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Migraine-A Review on Current Strategies in Diagnosis, Management and Evaluation Methods-An Update

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Abstract

Migraine is a chronic condition which occurs with symptoms such as nausea, photophobia and phonobia. Migraine has a throbbing kind of headache. Migraine is the main cause headache burden around the globe and it comes among the 20 leading causes of disability worldwide. One of the main characteristic of migraine is its inherited nature. The prevalence of migraine in women increases more rapidly than in men after puberty. An estimate of 30 percent patient has this and it is seen that migraine is mainly neurally driven. The brain tissues at the time of attack experiences a kind of electrical activity that is abnormal. Another element in migraine is the release of chemicals by the trigeminal nerve. One more reason behind migraine is cortical spreading depression. According to studies conducted about 70% of the migraneurs have a family history of migraine. Anti-migraine drugs can be classified into drugs that can abolish the pain and drugs that can prevent the pain. Triptans are mostly used anti-migraine drugs. For confirming the anti-migraine efficacy there are both *in vivo* and *in vitro* animal models. Currently there are drugs that are still under clinical trial.

Keywords: migraine, pathophysiology, anti-migraine drugs

1. INTRODUCTION

Migraine is regarded as one of the main cause of burden that causes decrease in quality of life. This is an issue which requires treatment and is a disabling disease. Although it is not well recognized or not diagnosed properly but it has a large prevalence. Migraine is also currently not treatable properly but the condition is such that it requires essential treatment. There are many conditions around the globe which leads to a disabling condition in life and amongst all those causes' migraine falls among the 20 leading causes as reported by the World Health Organization (WHO) [5]. Particularly on the cranium regulations are altered with altered afferent control in case of migraine. Some of the essential elements to be considered in case of migraine are:

- Genetics
- Anatomy involved with headache, particularly one with the trigeminal nerve
- Physiology of aura

One of the main characteristic of migraine is its inherited nature. According to studies done there is an evidence that migraine is also passed on from one generation to the next generation, thus indicating a positive family history. It is seen that among approximately 50% of the reported families with migraine, chromosome 19p13 has been assigned for Familial Hemiplegic Migraine. In some cases it is seen that there are certain symptoms related to visual, sensory and motor parts. The appearance of these symptoms before the actual attack is termed as migraine aura defined as a focal neurological disturbance [13]. About 30% of migraneurs experience transient sensory (most frequently visual) disturbances which is also known as migraine aura, whose neurophysiological correlate is now recognized to be cortical spreading depression (CSD) [8].

2. EPIDEMIOLOGY OF MIGRAINE:

Migraine stands at the seventh position as a cause of years lived with disability according to The Global Burden of Disease Study 2015[1]. The prevalence of migraine in women increases more rapidly than in men after puberty. According to studies and survey reports the prevalence rate of migraine is between 2.6 and 21.7%, with an average rate of approximately 12%. The global prevalence of migraine is around 10% according to meta-analysis studies [5]. In case of gender wise studies, it is seen that boys experience more migraine attack than girls before puberty. But the prevalence as well as incidence shifts to girls from boys when they approach towards adolescence. After the age of 40 the prevalence of migraine starts decreasing, and keeps on increasing throughout childhood and early adult life [22]

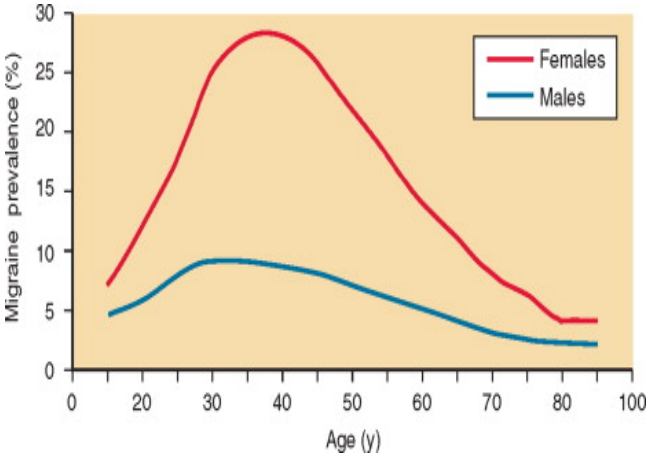

Figure No: 2.1 Graph indicating the prevalence of migraine (Source: sciencedirect.com Lipton RB, Stewart WF, Diamond S, et al: Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 2001; 41:646-657.)

According to literature reviews it is estimated that about 6-8% of men and 15-25% of women are migraneurs in western countries [37]. Migraine has affected 1-3% of the population of age group of 7 years and 4-11% of the population of age group between 7-15 years.

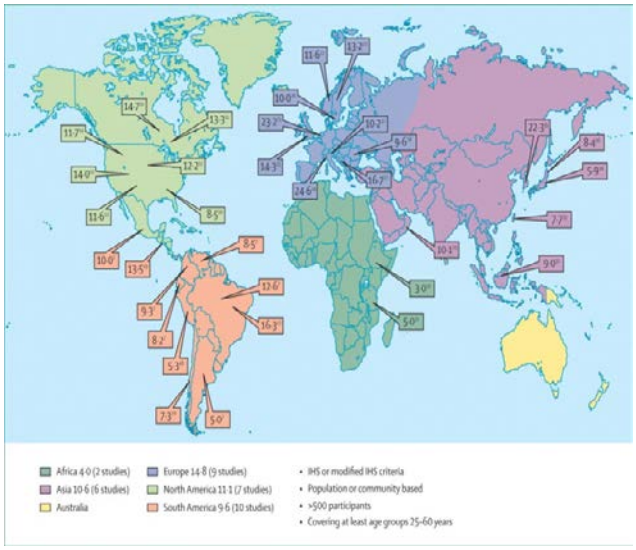

Figure No: 2.2 Prevalence of migraine in different countries
(Source: The Lancet Neurology)

3. PATHOPHYSIOLOGY OF MIGRAINE

The ophthalmic division of the trigeminal ganglion as well as the posterior fossa from the upper cervical dorsal roots gives rise to a network of large number of unmyelinated fibres that surrounds parts of brain including large cerebral vessels, large venous sinuses, pial vessels as well as the dura matter. Trigeminal ganglion mainly contains Substance P and CGRP. There are 4 major classifications of migraine attack that comes with aura. This classification is given by International Classification of Headache Disorders-3 (ICHD-3) which includes [12]

- migraine with typical aura (visual, sensory and language disturbance),
- migraine with brainstem aura,
- hemiplegic migraine (HM),
- Retinal migraine.

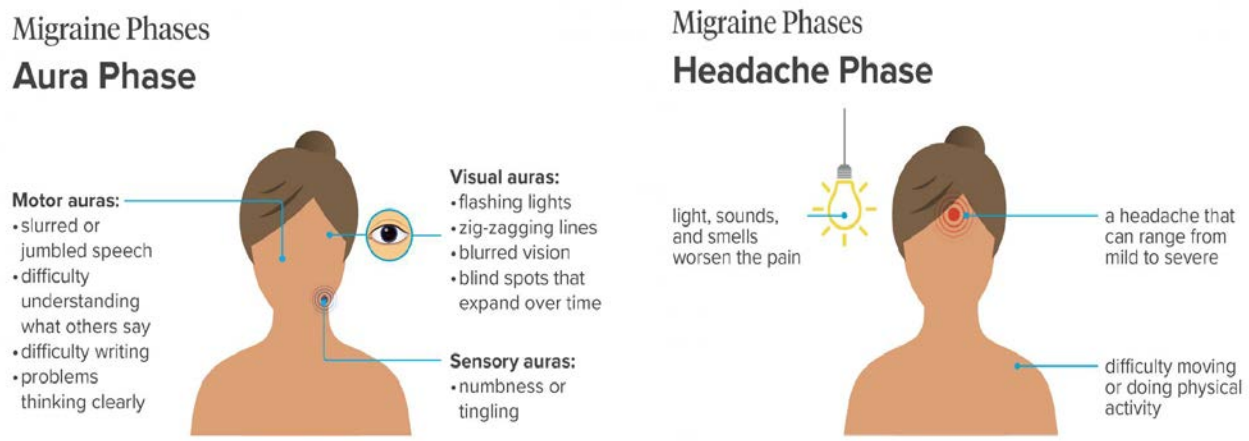

Figure No: 3.1 Phases of Migraine (Source: Medical News Today)

According to some experiments done, it is suggested that the pain of migraine may be a result of inflammation of the dura matter. Since 50 years it is seen that 5-hydroxytryptamine (5-HT) has an implication in pathophysiology of migraine. According to different literature survey there is a decreased central 5-HT disposition associated with an increase in 5-HT release during attack and this change of 5-HT metabolism has been regarded as the most convincing change in migraine. There's no low 5-HT level in case of peripheral studies on plasma/platelet. 5-HT reactivity studies have proven that there is reduction in the diminishing response to drugs which is also expressed as hypersensitivity. His characteristic is the most appropriate marker of alterations in neurotransmission. [29]During a migraine attack abnormal electrical activity occur in the brain tissues.

In migraneurs, after performing brain imaging studies it was found that there are areas with altered activity which is called "spreading depression". This is also known to represent a wave where the activity of nerve cells increases followed by decrease in its activity. Chemical release from the trigeminal nerve is regarded as an important element of migraine. The trigeminal nerve is responsible for supplying sensation to certain parts including lining of eyes, scalp, nasal cavity and sinuses, gums, teeth, joints of the jaws, parts of neck and ears, shoulders and also the entire face. The nearby tissues are supplied with inflammatory peptides by the trigeminal nerve. Due to the release of inflammatory peptides like CGRP, substance P, etc. the local blood vessels become "leaky," leading to losing of their serum into surrounding tissues. This results in swelling of tissues and thus becomes painful. Most of the migraneurs experiences a throbbing kind of headache which is mainly due to the inflammation of the trigeminal nerve that passes through the brain's lining [5].

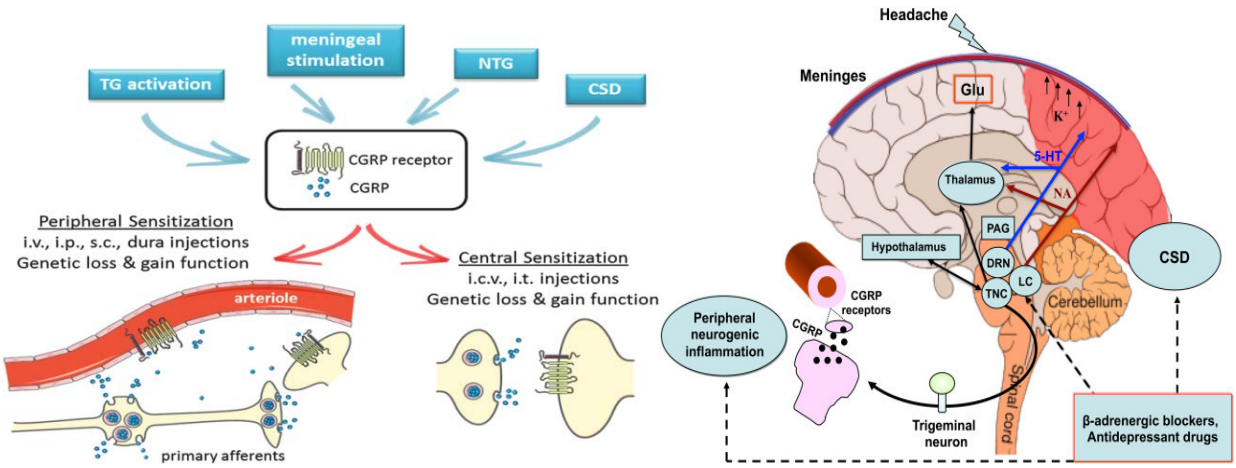

Figure No: 3.2 Pathophysiology of Migraine
(Source: https://www.researchgate.net/figure/Mechanisms-and-structures-involved-in-the-pathogenesis-of-migraine-with-aura-CSD_fig1_251567944)

One more reason behind migraine is cortical spreading depression. It leads to a long lasting neuronal suppression due to the spreading of transient intense spike activity along the cortex and according to many clinicians the migraine aura is basically due to neuronal dysfunction [3].

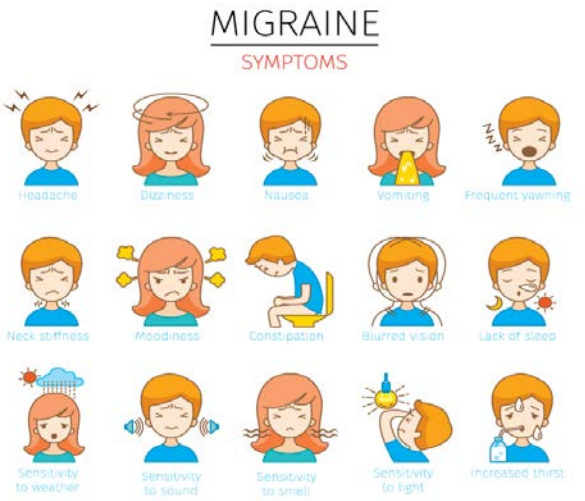

Figure No: 3.3 Symptoms of Migraine
(Source: https://www.askapollo.com/health-library/living-healthy/migraine-causes-symptoms-risk-factors-and-treatment)

4. Diagnosis Of Migraine

There are specifically four questions to identify if the patient is suffering from migraine or not. According to clinicians the patient should have more two or more positive answers to be considered as a migraneur. Positive Predictive Value of 98% is considered when a patient has positive answer for 3 out of 4 questions [36]

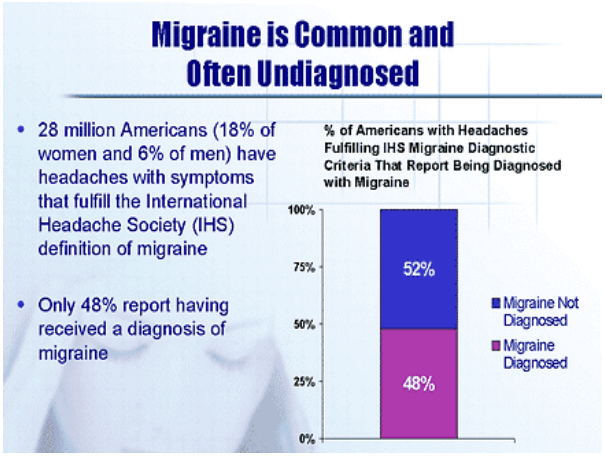

Fig No.4.1 Population diagnosed with migraine
(Source: https://www.medscape.org/viewarticle/451273)

The questions that help to identify that a patient is suffering from migraine are as follows:

History of migraine headache at any point of time. As because most of the patients or migraneurs are undiagnosed, so they should be asked if they have frequent headache with different intensity of pain including photophobia and phonophobia and also nausea associated with aura.

According to literature surveys most of the migraneurs have a history of motion sickness in childhood. It is seen that they have a feeling of nausea when they read something while travelling [24]. Most of the migraneurs have comorbid diseases such as anxiety, irritable bowel syndrome [14]. Family history of migraine if present or not should also be considered. According to studies conducted about 70% of the migraneurs have a family history of migraine. [13]

Generally in adolescent migraine lasts for 2-72 hours [31]. The pain occurs in the frontal or temporal regions. Sometimes the pain may be on one side only or it may also radiate to both the sides, and may be either moderate or severe in nature [36]. According to the Headache Classification Committee of the International Headache Society, children suffer from bilateral migraine pain and at adolescent stage it generally becomes unilateral and the same in adulthood also [2]. Photophobia, phonophobia, nausea and worsened pain are also reported by some patients. These are the reasons for children avoiding to go to school. Due to weather changes and some special kind of food consumption or due to certain kind of smells migraine headache is often triggered [17].

Migraine may also come with vertigo attack. If such things happen it is clinically called as vestibular migraine. There can be different kinds of vertigo that a migraneur can experience along with the headache, the types are: spontaneous, positional, visually induced and head motion induced nausea and dizziness. [19]

Only if 5 episodes occurs with vestibular symptoms lasting for a time period of 5 minutes to 72 hours and that is of moderate to severe intensity, it can be a vestibular migraine.

A study done on a group of patients reported that patients who had migraine also had clocking tinnitus. To reduce this symptom drugs like flunarizine or topiramate proved to be beneficial. So may be clocking tinnitus is an audiology symptom of migraine [10]

5. Current Therapeutic Approaches

There are two kinds of drug in the market:

- Agents that can abolish the pain
- Agents that can prevent the pain

Acute Migraine Treatment[a]

Medication	Formulation	Dose for Migraine
Aspirin	Tablet, oral solution	650 mg to 1000 mg
Ibuprofen	Tablet, oral suspension, capsule	400 mg to 800 mg Maximum initial dose of 1 g
Ketorolac[b]	Tablet	10 mg
Naproxen	Tablet, oral suspension	125 mg to 550 mg
Naproxen controlled release	Tablet	750 mg Maximum initial dose of 825 mg
Meclofenamate	Capsule	50 mg, 100 mg
Diclofenac potassium	Tablet, powder pack	50 mg
Etodolac	Tablet, capsule	200 mg to 500 mg
Ketoprofen	Capsule	50 mg to 75 mg
Ketoprofen extended release	Capsule	200 mg

[a] Nonsteroidal anti-inflammatory drugs carry US Food and Drug Administration Black Box warnings for gastrointestinal risk, cardiovascular risk, and bleeding.
[b] Renal toxicity is a concern with the use of ketorolac.

Fig No.5.1 Therapeutic approaches of migraine (Source: https://www.semanticscholar.org/paper/Acute-and-preventive-treatment-of-migraine.-Rizzoli/866c04116ea8b64cc0432f874b08d796c5329eac)

Generally patients need acute treatment but the patients those who suffer from frequent migraine attacks need prophylactic treatment in addition to acute treatment to reduce the number of attacks. According to studies the platelet 5-HT gets reduced, so in that case i.v. administration of 5-HT gives a relief [40]. Sumatriptan a 5-HT1 agonist has beneficial effects on the patients [15]. Other than triptans, ergotamines are also used like ketoprofen, ketorolac etc.

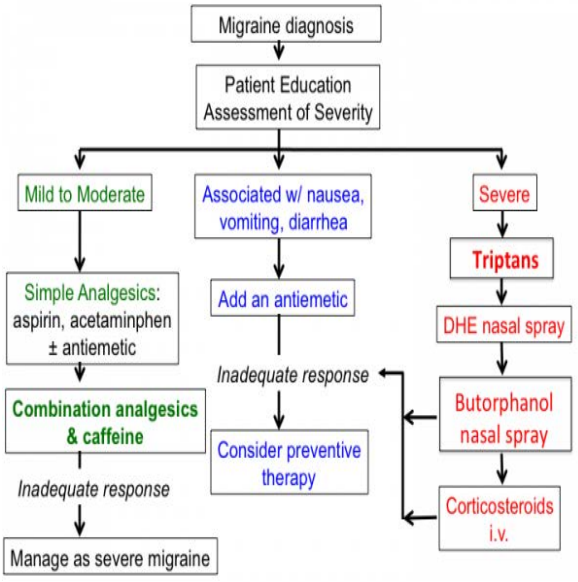

Fig No. 5.2 Migraine Diagnosis (Source: http://tmedweb.tulane.edu/pharmwiki/doku.php/migraine_headaches)

In the early 2019, FDA has approved certain neuromodulation devices for the treatment of migraine which will have no side effects. It is also said that even if it is overused it would not have the risk of conversion of episodic migraine to chronic one [38]. There are certain kinds of treatment for migraine known as non-specific migraine treatment. This type of treatment includes opioids, analgesics, neuroleptics and NSAIDS either given alone or in combination [23]. According to literature CGRP monoclonal antibodies have also shown very good and promising effect in the treatment of migraine [16]. In addition to all the above mentioned drugs there are certain nutrients that can help prevent migraine. The nutrients that can be classified as one of the preventive treatment for migraine are magnesium coenzyme Q10, vitamin B2, B3, B12, D and carnitine. It is seen that patients with chronic migraine have this kind of vitamin deficiency in comparison to that of episodic migraine patients. These vitamins act as preventive therapy of migraine by reduction of inflammatory mediators and also the antioxidant status is improved by them. [27]

6. Experimental Models Of Migraine

There are a wide range of animal models to test the anti-migraine efficacy of various drugs. The models include both *in vivo* as well as *in vitro* models [7].The list of models includes:

6.1 *In-vivo* experimental models

Nitroglycerin infused inflammatory model:

Nitroglycerin being a nitric oxide donor, when infused exerts a direct action on the meningeal tissues and leads to the formation of PPE. It upregulates all the pro inflammatory mediators and cause degranulation of mast cell, activates macrophage, and also leads to oedema formation. GTN infusion has the ability to activate type II NOS which is expressed in macrophages. Few hours after induction of GTN, NO is generated at a much larger quantity as compared to its other counterparts. This NO generation ultimately leads to inflammation and development of migraine. [33]

Model of vocalization in rats:

In this model bradykinin is used as an inducing agent for migraine. Bradykinin is known to have the ability to cause microvessels dilatation and cause vascular pain [42]. When few micrograms of bradykinin is injected into the common carotid artery or into the cistern magna of rabbits it caused vocalization and flight [5]. At a dose of 10µg in 10µl, when injected into the arterial catheter causes vocalization which is recorded with the help of microphone that in turn is connected to the polygraph for recording it [28].

Chemical induced plasma protein extravasation:

Rats are generally anesthetised and for the formation of PPE any of the chemicals like capsaicin, neuropeptides, histamine, bradykinin, PGE2 or 5-HT is injected via the femoral vein at a dose of 1 ml/kg. The thorax is cut opened and via the left ventricle saline is perfused after 15 minutes of injection of tracer. The dura is dissected and incubated, and by specific methods the amount of marker is determined to know the amount of PPE [25].

Electrical stimulation of vagus nerve:

Sprague-Dawley male rats were anesthetised with 3% of isoflurane before starting the procedure. VNS device was used in order to cause vagus nerve stimulation. After covering the electrode with electrolyte gel, it was placed on neck lateral to the trachea, over the vagus nerve in a parallel position before that it has to be shaved. A 1-ms pulse of 5 kHz sine waves, repeated at 25 Hz, for 2 minutes was administered. A recovery period of 2 hours was given for the animals after the stimulation before the testing of nocifensive behaviour [15]

The CGRP release following activation of the trigeminal vascular system

CGRP plays a crucial role in the pathogenesis of migraine. Trigeminal ganglion consist of C fibres release CGRP. Sumatriptan as well as dihydroergotamine attenuates the release of CGRP in humans during a migraine attack. After placing the rats in the stereotaxic apparatus, midline incisions is made to expose the skull and burr holes are drilled. Using stainless steel bipolar electrodes the right trigeminal ganglion is stimulated for 5 minutes. Using radioimmunoassay, the concentration of CGRP is estimated from the blood sample collected from jugular vein [21]

Laser Doppler flowmetry study to measure meningeal blood flow:

In order to predict the efficacy of anti-migraine drugs, laser Doppler flowmetry has proved to be a very useful method. Intravital microscopy as well as laser Doppler flowmetry can be combined to measure meningeal and cerebral changes. Dural sites are electrically stimulated that leads to increase in blood flow in meninges. This increased meningeal blood flow can be abolished by a CGRP antagonist and can be attenuated by 5-HT1 agonist [42]

6.2 *In-vitro* experimental models:

5-HT$_{1B/1D}$ and α-adrenoreceptor assays

The saphenous vein of rabbit is used in this method. It is cannulated in situ in polyethylene tubing. Modified Krebs bicarbonate buffer is used as PSS. Bath temperature is maintained at 37ºC aerated with carbogen gas. Resting force of 4g is required. Equilibration time of 60-90 minutes is maintained with repeated washing at an interval of 15 minutes. Using a combination of physiographic recorder and isometric force displacement transducers the changes in isometric contractions are recorded. Using atropine, ketanserin and chlorpheniramine maleate at a concentration of 1µM and also with the antagonist of all these the concentration response studies is done. Prior to the recording of response of test drug, response of KCl is also taken [4]

GABA receptor assay:

In this method terminal ileum of guinea pig is used. Tyrode solution is used as PSS and a resting tension of 1g is maintained with equilibriation time of 45-60 minutes. In the presence and absence of picrotoxin, the concentration response of GABA is obtained [4]

5-HT$_{2B}$ assay:

The longitudinal strips of fundus of rat are used in this assay method. PSS used is tyrode. Either in the presence of test drug or ketanserin the concentration response of test drug is taken. 10 minutes prior to the addition of 5-HT the tissue sample has to be incubated either with test drug or with ketanserin. [4]

Current investigational drugs and regimens

FDA has approved Botulinium toxin A for treating chronic migraine. Recently in 2019 *Abrus precatorius* known as Indian liquorice has also shown anti migraine activity. GC-MS is conducted for this plant, which shows it contains five phyto compounds which have interaction with CGRP protein [30]. Erenumab a fully humanised monoclonal antibody has the potential to antagonize the action of CGRP with 50% inhibition [9]. The dried rhizomes of *Ligusticum striatum* DC, has been widely used in the clinic for the treatment of migraine for centuries in China[32]. Lasmiditan a 5-HT1F receptor agonist has similar action to triptans but is devoid of vascular side effects. [40]

Even now-a-days it has been proved that wet cupping therapy or WCT can also extensively reduce the migraine headache. It also helps in reducing the disability in patients, if used continuously [11]

Acupuncture is also currently a treatment option for migraine for patients those who are ready to practice it [35]

Paeonia lactiflora has the potential to reduce the pain of migraine if the patient is pretreated with it. This plant helps in reducing c-fos and CGRP cells proving that it has a beneficial effect to alleviate pain. [20]

7. FUTURE PROSPECTS

Recently, researchers have proposed a hypothetical relationship between a disease named as Meniere's disease and migraine. This aetiology of Meniere's disease (MD) is not known yet, but is supposedly a chronic condition affecting the inner ear. According to clinicians MD is related to migraine that may have implications on the future treatment procedures for both the diseases. It is seen that about 51% of the population who are suffering from MD also suffers from migraine as compared to 12% of the rest of the normal population. The aura and symptoms of migraine is related to the cortical spreading depression theory which causes a leakage of substance P with inflammation in the neurons and ultimately leading to alterations in blood flow. The changes that are induced by the migraine attack becomes difficult to be managed or regulated by the chronic hydrophobic inner ears, thus may finally manifest as MD. [34]

8. CONCLUSION

Migraine as classified by WHO being a leading cause of burden on the human population needs immediate research. According to all epidemiological data women are mostly prone to migraine than men. Migraine is considered as one of the most disabling neurological disorder as reported by WHO (from results of Global Burden of Disease) [42] .It is also said that people suffering from migraine spend most of their lifespan in a disable manner [41]. There has been too many pathologies contributing to the development of migraine and among them 5-HT and CGRP being the leading causes. There are a wide range of animal models for preclinical screening of the anti-migraine nature of the upcoming drugs in the market. Till now triptans top the market for their efficient anti migraine nature, along with that ergotamine and other analgesics are also used. Recently CGRP monoclonal antibodies have been developed. Many herbal plants have also shown promising anti migraine effect.

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Conflict of interest:

There are no conflicts of interest.

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