A Review on Intricate Scheme of Therapeutic Approaches Involved in Control and Prevention of Episodic Migraine

Kashif Abbas¹, Mudassir Alam², Uzma Parveen³, Intiyaz Ali Zairy⁴
¹,² Department of Zoology, Aligarh Muslim University, Aligarh, India (202002)
³ HAQ: Centre for child rights, B ½, Malviya Nagar, New Delhi, 110025
⁴ Department of Biochemistry, Aligarh Muslim University, Aligarh, India (202002)

ABSTRACT: Migraine is a prevalent headache ailment while Episodic migraine (EM) is a paroxysmal disorder in which attacks occur at random, frequently in clusters lasting several days or weeks. The World Health Organization (WHO) currently ranks migraine as the 19th cause of years spent with a disability. The diagnosis of EM is based on clinical history and the exclusion of other headache disorders because there are no biological markers for migraine. Preventive migraine therapy is beneficial in individuals who have frequent migraine episodes, hindered daily activities, failure of acute pain management, debilitating aura, and limits in the use of acute treatment. Its goal is to reduce headache frequency and severity, enhance responsiveness to acute migraine therapy, and improve quality of patient’s life.

KEYWORDS: Acute migraine, Drugs, Episodic migraine, Therapeutic interventions, Tiptans.

1. INTRODUCTION

Episodic migraine (EM) is among the most common medical disorders and the most obvious reason for consulting a neurologist, despite the fact that many people suffering from the disorder do not seek treatment. Studied have shown that EM has prevalence of 22.6% in women and 9.6% in men annually [1]. Lower socioeconomic status individuals are more likely to experience migraines, which are a major cause of productivity loss and disability [2]. As there are no biological markers for diagnosis of migraine, the clinicians purely rely on clinical history and pathological data of the patient and the exclusion of other headache disorders. The International Classification of Headache Disorders (ICHD-2) 2nd edition describes migraine without aura as having all of the following symptoms:

1. Recurring headaches (at least five-lifetime episodes)
2. Untreated or unsuccessfully treated headache duration of 4 to 72 hours
3. At least two of the following pain characteristics: unilateral, pulsing, moderate or severe severity, or worsened by ordinary physical activity

In addition, migraine episodes are accompanied by at least one of the following symptoms: nausea/vomiting, photophobia, or phonophobia. Finally, other probable headache reasons must be checked out [3].

There are two types of treatment for migraines: prophylactic or preventive treatment and acute or abortive treatment. Acute treatment seeks to end the current attack, while prophylactic care aims to stop future headache attacks and enhance the quality of life for migraine sufferers. A combination of pharmaceutical and non-pharmacological methods is used in the prevention of migraines [4] (Figure 1). The mainstays of acute therapy should be simple analgesics, nonsteroidal anti-inflammatory medications, and triptans, which should be limited to no more than two to three days per week at most. First-line preventative medicines include β-blockers, amitriptyline, and anti-epileptic drugs such as topiramate and valproate. The effectiveness and adverse effect profiles of selective serotonin reuptake inhibitors (SSRIs), calcium channel antagonists, gabapentin, and herbal treatments are lower. A successful treatment plan must evaluate the patient's requirements and expectations, the impact of the headache on their life, their symptoms and co-morbidities, and past therapies [5]. Successful EM management depends on educating patients about their symptoms and the medications they are administered on.
2. TRIGGERS OF EPISODIC MIGRAINE

The most frequent causes of EM including stress, auditory stimulation, exhaustion, fasting, and menstruation, have been verified by extensive systematic studies [6]. When Kelman et al. examined triggers in 1750 migraine cases, they reported that 76% of responders had an average of 7 triggers apiece. Patients were more inclined to choose triggers from a list than to report them on their own. The most frequent triggers were stress, menstruation, fasting, changes in the weather, disturbed sleep, odour, alcohol, heat, and certain foodstuffs [7]. Furthermore, exogenous substances such as glyceryl trinitrate [8] and prostaglandin E2 [9] cause migraine headaches in vulnerable people. Various forms of EM triggers are depicted in figure 2.

**Figure 1:** Therapeutic interventions involved in control and prevention of EM

**Figure 2:** Most common factors which triggers the onset of EM
2.1 Dietary Triggers
Several research have been conducted to investigate the association between migraine and food allergies, with the goal of treating migraine with specialised diets such as elimination [10]. Fasting is one of the most researched and most consistent natural migraine triggers, and it gets more prevalent with prolonged fasts [11]. In a study, night-time snacking and, to a lesser extent, a late meal were shown to be protective against migraine caused by stress. Water deprivation has also been implicated as a migraine cause in a few studies [12]. One of the most widely often stated migraine culprits is alcohol. Alcohol metabolism may impact migraine risk, and one investigation discovered that particular genotypes of alcohol dehydrogenase 2 enzymes can reduce or increase migraine risk from alcohol [13]. Nitrites, such as those found in preserved meats, may cause migraines in certain people [14]. Based on the apparent link with dairy, alcohol, chocolate, and migraine episodes, biogenic monoamines such as tyramine have been proposed as a key trigger for migraine [15].

2.2 Menstrual Changes as Trigger
The most frequent migraine triggers for women are possibly the menstrual fluctuations. In a population-based survey, more than half of migraine tic women indicated that menstruation-related migraines were more intense [16]. Menstrual migraine is most likely caused by oestrogen withdrawal before to menstruation [17], which explains why migraine symptoms commonly begin prior to or on the first day of menstruation.

2.3 Stress as Trigger
Stress is the most widely reported migraine trigger, and several studies have established a correlation between chronic stress, pain, migraine, and catastrophic thinking [18]. Poor sleep quality is frequently recognised as a migraine trigger. It has been observed that sleep aids in the recovery of migraine attacks in many individuals. Casein kinase Iδ mutations are linked to advanced sleep phase disorder and migraine [19].

3. THERAPEUTIC INTERVENTIONS
The therapeutic interventions aim at:
I. Treatment of attacks and reducing its recurrence
II. Restoration of normal daily functionality
III. Minimisation of rescue medications
IV. Encouragement of self-care
V. Minimising side effect

![Aim of Therapeutic Interventions](image_url)

*Figure 3: Aim of therapeutic intervention in order to treat episodic migraine patients*
The choice of therapy is selected by taking following factors into consideration:

I. Relative comorbidities
II. Patient’s characteristics
III. Patient’s preference
IV. Drug characteristics

3.1 Choice of Drug

In patients with EM who are considering preventative medication, it is preferable to start with a low dose and gradually increase until the desired therapeutic aim or maximum acceptable dose is reached. A sufficient time of treatment with the chosen medication must be attempted because effectiveness can be observed in 4 weeks and can take up to 3 to 6 months. It is critical to assess the drug’s decision after a sufficient discussion with the patient, taking into account the patient's preferences, side effect profile, and the presence of comorbidities that may benefit from the drug's usage [20]. The major pharmaceutical drug classes that have been proven to be effective in the EM prevention therapy are as follows:

I. Antidepressant
II. Antiepileptics
III. Antihypertensive agents
IV. Miscellaneous agents

Physicians takes comorbidity into consideration while recommending the class of drug to be administered for treatment of EM (Table 1).

Table 1: Therapeutic approaches for EM patients with a particular comorbidity

<table>
<thead>
<tr>
<th>CHOICE OF DRUG</th>
<th>COMORBIDITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker</td>
<td>Hypertension, smoker</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>Hypertension, non-smoker</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Depression, mood disorder, Insomnia</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Obesity</td>
</tr>
</tbody>
</table>

3.2 Common Drugs Used For Treatment and Prevention of Episodic Migraine

3.2.1 Non-Specific Episodic Migraine Drugs

In mild-moderate migraine attacks, analgesics such as acetaminophen, ibuprofen, aspirin are considered first-line therapy, especially if used early in the attack and in conjunction with an anti-emetic medication[21]. Among all the above listed analgesics, clinical trial shows dose of 1000mg of aspirin helps to cope up with pain in up to 52% of EM patients and is well tolerated [22]. There is empirical evidence that people with migraines respond favourably to naproxen, diclofenac, tolfenamic acid, and indomethacin. If nausea is prevalent, adding antiemetics such metoclopramide or domperidone is advised. These pro-kinetic substances alleviate the stomach stasis brought on by migraine symptoms. The combination frequently seems to be more efficient than simple analgesia by itself.

3.2.2 Drugs Specific to Episodic Migraine

i) Ergotamine

Ergotamine is an ergot alkaloid. Ergotamine’s are in use since more than 50 years for the treatment of acute migraines. Although there is lack of concrete data to support its efficacy in EM patients. Ergotamine’s below par absorption and low oral bioavailability are its main limitations. Ergots cannot be used as first-line medications due to their negative effects and the fact that even modest dosages of them lead to prescription overuse [23]. Ergots should only be used on people who have persistent attacks or headache recurrence issues that generally did not resolved with triptans.
ii) Beta blockers

Beta blockers are a class of drug that are used to treat a wide array of ailments such as anxiety, high blood pressure, or angina and EM [24]. It is also one of the most often prescribed group of anti-migraine drugs. Beta-blockers work by inhibiting centrally placed β receptors, which prevents the interaction of 5 HT receptors with adrenergic pathways to increase alertness, and the serotonin system from being modulated [25]. According to a metaanalysis, there was a 44% decrease in migraine frequency compared to placebo. Timolol, atenolol, bisoprolol, and nadolol are also likely good migraine preventatives. Acebutolol, alpenrol, and pindolol are examples of β-blockers having intrinsic sympathomimetic activity (ISA), which are ineffective [26]. Despite being typically well tolerated, they might cause weariness, sluggishness, anxiety, and a decreased capacity for activity.

iii) Calcium channel blockers (CCB)

The precise mechanism through which CCB prevents migraine is unclear. However, some of the conceivable ways by which it may be mediated are as follows: (i) it prevents the release of serotonin and reduces neurovascular inflammation. (ii) by preventing the onset of and reduces the progression of cortical spreading depression. Among all the CCB drugs, flunarizine has shown to be more effective than placebo and compared to propranolol, pizotifen, and methysergide in terms of effectiveness [27]. Therefore, flunarizine may be beneficial in people who have a persistent or complex migraine aura.

iv) Anti-depressants

The anti-depressants drugs which could be useful in alleviation of migraine are

a) Selective serotonin reuptake inhibitors (SSRIs)

b) Serotonin–norepinephrine reuptake inhibitors (SNRIs)

c) Tricyclic antidepressants (TCA)

The most popular antidepressants for the prevention of migraines are tricyclic antidepressants (TCAs). Patients with migraines with a history of medication overuse, sleeplessness, tension headaches, or depression may benefit from them in particular. TCA is utilised in a variety of dosages, and the majority of the medicines are sedative in nature. As a result, it is usually best to begin with a minimal dose and gradually increase it. Because these medications have sedative property, they should be taken before going to bed [28]. Amitriptyline was proven to be efficacious in four clinical studies for migraine prophylaxis [29]. For patients with concomitant depression, a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine may be beneficial. A combination of SSRI and TCA may be effective in recurrent depression. There is insufficient data to support the use of SSRIs in migraine prophylaxis [30]. A small number of trials have demonstrated that the serotonin-norepinephrine reuptake inhibitor venlafaxine is superior to a placebo in lowering headache frequency [31]. However, the evidence which supports its efficacy are weak.

v) Anti-epileptic drugs

Anti-epileptic drugs (AEDs) are being used frequently to alleviate migraines, and several placebo-controlled studies have demonstrated their effectiveness. The following antiepileptic medications are helpful in preventing migraines: (i) Lamotrigine (ii) Valproic acid (iii) Topiramate. AEDs are especially effective for migraine patients with comorbidities such as epilepsy, mental problems, or bipolar disorder [32]. Both valproic acid and divalproex sodium are effective migraine preventives. Valproate reduces migraines by a variety of processes, some of which may be GABAergic in nature. In a triple-blind, placebo-controlled, cross-over research, the administration of a slow-release sodium valproate medication resulted in a 50% reduction in migraine frequency in 50% of the patients [33]. Three significant placebo-controlled studies have demonstrated the efficacy of topiramate in preventing migraines [34]. Topiramate's precise mode of action in preventing migraines is poorly understood. It also has mild carbonic anhydrase inhibitory action and may augment the inhibitory effect of GABA by blocking neuronal voltage-dependent sodium channels [35]. Patients with migraine and obesity, migraine and idiopathic intracranial hypertension, and maybe migraine and diabetes may find topiramate to be effective. Topiramate is often started at a low dose of 25 mg once day and then progressively increased by 25 mg per week to a dose of 50–100 mg twice daily [36]. Lamotrigine may help to alleviate migraines by blocking voltage-sensitive sodium channels and so inhibiting neuronal glutamate release [37]. Several open label trials had demonstrated that lamotrigine would be beneficial for the prevention of migraines with a persistent aura, but randomised control studies had not been successful in demonstrating this.

vi) Triptans

The acute management of migraine has undergone a revolution with the development of triptans. Triptans are reported to be efficient in 60 percent of non-steroidal anti-inflammatory drug (NSAID) non-responders and their effectiveness has been demonstrated in...
several randomised control and comparative trials [38]. Seven triptans in all have been formulated, albeit the countries in which they are available vary. There are several dosages and formulations of triptans available, including oral tablets, oral dispersible tablets, injectable, and nasal sprays. The specific properties of the medications must be matched to the demands of the patients because the pharmacokinetic profiles of the triptans vary. A summary of triptans formulations, time to peak plasma levels, elimination half life, bioavailability and dosage is given in Table 2 [39].

### COMMON TRIPタンS AVAILABLE FOR TREATMENT OF EM

Table 2: Summary of triptans formulations, time to peak plasma levels, elimination half life, bioavailability and dosage

<table>
<thead>
<tr>
<th>DRUG</th>
<th>FORMULATIONS</th>
<th>PEAK LEVEL DURATION</th>
<th>HALF LIFE (hours)</th>
<th>BIOAVAILABILITY(%)</th>
<th>DOSE (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolmitriptan</td>
<td>Oral tablet</td>
<td>1-1.5 hours</td>
<td>2.5-3</td>
<td>40-50</td>
<td>1.25-2.5</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Orally dispersible tablet</td>
<td>1-2 hours</td>
<td>2</td>
<td>40-50</td>
<td>5-10</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Oral tablet</td>
<td>1.5-2 hours</td>
<td>3.5</td>
<td>70</td>
<td>6.25-12.5</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>(i) Oral tablet</td>
<td>2-3 hours</td>
<td>2</td>
<td>14</td>
<td>25-100</td>
</tr>
<tr>
<td></td>
<td>(ii) Subcutaneous injection</td>
<td>12 min</td>
<td>2</td>
<td>97</td>
<td>6mg/0.5mL</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Oral tablet</td>
<td>2-3 hours</td>
<td>6</td>
<td>60-70</td>
<td>1-2.5</td>
</tr>
</tbody>
</table>

Source: Gladstone and Dodick

### 4. DISCUSSIONS

Migraine headaches can be incapacitating for the patient and interfere with everyday activities. After consultation with the patient, a well-designed oral preventive medication can help minimize the frequency and severity of headaches [40], enhance the response to acute therapy, and lessen impairment. When choosing the plan of therapeutic intervention, it's also important to take the patient's comorbidities into account. Through clinical practise and research, cutting-edge therapeutic approaches are being emphasised. There is some evidence that ACE inhibitors (Lisinopril) or angiotensin II receptor blockers (Zonisamide) are significantly more effective than placebo at treating migraine and have favourable side effect profiles. Anti-epileptic medications like levetiracetam and zonisamide have also been suggested to have beneficial effects on migraine in open trials. Magnesium supplementation could be advantageous, but more rigorous studies are required. Both riboflavin and coenzyme Q10, which are components of the mitochondrial electron transport chain, have been identified as prospective migraine therapy options. At least 40% of participants in small-scale open label and placebo-controlled trials reported that coenzyme Q10 reduced their incidence of headaches by 50% [41]. Studies have demonstrated that Riboflavin (vitamin B2) can potentially reduce headache frequency as compared to placebo [42].

The patient must be informed of the treatment plans, adverse effects, and time frame for therapies before any prophylactic medicine is started. Drug dosages should be gradually increased until a therapeutic benefit is observed, the maximum dose is reached, or adverse effects become unbearable. Before a medicine is declared ineffective, it should be tested at an appropriate dose for at least 6 to 8 weeks. The majority of individuals require at least 6 months of therapy to control their migraines, following which the medicine can be gradually tapered off. Effective migraine treatment programmes focus on patient education. Regardless of the medication used, the patient's reaction should be assessed after two to three months, and headache diaries should be kept. Limiting acute medication is essential to avoid headache from drug overuse, which would undermine the effectiveness of prophylaxis. Although further high-quality clinical research on medications that can prevent migraines are required, for the time being, we must follow our patients' reactions and preferences.

**Conflict of interest:** Authors declare no conflict of interest.
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