Commentary

Headache Algorithm : A Guide to Differential Diagnosis and Management of Headache Disorders by Indian Medical Association

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Headache, characterized by pain or discomfort in the cephalic or facial regions, can manifest with or without accompanying symptoms. Most cases of headache encountered in clinical practice are primary in origin and are often benign. Yet, they are the most prevalent cause of temporary disability in patients of all age groups. The presence of more serious and life-threatening if untreated secondary causes make the situation worse. The current review focuses on developing algorithms for differential diagnosis of various headache disorders, so that secondary causes can be addressed promptly, while providing an accurate approach towards diagnosis of primary headaches. This review will also provide guidance regarding the management and treatment options available for primary and secondary headaches. The review is developed and reviewed by eight panel members of the Indian Medical Association (IMA).

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Headache is a painful and disabling feature of multiple conditions including primary headaches like migraine, tension type headache and cluster headache or a secondary symptom of underlying condition. It is estimated that headache disorders affect approximately 40% of the population and are more common in females compared to males[1]. According to Global Health Estimates (2019), headache disorders were found to be the third highest cause of Disability-adjusted Life Years (DALYs) worldwide, after stroke and dementia[1]. Headache disorder was the most prevalent neurological disorder in India in 2019, affecting 488 million[2]. The International Classification of Headache Disorders (ICHD-III) classifies headaches into three categories: primary headache disorders (includes tension type headache, migraine, and cluster headaches), secondary headache (includes headaches due to potentially life-threatening etiologies such as traumatic brain injury, vascular cranial disorders, substance abuse, infection etc) and cranial neuropathies, such as trigeminal neuralgia[3]. Primary headaches are more common in practice than secondary headaches. The scope of the current review is to provide algorithms for differential diagnosis and management of headache disorders. The review is developed and reviewed by eight panel members of the Indian Medical Association (IMA). The IMA recommended panel members included headache experts from different specialties including neuro-physicians, neurosurgeons, clinical physicians, ENT, and general practitioners, who discussed issues related to the stepwise management of headache.

Primary Headache :

In routine practice primary headaches comprise more than 90% of all headache cases[4]. Primary headaches are generally not life-threatening but can cause pain, discomfort and decrease the overall Quality of Life (Table 1).

Migraine :

Migraine is a chronic neurological disease with episodic acute attacks of head pain and is characterized by attacks of moderate-to-severe headache and reversible neurological and systemic

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	Migraine	Tension Type Headache	Cluster Headaches
Pain Description	Throbbing, moderate to severe, worse with exertion/daily activity	Pressure, tightness, waxes and wanes	Abrupt onset, deep, continuous, excruciating, explosive
Associated Symptoms	Photo/phono- phobia, nausea & vomiting, aura	None	Tearing, congestion, rhinorrhea, pallor, sweating
Location	Unilateral	Bilateral	Unilateral
Duration	4-72 h	Variable	0.5-3 h, many per day
Patient Appearance	Resting in quiet dark room	Remains active or prefers to rest	Remains active, prefers hot shower
Patient profile	Young female	-	Male, smoker

Table 1 — Common types of Primary Headaches

symptoms in some patients. Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts. In India, the prevalence of migraine is 214 million and it is the second largest contributor to the disability due to neurological disorders (Fig 1)[2].

While migraine was previously regarded as primarily vascular, the importance of sensitization of pain pathways and neurogenic origin of attacks in the CNS, have gained increasing attention. Several internal and external factors, called as triggers, either induce or exacerbate migraine and associated symptoms via activating trigemino-vascular system. Some common triggers include nuts, chocolate, processed foods, wine, coffee, tea, cheese, weather changes, bright light, odours, travel, missed meal or fasting, dehydration, stress, sleep disturbances, menstruation and menopause. Identification of these triggers can help in the management of migraine[5]. However, it is important to note that different patients have different triggers for migraine; a migraine patient need not have all possible triggers.

Increasing headache intensity and frequency are associated with comorbidities related to psychiatric disorders (depression, anxiety), sleep conditions (insomnia) and inflammation (IBD). People with migraine were significantly more likely to report

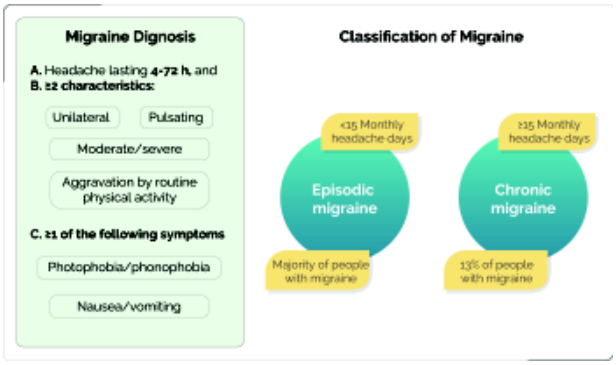

Fig 1 — Migraine Diagnosis and Classification

insomnia, and depression, anxiety among other conditions[6].

Abortive Treatment of Migraine :

Patient life style modifications and trigger avoidance can help reduce the migraine frequency and severity. These include sitting in dark isolated places to avoid light and sound, avoiding work and exertion, taking rest and trying to sleep[7].

Abortive drug therapy targets individual headache episodes in patients with episodic and chronic migraine. NSAIDs are first line abortive treatment of migraine along with simple and combination analgesics**.**

Naproxen sodium is found to be effective in the treatment of migraine, when given in dosage 500 mg, it relieved the symptoms of migraine and reduced the severity in a time dependent manner[8]. Antiemetics like domperidone alleviate incapacitating symptoms of nausea and vomiting and enhance the bioavailability of the co-prescribed NSAIDs[9]. Paracetamol and aspirin (ASA) have a longstanding history in the treatment of migraine attacks.[10] Ibuprofen, a propionic acid derivative, is a widely used antimigraine drug. Doses of 800 mg to 1,200 mg or 400 mg as an arginine salt were superior to placebo[10].

Sumatriptan (oral, SC and nasal), and the newer triptans (zolmitriptan (oral and nasal), naratriptan (oral), rizatriptan (oral), eletriptan (oral), almotriptan (oral) and frovatriptan (not available in India)) display high agonist activity at mainly the serotonin 5-HT1B and 5-HT1D receptor subtypes. Triptans are most effective when taken early in an attack, when the headache is still mild. Upon relapse, triptan treatment can be repeated or combined with fast-acting NSAIDs eg, naproxen sodium, ibuprofen lysine or diclofenac potassium[11]. Triptans are contraindicated in patients with Coronary Artery Disease (CAD).

Ergotamine oral because of their erratic absorption and frequent side effects of nausea, vomiting, muscle cramps and vasoconstriction and cardiac effect ergotamine are rarely used now. Lasmiditan is newly introduced centrally and peripherally acting 5-HT1F receptor specific agonist. Dose is 50 mg and 100 mg tablets per day[12]. A patient should refrain from driving for at least 8 hours after taking[13].

Prophylactic Treatment of Migraine :

Recurrent migraines are often functionally disabling and can impair Quality of Life. Prophylactic therapy may decrease the frequency, severity and duration of migraine attacks, increase responsiveness

to acute migraine therapy and improve Quality of Life.

Lifestyle modifications have been suggested as a potential preventive countermeasure for the prophylaxis of migraine and include dietary, sleep and stress management. Avoiding known triggers for migraine headache may play an important role in reducing the severity and frequency of migraine episodes[7]. Some studies suggest low fat and high protein in diet as a putative preventive measure against migraine. Ketogenic diet for reducing the occurrence of migraine attacks have been suggested[14]. Certain nutraceuticals like riboflavin, magnesium and coenzyme Q10 may be well tolerated and effective in the adult prophylaxis of migraine[14]. Daily Walk and moderate cardiovascular/ aerobic exercise have been shown to be effective in reducing the frequency of migraine[15].

Amitriptyline, a tricyclic antidepressant, is commonly used in the prophylaxis of migraine and Tension Type Headache (TTH) and treatment of depression and neuropathic pain[15]. It is also prescribed in medication overuse headache. Because of its multimodal actions, many international guidelines and an Indian expert consensus recommend that amitriptyline is useful in migraine with co-morbidities[16-20].

Propranolol, a beta-blocker, reduces central hyperexcitability through β1- adrenoceptor-mediated inhibition of noradrenaline release, thus reducing central catecholaminergic hyperactivity. Some other prophylactic medications are flunarizine, topiramate, and divalproex.

In a network meta-analysis done by Jackson, *et al* in 2015, they found amitriptyline to be better than several other medications including candesartan, fluoxetine, propranolol, topiramate and valproate and no different than atenolol, flunarizine, clomipramine or metoprolol[21]. Although, the literature indicates amitriptyline to be more effective than other prophylactic drugs, in real World the efficacy of a particular prophylactic medication varies from one individual to another.

Second line prophylactic therapy includes botulinum toxin, monoclonal antibodies (eg, Only Erenumab is available in India) and, neuro-modulation methods like remote electro-neuro-modulation devices (eg, Nerivio) and vagus nerve stimulation (Table 2) [22].

Diagnosis

If lasting from **4-72 hours** *AND*
≥ 2 features: Unilateral, Pulsating, Moderate/severe or Aggravation by routine physical activity *AND*
≥ 1 of the following symptoms: Photophobia/Phonophobia or Nausea/Vomiting

Abortive Treatment

1st Line
Naproxen sodium 250/500 mg SOS
Paracetamol 1000 mg SOS, Ibuprofen 400 mg SOS, Aspirin 1000 mg SOS
If, nausea vomitings are one of the most bothersome symptoms then,
Naproxen + Antiemetic drugs (Domperidone 10 mg or Metoclopramide 10 mg) BD/SOS
If no optimal response on above therapy then refer to headache specialist for further treatment:
2nd line: Triptans, Triptan + Naproxen; 3rd line: Lasmiditan

Prophylactic Treatment

Provide prophylactic drug treatment, if any of the following is present: Attacks significantly interfere with patients' daily routines despite acute treatment/ Frequent attacks/ Contraindication to, failure, or overuse of acute treatments/ Adverse Events with acute treatments/ Patient preference.

Migraine without Co-morbidities

Amitriptyline	Propranolol	Flunarizine	Topiramate	Divalproate sodium
Starting Dose: 5-10 mg at OD bedtime Maximum tolerated dose: Up to 25-50 mg Duration of therapy: 3-6 Months	Starting dose- 20 mg BD Maximum Tolerated dose- Up to 80 mg BD Duration of therapy: 3-6 Months	5-10 mg at bedtime, for 3-6 months	25-50 mg BD	500-1000mg daily, for 3-6 months

Migraine with Co-morbidities

Anxiety	Depression	Insomnia	Tension type Headache	Neuropathic Pain	Diabetes	Asthma	Hypertension	Epilepsy	Obesity	Kidney Disease
Amitriptyline*, Topiramate, Divalproate Na	**Amitriptyline***, Topiramate, Divalproate Na	**Amitriptyline**	**Amitriptyline**	**Amitriptyline***	**Amitriptyline**	**Amitriptyline**	**Propranolol**	**Topiramate, Divalproate Na**	**Topiramate**	**Propranolol, Flunarizine**
Avoid										
Propranolol, Flunarizine	Propranolol, Flunarizine	Propranolol			Propranolol	Propranolol		Amitriptyline	Flunarizine, Amitriptyline, Divalproate Na	Topiramate

** Starting Dose: 10-25 mg at OD bedtime. Max dose: Up to 50-75 mg*

Table 2 — Diagnosis and management of Migraine

Secondary Headaches :

A secondary headache is caused by underlying structural or infection conditions that trigger pain-sensitive areas in the neck and head. Secondary headaches are uncommon, but they are more serious than primary headaches.

The ICHD-3 provides a list of eight categories and 46 subcategories for causes of secondary headaches including trauma or injury to the head and neck; cranial and cervical vascular disorders; nonvascular intracranial disorders including neoplasm; a substance or its withdrawal; infection; disorders of homeostasis; disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure and psychiatric disorders[3].

Approach to a suspected case of secondary Headache :

- Check vital signs.
- Perform focused history and examination: If red flags (Fig 2) are present: refer to The right specialist.

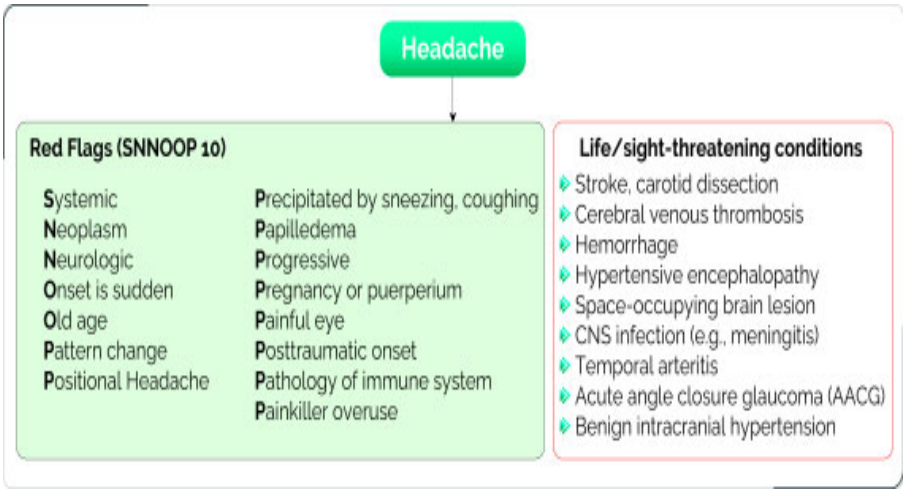

Fig 2 — Red flag signs of Secondary Headaches[23]

Tension Type Headache	Cluster Headache	Menstrual Headache	Medication Overuse Headache	Sinus Headache	Hypertension Headache	Exertional Headache	Head-Injury Headaches
Etiology							
Cause: Various factors, such as nutrition, muscle tension, environment, and genetics.	Pathology in trigeminal nerve.	Hormonal changes during and around menstruation in female leading to migraine headache.	Chronic medication overuse is the most significant risk factor. The risk from lowest to highest is: triptans, ergotamine, NSAIDs, paracetamol, and combination analgesics containing opiates or barbiturates.	Referred pain originated from intense mucosal irritation (DNS, polyps and septal spurs) and blocked sinus (polyps or edematus turbinates).	High blood pressure (greater than 180/120) can cause a headache in some patients.	Strenuous physical exercise, with the following triggers: running, jumping, weightlifting, sexual intercourse, bouts of coughing or sneezing.	Headache immediately or soon after a head injury. Headaches can also develop months after the original head injury.
Signs and Symptoms							
Recurring bilateral headaches with mild to moderate, dull, pressing sensation in the temporal and forehead area, neck, shoulder, and occasionally retro-orbital. Not exacerbated by routine physical activity.	Severe, unilateral headache lasting from 15 to 180 minutes, with symptoms concentrated around the orbit, supraorbital, and/or temporal regions. Autonomic symptoms (on the side of headache): redness and tearing in the eye, a stuffy or runny nose, sweating, constricted pupils, drooping eyelids, or swelling around the affected area.	Symptoms of migraine during a 5-day menstrual period in at least 2 of every 3 menstrual cycles (Pure Menstrual migraine). Menstrually-related migraine: Pure Menstrual migraine and additionally at other times of the month outside the cycle.	Symptoms of any primary headache- Migraine, tension type headache or Cluster headache.	A dull, throbbing pain around the eyes, cheeks, and forehead with or without history of allergy.	A hypertension headache usually occurs on both sides of your head and is typically worse with any activity. It often has a pulsating quality.	Usually very short-lived but can sometimes last up to 2 days. They present as throbbing pain throughout the head and are more common in those with a family history of migraine.	Headache with or without warning symptoms including unconsciousness, seizures, vomiting, memory loss, confusion, vision or hearing problems.
Management							
Abortive treatment: Paracetamol, Aspirin, NSAIDs (Ibuprofen, Naproxen) or their combinations with caffeine. **Preventive Treatment:** Amitriptyline (10-50 mg OD at bedtime) is the primary choice for preventive treatment, followed by Mirtazapine and Venlafaxine.	**Refer to headache specialist. Abortive treatment:** Primary: Subcutaneous sumatriptan and high-flow oxygen. Alternate: Intranasal triptans. **Preventive Treatmnet:** First line-Verapamil and lithium. Second line: Melatonin and topiramate.	Abortive (e.g. Naproxen + Domperidone) and preventive treatment (Amitriptyline 10 mg) are same as that for migraine. **Refractory patient shall be referred to headache specialist.** The hormonal treatment may also be offered.	**Refer to headache specialist.** Amitriptyline (10-75 mg OD at bedtime) may help.	**Primary care:** Antibiotics, Antihistamines, Oral Decongestants (not >3 days), Steam inhalation and warm compresses. **If no resolution, refer to Otorhinolaryngologist.** Muco-ciliary clearance is obtained with medical and/or surgical interventions.	Primary care: Antihypertensive Agents as per patients medical and drug history. **It can be an emergency and refer to higher center if following is present-** changes in vision, numbness or tingling, epistaxis, chest pain, shortness of breath.	Headache is usually very short-lived but **frequent, longer and chronic exertional headaches should be referred to headache specialist.**	Imaging tests may be required. **If warning symptoms are seen, after a primary care, always call emergency and refer to specialist.**

Table 3 — Common Headaches other than Migraine

- If no red flags are present and suspicion for life-threatening causes is low: identify the underlying cause through appropriate investigation. CT/MRI imaging or CSF analysis or lab testing may be necessary for secondary headaches.
- Provide supportive care.

All clinically relevant headaches other than migraine are listed in Table 3 along with their etiology, signs, symptoms and management options.

Conclusion :

Effective management of headache disorders is dependent on accurate differentiation between primary and secondary headaches. This review emphasizes the importance of a structured approach to diagnosis and outlines management strategies, including pharmacological and non-pharmacological therapies, to improve patient outcomes. Triggers identification and use of prophylactic agents play an important role in reducing clinical burden of primary headache.

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