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An Overview of Current Treatments of Migraine

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Review Article

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Abstract: The name 'migraine' has its origin from the Greek word *hemicrania*, which means 'half of the head', indicating the main feature of migraine i.e it affects only half portion of the head. It is the most widespread neurological disorder, characterized by persistent headache. It is ranked 7th most disabling by World Health Organistaion (WHO). Migraine affects approximately 15% of the people, affecting women more than the men. It significantly impacts the quality of life (QOL) of patients. There are mainly three ways to treat migraine- lifestyle and trigger management, acute treatments and preventive treatments. Maintaining a headache diary or calendar is recommended. There are nutraceutical and herbal options also available for the treatment of migraine. Such therapies have added advantage of negligible adverse effects. Recently, both invasive and non-invasive methods have gained popularity. Botox injections, targeting of greater occipital nerve and neurostimulation are some of the newest options. Migraine therapy through calcitonin gene related peptide is the area where current research is going on. The future prospects of migraine management are both inspiring as well as demanding. This article reviews the path physiology, diagnosis and current treatments options for management of migraine.
Keywords: Hemicrania, Nutraceutical, Herbal, Migraine, Neurological disorder.

INTRODUCTION

Headache disorders are mainly characterized by persistent headache, and it's one of the most common disorders of the central nervous system. It is mainly painful and characterized by some of the features like primary headache disorders, namely tension-type headache, migraine, cluster headache.

The name 'migraine' initially comes from the Greek word *hemicrania*, which means 'half of the head', representing one of the main salient features of the state: in many conditions pain only affects one half portions of the head. However, pain is felt bilaterally, at front or the back portion of the head, sometimes rarely in the face, and rarer still in the body ('migrainous corpalgia'). The pain is usually tender in nature, and usually made inferior by any kind of movement or even modest action [1]. The classification of migraine is depicted in Figure 1.

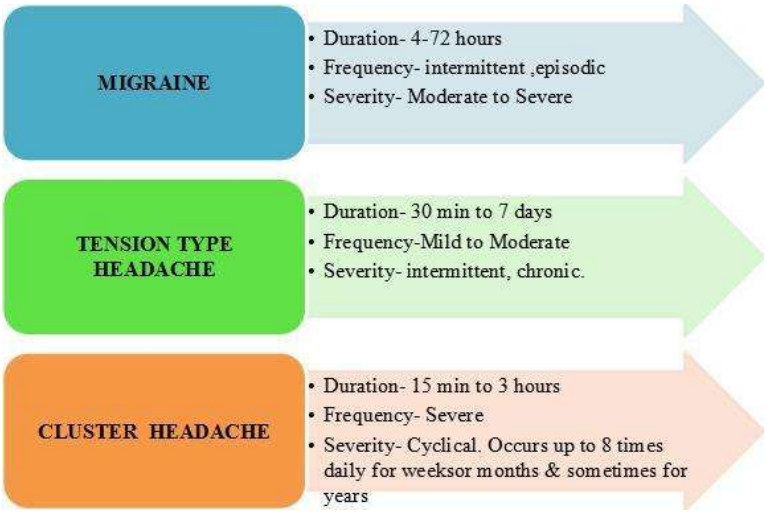

Fig-1: Features of primary headache disorders [2]

It is the most widespread neurological disorders which affects human beings, and is ranked 7th most disabling by the World Health Organistaion (WHO) [3]. Migraine is a frequent chronic headache disorder which mainly results in recurrent attacks which lasts 4–72 hours, of a pulsating feature, moderate or severe amount provoked by physical activity and also includes nausea, photophobia, vomiting or phonophobia [4]. It is a clearly disabling state, and results in condition like pain and imparied quality of life. Migraine is a heterogeneous disorder, with frequent headache attacks which are changeable in frequency and duration. It occurs in people with a genetically perceptive nervous system [5]. Migraine has occurrence of approximately 15% of the people, affecting women (18%) mainly more than the men (8%). It is having significant impact on the quality of life (QOL) of patients and therefore termed as seventh disable disorder. A division of patients suffers from having episodic migraine (EM) to chronic migraine (CM). It is a slow process, varying from low-frequency EM to a high-frequency phase and finally to CM. Chronic Migraine is defined as a headache on ≥15 days per month for ≥3 months, of which ≥8 days results in the criteria for migraine with or without aura or respond to detailed treatment .It is having major psychological, social, and economic impacts [6].

Migraine attacks may also be triggered by

- Changes in hormonal levels of woman's menstrual phase or usage of birth control pills.
- Withdrawal of caffeine
- Changes in sleep patterns
- Exercise or other physical activity
- Skipping of meals
- Smoking

- **Migraine can also be triggered by certain kind of foods. The most frequent are**
- Any fermented, pickled, or marinated foods products
- Foods that include monosodium glutamate (MSG)
- Baked products, chocolate, peanut butter, and dairy products
- Foods containing tyramine, which includes red wine, aged cheese, smoked fish, chicken livers
- Fruits (like avocado, banana, citrus fruit)
- Meats containing nitrates (bacon, hot dogs, cured meats) [7]

Signs and Symptoms

The aura occurs in both eyes and may involve any or all of the following:

- A temporary blind spot
- Blurring of vision
- Pain in the eyes
- Seeing stars
- Other signs include yawning, vomiting, nausea, and difficulty in deceiving the correct words.

- Increased urination
- Fatigue
- Loss of hunger
- Lack of sensation, weakness
- Sensitivity to light or sound
- Sweating [8]

Diagnosis

Diagnosis of Migraine can be prepared by taking history with help of orthopedic tests, Cranial nerve examination, Complete blood count; urinalysis and Cranial magnetic resonance imaging was also taken if required [4]. According to The International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta) Migraine has two major subtypes. Migraine without aura is a clinical condition featured by headache with precise features and related symptoms. Migraine with aura is mainly featured by the transient neurological symptoms that frequently precede or sometimes go along with headache. Diagnostic criteria for migraine without aura and with aura are depicted in figure 2 and 3 respectively. Some people also experience a premonitory stage, occurring hours or days before the headache, and a headache resolution stage. Both stages include symptoms like hyperactivity, hypoactivity, cravings, yawning, depression, and fatigue and neck stiffness.

MIGRAINE WITHOUT AURA

Common name- hemicrania simplex.
Diagnostic criteria:
A. At least five attacks
B. lasting 4-72 hours
C. at least two of the following characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity
D. During headache at least one of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia
E. No other cause apparent

Fig-2: Diagnostic Criteria for Migraine Without Aura[9]

MIGRAINE WITH AURA

Classic or classical migraine; ophthalmic,aphasic migraine
A. At least two attacks with:
B. Aura with visual, sensory, and/or language, brain stream, retinal symptoms, each fully reversible
C. At least two of:
1. At least one aura symptom spreads gradually over_5 minutes and/or two or more symptoms occur in succession
2. Individual aura symptoms last 5-60 minutes
3. At least one aura symptom is unilateral
4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another diagnosis (eg, transient ischemic attack, etc)

Fig-3: Diagnostic Criteria for Migraine with Aura [9]

EPIDEMIOLOGY

Headache is a sore and frequent symptom. Primary headache disorders like tension-type headache, migraine and cluster, and these disorders report for approximately 95% of headache [10]. The occurrence of chronic migraine around the world range from 0% to 5.1%. The incidence of chronic migraine in Unites States increases all through adolescence, peak in midlife, and then decreases after 50 years of age .The maximum occurrence is in women aged about 18-49 years [11]. It is more common in women relation to 19% than men about 11%. About 6% of men and 18% of women are suffering from migraine in United States and lifetime risk of about 18% and 43% respectively. In Europe, migraine influences 12–28% of the population get affected with 6–15% of men and 14–35% of adult women. Rates of migraines are slightly lower in Asia and Africa than in Western countries. Chronic migraines occur in approximately 1.4 to 2.2% of the population [10].

PATHOPHYSIOLOGY

Migraines are common than a headache, and their pathophysiology is not totally known. Migraines are neural brain condition that alters various part of brain such as cortical, brainstem and sub cortical. During migraine attack carotid vessels are expanded and using vasoconstriction drugs for treatment. In 2013 Amin *et al.* disgraced this theory. Migraine without symptoms was studied on various participants and using magnetic resonance angiography their extracranial and intracranial arteries were evaluated. Results contraindicate extracranial arterial dilation was not cause of migraine pain but intracranial arterial dilatation can be a cause for migraine pain. Various studies have explained that a neural pathology leads to migraine pain and intracranial vasodilatation exploit discharge of plasma protein, degranulation of mast cells and inflammation in animal tissue that defrayal to the migraine pain.

A migraine is liable to occur in susceptible individuals as a outcome of hypothalamic and brainstem reaction to stressors such as hypoglycemia, inadequate sleep, decreased caffeine ingestion, hormonal alteration during menstruation, maternity, weather alteration. It is conception that hypothalamic neurons which modulate equilibrium and circadian cycles are cause of prodromal

symptoms. So it is noted that migraines are partly a dysfunction in sensory motor processing.

Spreading Depolarization and the Trigeminovascular Neural System

Spreading depolarization or CSD is charcterized by the occurrence of depolarization waves of neurons and neuroglia tha propagates across the cortex. The process of Cortical spreading depression has been concerned in causing the symptom related with migraine pain. Trigeminovascular neural system activated by the CSD. The trigeminovascular system consists of neurons in the trigeminal nerves that stimulate cerebral blood vessels. Sensitive information from meninges to brain is passed by this system. In addition, the trigeminal nerves deport pain sign to the cortex in the thalamus. Stimulation of trigeminovascular neural system during migraine attack causes action of various neurotransmitters, for eg. Serotonin, ACh, VIP, CGRP and nitric oxide. Several of these neurochemical are vasoactive and can stimulate expansion of intracranial arteries and liberation of inflammatory mediators. CGRP stands for calcitonin gene related peptide is a effective vasodilator which release during migraine present in the nerve ending neurons of trigeminovascular neural system. Raised levels of Calcitonin gene related peptide show a important function in central and peripheral tract that reason of a migraine by exploit intracranial dilation and by forwarding pain sign from the trigeminal neural system to the CNS. Recently various researchers are investigated that use of CGRP antagonists for the treatment for migraines.

Predisposition of Pain Effect

Serotonin activation plays a important role in pathophysiology of migraine by raising potent transmission of neural signal. When nerve cell in the trigeminovascular neural system become hyper sensitive, the pain outset is decreased, and an enhanced pain response result. When trigeminal nerves become susceptible periodically during migraine ache, the outset for effect can reduce and result can modifiy, thereby enhancing the no. of headaches with fewer stimulus, which effect in chronic migraine ache [12].

Role of Genetic Factors

One of the crucial features of the migraine pathophysiology is the genetic nature of the condition. It is distinct from clinical activity that some patients have relatives who also endure from migraine. In 17th century various published studies have reported transmission of migraine from parents to children.

Hereditary Epidemiology.—Examination of twin pairs are standard method to analyse the comparative importance of hereditary and biological factors. A Danish survey enclosed 1013 mono zygotic and 1667 di zygotic duplicate pairs of the identical gender, acquird from a population based duplicate record. The pairwise index rate was importantly less in dizygotic duplicate pairs as compared to mono zygotic ($P < .05$). Duplicate studies indicate that migraine without symptom is a complex condition, caused by a unit of hereditary and biological factors [13].

Genome hereditary survey have noted 38 new genomic loci, from which consider the X chromosomes for migraine aches. Out of this three genes modulate glutamatergic neurotransmission and justify the neural hyper reactivity of migraine brain. In vascular and smooth muscle tissue these genes are present. Spreading depolarization has been known as hold a hereditary connection as well [12].

Current treatment for migraine

Migraine is a significantly discomforting condition and is treated with acute and preventive medications. Recently, many novel therapies for treating migraine have been developed out of which, non-invasive neuromodulation has gained popularity and support due to patient compliance [6]. There are mainly three ways to treat migraine- lifestyle and trigger management, acute treatments (the ones taken during attacks or worsening of chronic pain), and preventive treatments (taken to reduce the tendency and frequency to have attacks). Many patients feel that lifestyle modifications like sleep adjustments, coordinated meals and regular exercise are sufficient to control their migraine headaches, but in case of chronic migraine, medications and clinical treatments become indispensable [1]. Before beginning the treatment for migraine, it is imperative to first correctly diagnose the condition and develop an appropriate treatment strategy. It is important to identify risk factors like depression, obesity that might further lead to exacerbation of migraine attacks. It is also important to encompass an effective prophylactic regimen which reduces the requirement of acute medication [14]. Maintaining a headache diary or calendar gives sufficient clinical information regarding triggers and frequency. It helps in optimizing treatment and dosage regimen [15].

The overall treatment for migraine can be divided specifically into five categories-

- Lifestyle and trigger management
- Acute Pharmacological Therapy
- Pharmacological Prophylactic Therapy (for acute and chronic migraine)
- Non- pharmacological Therapy
- Invasive therapies

Lifestyle and trigger management

Some factors directly influence the frequency of migraine attacks. There is no fixed list of factors as it can vary according to individual and environment. But some common ones are-

- Fluctuating eating routine
- Varying sleeping hours

- Stressful routine
- Extra caffeine intake
- Lack of exercise
- Obesity and diabetes

Such factors are known as triggers. They indicate when an attack is most likely to occur. If they are known, it is advised to avoid contact with them or if the attacks are due to a pre-existing condition then treatment of that condition is important. The very first step towards dealing with frequent migraine headaches is to avoid the triggers which are causing them. It is advised to alter and improve lifestyle like regularizing meals and exercise, adjusting appropriate sleeping hours etc. It is very helpful to maintain a headache diary regularly. That makes identification and assessment of possible triggers easy [16].

ACUTE PHARMACOLOGICAL THERAPY

For Acute Migraine

The main aim of treatment for acute migraine is to treat the headache effectively and rapidly without inducing any side effects. There must be regular monitoring of the medication to check if there is a need to change the regimen. It is generally advised to take the medicine when the migraine attack is about to initiate, to enhance the chances of quick recovery. NSAIDs, acetaminophen and triptans are widely prescribed medications for acute migraine **[16].** The absolute goal is to achieve rapid pain relief. In many cases, just taking simple analgesics solves the problem but some patients have suboptimal response to analgesics. For such patients, triptans are recommended. Opiods must be kept as a last option for treatment.

Analgesics

The first choice of treatment of mild to moderate migraine attacks are analgesics. Various analgesics have proved their efficacy in treating acute migraine attacks. They are-

Paracetamol- It has the advantage of causing less gastric irritation [6]. It has low cost, easy accessibility and less side effects. This makes it as first choice drug though its efficacy is still lower than other analgesics [4].

Ibuprofen- It is one of the most widely used NSAID. Its efficacy is comparable to aspirin and gastric side effects are lesser too [6]. Ibuprofen 400mg relieves from pain due to acute migraine but not complete relief [4].

Diclofenac- It has a rapid onset of action [6]. Oral diclofenac 50mg has proved to be very effective for treating acute migraine but complete pain relief is seen only in minority. Side effects are minimal with this drug **[4]**.

Naproxen- It has slower onset of action but longer half-life [6]. It is used as Naproxen 500mg but has not proved too much effective for treating acute migraine headache [4]. It is also observed that the combination of aspirin, paracetamol and caffeine is more effective than either of the drug taken alone. These analgesics should be taken at the beginning of the attack as soon as possible. It is generally recommended to use an anti-emetic along with analgesics to treat the associated nausea and vomiting. They also enhance the absorption of analgesic taken along with them [6]. Metoclopramide 20mg is effective in most of the cases [4].

Patients should avoid analgesics as far as possible; once in 15 days medication is recommended to prevent medication overuse headache [6]. As far as opioid analgesics are concerned, they are good alternatives but due to their psychiatric side effects and addiction problems, they are recommended only in the last when the first line analgesics are contraindicated [4].

Triptans

These form the second line therapy for acute migraine. Oral triptans are drugs of choice when simple analgesics have failed to control previous migraine attacks. Nasal sumitriptan and nasal zolmitriptan are helpful when oral triptans are ineffective. In cases of severe migraine, subcutaneous sumatriptan is considered. Because of its subcutaneous route, it does not cause nausea and vomiting. Triptans are contraindicated in patients with cardiovascular diseases as they are vasoconstrictors [16]. There are seven triptans which are currently in market to treat migraine. They are sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan. Oral triptans treat acute migraine attack within 30 to 60 minutes. There must be a gap of at least 10 days before taking another triptan medication [6].

Ergot derivatives

Egotamine tartarate and dihydroergotamine are the only two compounds available for treatment of migraine. The available data have shown that the efficacy of ergot derivatives is less than triptans. It is regarded as a third line treatment when people give inadequate response to triptans[6]. Dihydroergotamine is available as a nasal spray for attacks of moderate to severe intensity. Ergotamine on the other hand is often prescribed as a routine medication when triptans cannot be used. It is contraindicated in patients with cardiovascular or cerebrovascular diseases as it is a vasoconstrictor [16].

Pharmacological prophylactic therapy (preventive treatment)

For episodic migraine

Prophylactic or preventive medications are prescribed to patients along with positive lifestyle

changes and avoiding triggers, in order to reduce the occurrence of migraine attacks [16]. Preventive therapy of migraine is prescribed to patients when,

- The frequency of headaches is more than two per month but less than 8.
- Duration of a migraine attack is long
- Headache does not respond to on the spot treatment
- Therapy for acute migraine has contraindications
- Migraine comes with prolonged aura or hemiplegic migraine.[4]

Many drugs are available in the market for preventive treatment of migraine, many of which belong to the categories of beta blockers, anti-epileptics, tricyclic antidepressants, calcium channel modulators etc [17]. The preventive treatment for migraine should begin with topiramate. The second option is OnabotulinumtoxinA. Regular monitoring of patient medication is important as many patients fail to take medicines according to prescribed regimen [15].

Beta- blockers

The beta blockers recommended for treatment of migraine are Propranolol, metoprolol and nadolol. These are effective in patients having comorbid anxiety. They are likely to be contraindicated in patients with asthma, diabetes and cardiovascular diseases [16]. The beta blockers best effective in prophylactic treatment are propranolol and metoprolol. Propranolol is effective in doses of 80 to 240mg [6].The prophylactic therapy should be continued for a year and should be assessed for 3 months in the beginning. After that the treatment can be discontinued but only slowly and gradually to avoid any complications [4].

Antidepressants

The usual recommended antidepressant for prophylaxis is amitryptylin. The dose should be started with low value and then gradually increased according to requirement. It is generally preferred in patients with depression, anxiety, insomnia etc. Common side effect is sedation and dry mouth. Other alternatives are nortryptylin and venlaflaxin [16].

Anti- epileptics

Topiramate and divalproex sodium are two anticonvulsants which are prescribed as prophylactic treatment for migraine. Topiramate is preferred in patients with obesity [16] Topiramate at a dose of 100 mg daily was effective as a preventive therapy for chronic migraine [14]. Overall, antiepileptics are well tolerated. The main side effects of topiramate are weight loss and dysesthesia. Sodium valproate is used as a first line antiepileptic for treating migraine. But it is not good for female patients as it can cause weight gain and polycystic ovary disease [18]. Valproic acid is found to be equally effective as propranolol for prophylaxis. But it is teratogenic [6].

Calcium channel modulators

Flunarizine is the best calcium channel antagonist which is used in the prophylaxis of migraine [6]. Flunarizine 10mg is taken at night. This drug should not be used in case of patients who are having or had a history of depression [16].

FOR CHRONIC MIGRAINE

The case of migraine where headaches occur more than 15 days in a month is generally regarded as chronic migraine. Some drugs can be used for prophylaxis in the case of both, episodic as well as chronic migraine. Topiramate and Onabotulinumtoxin A are such drugs. Amitryptylin can also be used but is inferior in efficacy to the mentioned drugs [16].

Botulinum toxin type A is a neurotoxin generated by anaerobic bacterium Clostridium botulinum. It has the ability to work against several painful conditions including migraine. It is however an expensive treatment. But the cost can be reduced by decreasing the use of triptans for acute migraine attacks [15]. It is currently approved for prophylaxis of migraine in more than 40 countries, including UK and USA [14].

Topiramate has been recently cited as the first-line preventive medication for chronic migraine by NICE based on the results of high- quality clinical trials. But most of the times, clinicians and doctors prescribe older medications as the first drugs for treatment like antidepressants, beta blockers, anticonvulsants, calcium channel blockers. Flunarizine is the preferred drug for the patients in whom migraine attack is accompanied with prolonged aura, hemiplegic attack or prominent vertigo. Angiotensin blockers like candesartan are also found to be quite effective in the preventive treatment of chronic migraine. If these first and second line treatments fail, then non-pharmacological treatments are recommended like occipital nerve block or Botox [1].

Out of the drugs prescribed for the prophylactic treatment, onabotulinumtoxinA is the only drug which is FDA approved. Sodium valproate, gabapentin and tizanidine were also found to be effective. To increase the efficacy, combination of drugs can also be used. Sometimes, the patients with chronic migraine are resistant to conventionally used medications. Such patients are said to have refractory chronic migraine. Refractory chronic migraine patients constitute about 5% of the total migraine patients visiting the clinic [11].

NON PHARMACOLOGICAL TREATMENT

Many clinical trials have been conducted for non-pharmacological treatments like relaxation training, biofeedback, cognitive behavioural therapy and acupuncture. These techniques have shown to be effective though the methodology of clinical trials is

still criticized [16].

Acupuncture

Acupuncture can be used in prophylaxis of migraine and is beneficial most when considered along with medications [15, 16]. A clinical trial (non-blind) was conducted where patients did acupuncture in 24 sessions for around 12 weeks. The results were compared with those of topiramate. A significant reduction in the frequency of headaches was observed in the case of acupuncture as compared to topiramate [15]. The regimen recommended for acupuncture in case of migraine is one or two sessions per week for two or more months, with the duration of each session being more than 30 minutes [16].

Cognitive behavioral therapy (CBT) and other therapies

To combat chronic migraine, there are several behavioral techniques that are quite helpful. They are relaxation training, thermal biofeedback, electromyography biofeedback and cognitive behavioral therapy. Biofeedback training is based upon physical response targeting which are involved in causing migraine pain. Cognitive therapy, on the other hand, works more upon reaction to the pain.

The main objectives of the CBT are –

- To decrease overuse of medicines
- To prevent the side effects due to medication
- To reduce the frequency and intensity of migraine headache

CBT can prove to be effective when it is used in combination with other treatments, even the medical treatment. It is helpful in patients who have history of medication overuse or have any kind of stress. Stress includes stress due to pregnancy or due to pain coping [15].

INVASIVE THERAPIES

OnabotulinumtoxinA injection

Botox injection has been quite effective in prophylactic therapy for migraine. 100U of onabotulinumtoxin A was given to around 60 patients and its efficacy in bringing down the headache was found to be better than placebo [6].

Greater Occipital Nerve Block (GONB*)*

The greater occipital nerve has sensory fibres which emerge from C2 segment of the spinal cord [19]. The main reason behind greater occipital nerve block is the anatomical link it forms between nociceptive trigeminal and upper cervical afferent neurons. This technique is regarded as safe although clinical trials analyzing its benefits are lacking. This technique does have some side effects like dizziness, light headedness and hypersensitivity reactions which limit its use. Also, it is fewer patients compliant because of its invasive route. But it is a good option of treatment in patients who are resistant to medical treatment for migraine [6]. The migraine patients who exhibit occipital tenderness are more likely to respond to this treatment [19].

NEUROMODULATION

Neuromodulation is one of the recent techniques which are gaining acceleration for prophylactic therapy of migraine [17]. Neuromodulation focuses on the pain signals by using electric currents for modulation of nociceptive system function [6]. Neuromodulation includes techniques like occipital nerve stimulation, sphenopalatine ganglion stimulation and transcranial magnetic stimulation. These include advanced non- invasive devices that act transcutaneous [17]. According to European Headache Federation, neurostimulation for chronic migraine should be the choice after all medications and behavioral therapies have failed to treat headaches [15].

Occipital nerve stimulation

Occipital nerve stimulation is one of the invasive techniques initially employed for the treatment of chronic cluster headache. Its long term safety and efficacy still need to be analyzed [6]. This technique has been approved in USA and can be recommended to patients who are resistant to normal medical treatment. Its main side effects are device-related like pain at the site of incision or implant, infection, sensory symptoms and lead migration [21]. This technique is overall safe even if it is invasive and costly. Occipital nerve stimulation can also cause paresthesias [15].

Transcranial magnetic stimulation

Transcranial magnetic stimulation releases fluctuating magnetic field which induces electric currents in the brain that disrupts CSD. While TMS with single pulse is found to be effective acute treatment for migraine with aura, repetitive TMS is suitable for prophylaxis. This technique is generally safe with seizures as the only but rare side effect. It should be avoided in patients with ferromagnetic implants as chances of interaction are high. The activation of the device occurs though a SIM card similar to those in mobile phones. Although the treatment is recommended by NICE, it is still expensive. There is also issue with the size of the device. Overall, this technique is safe for use [6].

Supraorbital Nerve Stimulation

Nerve stimulation involves applying electric current to influence pain signals. It is used in the treatment of chronic migraine [19]. It is used in combination with occipital nerve stimulation for the treatment though its effect alone has not been confirmed. The main adverse effects include lead migration, infection, and supraorbital lead allodynia. A better approach for the treatment of migraine is non-invaisve supraorbital transcutaneous stimulator. It employs a device called Cefaly device. It is safe and well tolerated in migraine patients. It has been approved

by US FDA for marketing in March 2014. The price is also low and reasonable [6].

Nutraceutical and herbal treatment for migraine

Herbal therapies are medieval treatments that are widely accepted in the modern world too. There are nutraceutical and herbal options available for the treatment to migraine also along with million other diseases. The treatment with medications has the issue of insufficient effects with many side effects, sometimes, intolerable to patients. Some of the herbal constituents like those obtained from Gingko biloba and feverfew have shown positive effect in the treatment of migraine [22]. So this is why there has been an increasing interest in nutraceutical and herbal preparations for prophylactic therapy of migraine. Nutraceuticals includes vitamin supplements and herbal constituents. The nutraceutical and herbal therapy have shown promise in the prophylaxis of migraine and has the added advantage of negligible adverse effects. It should be included by the physicians in the prophylactic therapy on long-term basis [23]. Herbal products will be discussed first followed by nutraceuticals.

HERBAL PRODUCTS

Feverfew

Feverfew is Tanacetum parthenium L. belonging to the family Asteraceae. The main active constituents are sesquiterpene lactones like parthenolide, flavonoids and volatile oils. Earlier many studies were conducted to prove its efficacy in migraine but failed. Also, feverfew withdrawal was found to have an adverse symptom called post feverfew syndrome marked by severe headache, joint pain etc. Later, the efficacy of carbon dioxide extract of feverfew was evaluated for migraine in a dose-finding study. The extract is referred as Mig-99. After the results came out, Mig-99 was stated as effective in prophylactic therapy of migraine by Quality Standards Subcommittee of American Academy of Neurology. So, overall, feverfew is well tolerated in patients except some mild side effects which are mostly of contact type like mouth ulceration and gastric discomfort [22]. In Cochrane review based upon double blind randomized clinical trials in 2004, 2015, it was revealed that there is not enough evidence to prove efficacy of feverfew in migraine prophylaxis against efficacy of placebo [23].

Butterbur

Butterbur, the Petasites hybridus root extract, has shown significant efficacy in the prophylaxis of migraine. Its exact mechanism is not known but it works through calcium channel regulation and inhibition of peptide leukotriene biosynthesis, indirectly affecting mechanisms involved in migraine. The active constituents in butterbur are petasin and isopetasin. Its marketed preparations include Petadolex, Petaforce and Petadolor. In a study conducted by German authors, a decrease in migraine frequency by 60% was observed with Petadolex. Its adverse effects include mild gastric problems like burping. But recently, four cases of reversible cholestatic hepatitis have been found in patients receiving long term therapy for migraine. Overall, it is well tolerated and safe and may be a good choice in the prophylaxis of pediatric migraine. From recent evidence based guidelines, Petasites can definitely be used in the prophylaxis of episodic migraine also [22].

Ginkgo biloba

Ginkgolide B, a herbal compound of Ginkgo biloba, is a diterpene mainly involved in treatment for migraine. It anatagonises Platelet activating factor receptor. PAF is nociceptive agent liberated during inflammation process. Migraine and associated aura frequency significantly dropped by the combination of ginkgo biloba terpenes phytosome, coenzyme Q and vitamin B2. Only mild adverse effects were observed with ginkgolide B like gastric disturbances [22].

NUTRACEUTICALS

Magnesium

Migraine frequency has been directly related to magnesium deficiency. Taking extra supplements of magnesium significantly reduces migraine frequency and is quite helpful in short term prophylaxis of menstrual migraine. Magnesium, both oral as well as intravenous, can be beneficial in this regard [23].

Riboflavin

Deficiency of riboflavin in mitochondrial energy metabolism may be responsible for the occurrence of migraine. Giving the patients riboflavin supplements significantly reduces migraine frequency and is a very good alternative in prophylactic therapy. It is effective and well tolerated in patients so can be used for long term therapy too. But riboflavin has no role in prophylaxis of pediatric migraine [23].

Coenzyme Q10

It is involved in mitochondrial energy metabolism just like riboflavin. Supplementation of coenzyme Q10 significantly reduces frequency and severity of migraine attacks. But it is not so effective in pediatric or adolescent migraine [23]. Recent studies indicate that a combination of nutraceuticals is more effective in preventive treatment of migraine rather than taken alone. Magnesium, riboflavin and coenzyme Q10 is one such combination. Even feverfew and ginger combination is very effective in migraine. It is a common notion that nutraceuticals are safe because of their natural origin but patients as well as clinicians need to be vigilant about their adverse effects. Take for example hepatotoxicity caused by butterbur. Though nutraceuticals are effective in reducing migraine frequency and severity, their long term safety cannot be confirmed [23].

CURRENT RESEARCH

Migraine has recently been declared as the 7th most disabling condition. It affects almost 15% of the world's population with women (18%) being at more risk than men (8%). Migraine directly affects the productivity of an individual by reducing the hours the patient would have otherwise utilized in work. Recently, both invasive and non-invasive methods are gaining acceleration in the migraine therapy. Botox injections, targeting of greater occipital nerve and neurostimulation are some of the newest options. Migraine therapy through calcitonin gene related peptide is the area where current research is going on [19].

Calcitonin gene- related peptide

Calcitonin gene related peptides (CGRPs) are currently being seen as potential targets for the treatment of migraine. CGRPs are the neuropeptides which can cause vasodilation in cerebral arteries and hence are involved in cluster headaches. The antagonism of this neuropeptide causes vasoconstrictive effects which are helpful in migraine patients as well as patients with cardiovascular disorders [24]. CGRP receptor antagonists called as 'gepants' were developed for the treatment of migraine and their activity and effectiveness was observed to be similar to triptans. Olcegepant was used as an intravenous infusion thereby limiting its patient use [19]. Merck has discontinued the development of telcagepant, an oral CGRP receptor antagonist, after speculation on its hepatotoxicity. Another CGRP receptor antagonist, MK-3207, also suffered the same fate. Currently, BI 44370 is undergoing clinical trials and showing good efficacy but more studies will be required to confirm its effectiveness and risks associated [24]. BMS-927711 is also undergoing clinical trials and has shown good tolerability but its long term safety still needs to be evaluated**.** Apart from CGRP receptor antagonists, monoclonal antibodies (mAb) are also being currently used to target CGRP receptor for treating migraine. Because of their biological origin, they tend have to a longer half-life and therefore do not need to be administered frequently. More they can be modified in a way so as to decrease side effects and increase targeting potential. Four monoclonal antibodies have already been designed but none has come out of clinical trials yet. LY2951742 is undergoing trial in 217 patients suffering from episodic migraine. The full results of ALD403 trial are yet to come. LBR-101 is undergoing trial in patients of both episodic as well as chronic migraine prophylaxis. Its safety was found to be excellent [19].

Serotonin receptor agonists

Generally, triptans act by binding to the 5-HT1B and 5-HT1D receptors, but some triptans bind to 5-HT1F receptor also. Lasmiditan is selective agonist at only 5-HT1F receptor and has practically no action on 5-HT1B or 5-HT1D receptors. The drug has shown efficacy in acute migraine when administered as intravenous injection. Overall, it is well tolerated with mild adverse effects like dizziness, paraesthesia and limb heaviness. Clinical studies are still going on this drug [24].

Nitric oxide antagonists

Nitric oxide is sometimes responsible for causing headache in patients of migraine without aura. The enzyme accountable for its synthesis is NO synthase. Research is going on a particular drug molecule which is still in the fetus stages of development. This drug is believed to selectively inhibit NO synthase enzyme and has agonistic action on 5-HT1B and 5-HT1D receptors also[24].

Future directions

The future cannot be accurately foretold but the treatment area of migraine has been expanding since the past two decades. Pathophysiology and the associated mechanisms of migraine need to be explored in depth. This will lead better understanding and hence better management of migraine. Also, unfolding of more mechanisms will introduce many new targets where research could be directed. Nowadays, research is being carried out on triptans, calcitonin gene related peptide (CGRPs) antagonists and nitric oxide synthase inhibitors. In future, more research could be focused on these areas to treat migraine. Perhaps, neuroimaging can provide scope for more exploration in research areas [25]. Also, improvement in the understanding of mechanisms involving progression from episodic migraine to chronic migraine and reversion to episodic migraine will help in treatment and management of migraine. Moreover, more focus should be given on analyzing the concentration of biomarkers like CGRP to help in predicting any distinctive activity that could be instrumental in prophylaxis of migraine. In future, genetic studies should be give attention which predispose an individual to migraine. Phenotypic, biologic and neuroimaging information could influence and direct more research in treating chronic migraine. More research should be directed towards development of drugs with better efficacy and least side effects. Already many clinical studies are being carried out like development of transdermal delivery system for sumatriptan, a bidirectional nasal delivery system for sumatriptan. Techniques like transcranial magnetic stimulation, transcranial direct current stimulation and vagal nerve stimulation need more investigations to establish safety and efficacy data [11]. So, the future prospects of migraine management are both inspiring as well as demanding. There can be innumerable directions in which research could be directed. Hopefully, there will be more influx of ideas in this area and research for the treatment of migraine will continue to improve [25].

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