, kidney, liver, prostate and thyroid disease, glaucoma, hypotension, seizure disorder and use of a monoamine oxidase inhibitor.
- Tricyclic drugs should be used with caution in elderly patients because of anticholinergic side effects. Most often tricyclic drugs have been used for migraine prophylaxis also.

Serotonin receptor antagonists

- Methysergide is indicated for the prophylaxis of severe, recurrent migraine attacks unresponsive to other medications.¹⁸
- Methysergide should not be used for more than 6 months without a break in treatment of 1-2 months to prevent retroperitoneal fibrosis. The dose should be decreased gradually before treatment is stopped.

Anti-epileptic drugs

- Sodium valproate, divalproex sodium, particularly the extended release forms and more recently topiramate have been found to be effective for migraine prophylaxis in randomized clinical trials.¹⁹
- Side effects with divalproex include nausea, alopecia, tremor and weight gain.

- They may also cause neural tube defects and should not be given to women who are pregnant or considering pregnancy.

Guidelines for Non-Pharmacologic Therapy

Nonpharmacologic treatment may be combined with preventive therapy to achieve additional clinical improvement for migraine relief. Behavioral treatments are classified into three broad categories: relaxation training, biofeedback therapy, and cognitive-behavioral training (stress-management training). Physical treatment includes acupuncture, cervical manipulation, and mobilization therapy. These are treatment options for headache sufferers who have one or more of the following characteristics:

- Patient preference for non-pharmacologic interventions
- Poor tolerance to specific pharmacologic treatments
- Medical contraindications for specific pharmacologic treatments
- Insufficient or no response to pharmacologic treatment
- Pregnancy, planned pregnancy, or nursing
- History of long-term, frequent, or excessive use of analgesic or acute medications that can aggravate headache problems (or lead to decreased responsiveness to other pharmacotherapies)
- Significant stress or deficient stress-coping skills

Specific recommendations regarding which of these to use for specific patients cannot be made. The benefits of non-pharmacological treatment are not exploited much in our setting in the treatment of even chronic migraine patients.

FINAL RECOMMENDATIONS

In addition to the application of standard guidelines, to alleviate the burden of migraine, we need to 1) focus and make an effort to regionally change the attitude towards headache of both patient and physician 2) we need to influence insurance agencies and 3) we need to improve healthcare systems.

With more interest in headache management, these guidelines will in future become more extensive and focused and will be uniformly applied as the standard method of managing migraine in India. The Global Campaign recently launched jointly by the WHO, IHS, WHA and EHF to reduce the burden of headache augurs well for headache sufferers. Hopefully, in the future, we can look forward to a world with less headache.

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