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REVIEW ARTICLE

Design and Developing a Device for Migraine Treatment: A Review

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ABSTRACT

Migraine is usually somatosensory input to the head involving pseudo-unipolar trigeminal and upper cervical branches. It is a very common disorder involving visual perception difficulties, thereby causing cognitive decline. Advancement in migraine treatment is always a crucial point of research for every neuro-ophthalmologist.

Results: Many novel treatment approaches have received Food and Drug Administration approvals for well-outlined therapies in migraine treatment. In this review, we summarize this treatment methodology and prototype a device that can cater to the limitations of already available migraine treatment devices in the market. Many novel and stirring therapies continue to evolve for the therapy of migraine. Though highly advanced and sophisticated, this therapy gets knock-down due to many limitations. This limitation renders them from being effective. Being on track with this commonly occurring disorder is important in reducing the disability from it.

Keywords: Aura, Migraine, Migraine devices, Neuromodulation, Transcranial stimulation, Vagal nerve stimulation.

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INTRODUCTION

Migraine is a multifarious, socially important disease that shows severe bouts of pulsating headaches.[5] These phenomena lead to the decline in the quality of general, professional and family life of many people. In adherence to the visual aura, migraine headaches are commonly unilateral and usually linked with severe headaches and other symptoms including nausea, vomiting, etc.[1] According to IHS, migraine constitutes 16% of primary headaches.[2,3] Migraine is under-diagnosed and undertreated.[2-4]

Many neurological hypotheses has been proposed as the explanations for the etiology of migraine (Figure 1). But the main causes are-

- Variations in the sub-cortical aminergic sensory modulation affect the brain.[2-8]
- Dilation, swelling, and/or inflammation of cephalic arteries and intracranial extra cerebral arteries leads to migraine headaches.
- The migraine-related symptoms outcomes from the stimulation of the sympathetic nervous system are caused by the pain.
- It is also caused by a lack of lungs ability to get rid of CO_2.

Types of Migraine[2-4]

- Migraine unaccompanied by aura
- Migraine accompanied with aura
- Migraine with brainstem aura
- Silent/Acephalgic Migraine
- Chronic migraine-occurs 15 or more days in a month over a period of 3 months or more
- Retinal migraine

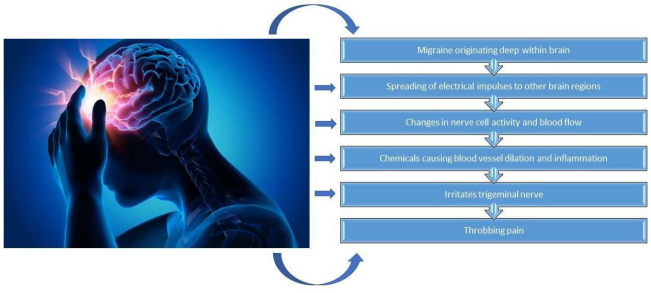

Figure 1: Depicting the etiological causes of migraine

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- Status migraine-debilitating migraine attack that lasts for greater than 72 hours
- Hemiplegic migraine

Phases of Migraine

- *Prodrome:* Vague premonitory symptoms. The initial stage persists for a few hours, or it can last for days from 12–36 hours before the aura and headache.[3-5]
- *Aura:* The stage of aura can persist as long as 60 minutes or as little as five.[3-5]
- *Headache:* From 4 to 72 hours is the duration for which the headache continues.[2-6]
- *Postdrome:* The postdrome phase continues for one day or more than that.[2-6]

PATHOPHYSIOLOGY

Vascular Theory[2-6]

- Intracranial/Extracranial blood vessel vasodilation causes headache
- Intracerebral blood vessel vasoconstriction causes aura

Serotonin Theory[2-6]

- Decreased serotonin levels linked to migraine
- Specific serotonin receptors found in blood vessels of brain

Diagnosis Methods[5]

Below given are the diagnostic methods used for migraine (Figure 2). Almost everyone with migraine needs no investigation. This investigation aims to exclude other causes of migraine- like symptoms, not to confirm migraine- which this diagnostic test can never do.

For an accurate diagnosis, a General Practitioner must identify a pattern of recurring headaches along with the associated symptoms.

- Medical history
- Headache diary
- Detection

Computed Tomography scan

A medical imaging technique that employs a combined sequence of X-rays to produce cross-sectional images of brain.

Magnetic Resonance Imaging

The best diagnostic accuracy has been achieved at 72.5% and it is also recommended for severe headache in pregnancy without contrast media.

Sinus X-ray

Although this test does not confirm a migraine presence, if this sinus X-ray fails to show sinus inflammation, the patient is more likely to have migraine.

Electroencephalogram

The EEG and 24- hour closed-circuit television EEG recording can help to distinguish between migraine aura and epileptic aura. This process might also help in the diagnosis of migraine and also migralepsy syndrome. EEG-based diagnosis of migraine have 88.4% diagnostic accuracy.

Eye Exam

This test measures the amount of pressure to compress a portion of your cornea. Pressure readings help the doctor to diagnose and keep track of glaucoma. Migraine symptoms include visual changes, loss of vision, sensitivity to light or eye pain.

Therefore it makes sense to undergo an eye exam to preclude an eye injury or other eye disorder which may be responsible.

BACKGROUND- SOME CONCEPTS ABOUT PATHOPHYSIOLOGY AND THE THERAPEUTIC FIELD OF MIGRAINE

Migraine has been listed by World Health Organization (WHO) amongst top 10 most disabling conditions.[7-13] Thus, it is important for neuro-ophthalmologists to be in-line with the advances in migraine therapies (Figure 3).[12-18]

Migraine has very tortuous pathophysiology, including the central and peripheral nervous systems.[7,14] A somatosensory input involves pseudo-unipolar trigeminal and upper cervical branches.[7] There is a physiology for each stage of migraine attack, including prodrome, aura, and postdrome.[7,9] In an acute migraine attack, a trigeminal vascular system is activated.[7,9] This system involves trigeminal nuclei in brainstem, trigeminal

Figure 2: Currently used diagnosis methods for migraine detection

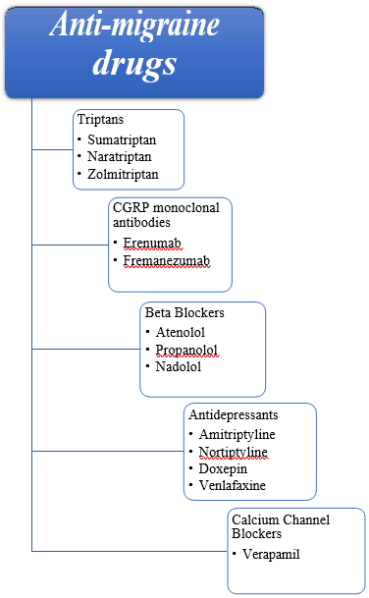

Figure. 3: Therapeutical Classification of anti-migraine drugs

ganglia, and ophthalmic division that invigorate blood vessels and subserve the pain.[7,15] With an activated pathway, the trigeminal nerves release neurotransmitters such as calcitonin-gene related peptide (CGRP), Substance-P, glutamine, pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38). The levels of these peptides are elevated during the migraine headache attack.[7,15]

ADVANCES IN ACUTE MIGRAINE THERAPY

Three over-the-counter drug products that have gained approval by the FDA for migraine headaches are:

- Excedrin® Migraine
- Advil® Migraine
- Motrin® Migraine Pain

Prescription Drugs for Migraine Headaches Include[2]

Medications for migraine pain relief work best when taken during the first sign of a succeeding migraine, as soon as the onset of signs and symptoms for migraine (Figure 4). Medicaments that are used to treat migraine include:

"The newest drugs for the acute treatment of migraine are Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant), both orally-administered calcitonin gene- related peptide (CGRP) receptor antagonists (gepants)"

ADVANCES IN MIGRAINE PREVENTION

Prevention is indicated when migraine is too frequent or severe to face it recurrently. OnabotuliniumtoxinA is approved for the prevention of chronic migraine and was the first drug specifically mandate for that disorder.[2]

Later on, with the arrival of monoclonal antibodies for disorder modification, anti-CGRP monoclonal antibodies evolved as first "designer drug" for migraine prevention[2]. Although many pieces of evidence support the therapeutic classes of drugs (calcium-channel blockers, triptans, beta-blockers, etc.,), monoclonal antibodies are specific therapies for preventing chronic and episodic migraine.[2] These monoclonal antibodies do not cause liver toxicity as they do not cross the blood-brain barrier and hence are metabolized by the reticuloendothelial system. They are administered as SC and

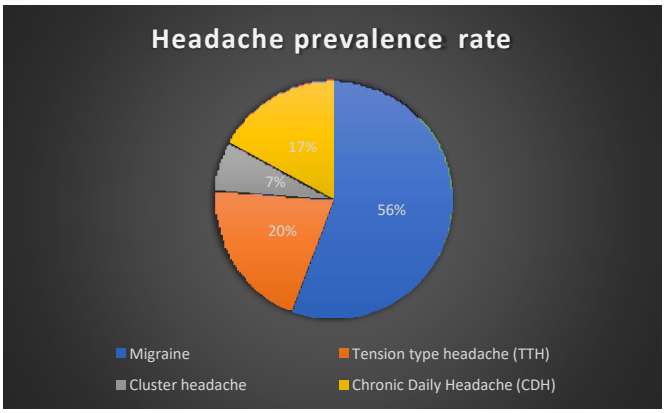

Figure 4: Migraine Headache Prevalence Rate

Table 1: Comparison chart of FDA approved neuromodulation devices

Sr. No.	*Parameters*	*Gamma Core*	*eNeura*	*Nerivio*	*Cefaly*
1.	Company Name	Electro Core	eNeura Therapeutics	Theranica bio- electronics	CEFALY Technology
2.	Price	$598 per month	$100 – $150 a month for unlimited use	$99	$299 and $25 for a set of 3 reusable electrodes
3.	Country	Morris Plains, NJ,	San Francisco, CA	USA	Darien, Connecticut, USA
4.	Approvals	FDA (only for cluster headaches and not migraines)[18]	FDA	FDA Authorized in USA and Europe (first FDA approved for acute migraine treatment)[4]	FDA
5.	Advantages	Can be used multiple times a day or month[10]	rTMS doesn't cause seizures or require sedation with anesthesia	Drug-free	Drug-free Wireless Portable
6.	Limitations	Application site reaction (irritation, parasthesia, rash) Muscle pain/twitching	Bigger in size, momentary lightheadedness and ringing in the ears during the treatment[16]	Software failure may directly result in injury, user error that may cause discomfort, injury or delayed t/t, sensations in the extremity[17]	Skin irritation may develop from the sticky electrode patches, contraindicated with skin abrasion forehead[7]
7.	Working principle	Stimulates the vagus nerve through neck skin hence blocking pain signals caused by migraine[7]	Uses pulses of magnetic energy to disrupt the waves from brain	Works by stimulating C and A delta fibres in upper arm[9,17]	Works by stimulating trigeminal nerve
8.	Accuracy rate	56.3% (in 1-hour) 64.6% (in 2 hours)	50–60%	66% 37% (complete alleviation of headache)	46%

IV and have a long half-life, so they are given on a month-to-month basis.[2]

ADVANCES IN NEUROMODULATION DEVICES FOR MIGRAINE

Neuromodulation is used for the treatment of both acute and chronic migraine (Table 1). It has been used for years for treatment of epilepsy and mostly in depression[2]. Although many neurostimulators require surgical intervention for placement,[2,11] Four devices approved by FDA are non-invasive. These devices are:- vagus nerve stimulation (Gamma Core), supraorbital stimulation (Cefaly), single-pulse transcranial magnetic stimulation (eNeura) and remote electrical neuromodulation (Nerivio). These four devices are available by prescription (Table 1).[2]

These devices are potent enough for migraine treatment in pregnancy and other vulnerable groups.[19-23] But the below drawbacks renders them ineffective:

Gamma Core

Though being effective for cluster headaches yet not approved for migraine, limitations such as Irritation at target site; Parasthesia; Vasovagal syncope; etc., limits their use.[18]

eNeura

This device developed by eNeura Therapeutics is effective for acute migraine and prophylaxis (aged 12 years or older) and uses pulses of magnetic energy to block pain transmission waves from brain. But has the main drawbacks- Bigger in size (weighing 1.5 kg); Tinnitus; Lightheadedness.[16]

Cefaly

This device stimulates trigeminal nerve with an accuracy rate of about 46%. Though FDA approved, this device has major limitations like skin irritation due to sticky electrode patch; unknown for use in pregnancy and people having pacemakers; strange and unusual sensation post- treatment.[7]

Nerivio

This drug-free, smartphone-controlled, first FDA-approved device for acute migraine has the mechanism of blocking pain transmission by stimulating C and A delta fibres in upper arm via an electrical signal.[7,9,17-26] Though effective with more than 50% accuracy rate, it has many drawbacks- Software failure ultimately resulting in patient injury and delay in the treatment; Lower accuracy rate for complete alleviation of headache; Irritation at the site of application; Muscle spasm; Re- usable for only 12 treatments.[9]

PHOTO-BIOMODULATION (PBM) FOR MIGRAINE TREATMENT

This approach, adopted by North American Association of Photo-Biomodulation Therapy, refers to a non-thermal process that utilizes non-ionizing light sources with visible and infrared spectrum (Figures 5 and 6).[27-30] This method involves endogenous chromophores, which excite photochemical events. Therefore, these events lead to therapeutic effectiveness in relieving pain or inflammation and promote wound healing and tissue regeneration[30].

In this method, light photons penetrate the skin and stimulate the endogenous light receptors, providing a therapeutic response and hence can be used therapeutically to decrease the pain[30].

Parameters of Photo-Biomodulation (PBM)

The light parameters and the doses implemented are fundamental in PBM. Low level light therapy indicates employing the light in the red or near-infrared region, having wavelengths in the range of 600 to 700 nm and 780 to 1100 nm, and the laser or LEDs typically with an irradiance or power density between 5 $mW.cm^{-2}$ to 5 $W.cm^{-2}$. Such irradiation can be in a continuous wave or a pulsed light consisting of a relatively low-density beam (0.04 – 50 $J.cm^{-2}$), whereas the output power can vary widely from 1 mW upto 500 mW in order not to allow thermal effects.

Moreover, red/NIR light is selected because of its maximum penetration by the tissue at the designated wavelength range and because of lower scattering and absorption by tissue chromophores. Continuous or pulsed light sources have

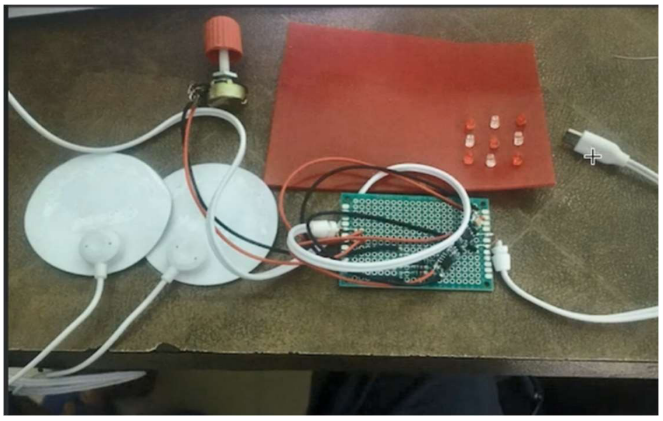

Figure 5: Proof of Concept of the device in progress

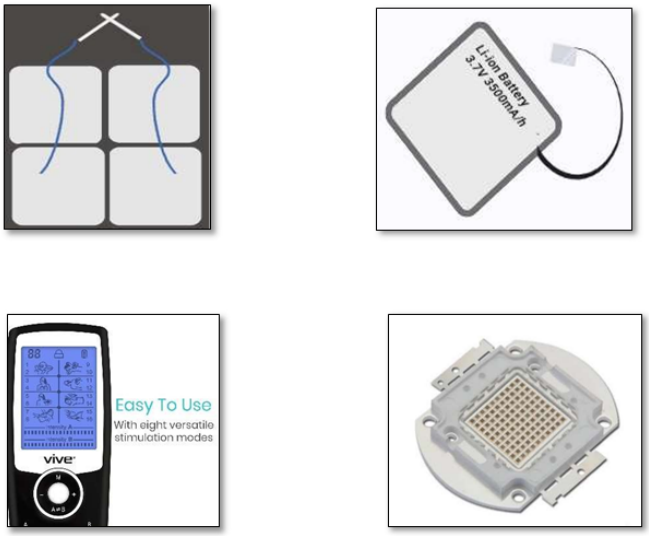

Figure 6: The above figure shows- (a) Carbon-hydrogel electrode patch which can be reused multiple times; (b) Lithium-ion battery of 3500 mAh energy without having memory effect; (c) Hand-held programmer device for adjusting the intensity level with different stimulation variations; (d) Infrared radiation chip having wavelength of 680–1050 nm

both been utilized. The studies done for PBM on acute pain and preoperative analgesia showed that a single treatment (usually 30–60 seconds) is enough to cause analgesia, but more treatment sessions are applicable for chronic pain and few degenerative conditions.

In a study conducted in 2016 to evaluate the effectiveness of red light for migraine pain relief, a near-infrared laser of 830 nm was applied to masseter and mandibular muscle tender points for 34 seconds.[29-32] Researchers measured blood flow velocity and neurotransmitter levels, specifically serotonin and cholinesterase, before and 3 days post-treatment. They found a decrease in blood flow velocity and an increase in neurotransmitter levels 3 days post-treatment.[29] Also, 64% reduction in pain was found post-treatment. From this study, the researchers concluded that red light therapy has the potential to reduce migraine pain.[29]

CONCLUSION

The prevalence rate of migraine is more than 30% worldwide.[2] Devices for migraine treatment is the locus of research for many neurologists. These devices can be highly effective in developed and underdeveloped countries. These devices are designed to provide immediate relief from migraine pain and completely alleviate headaches. After going through various articles and understanding them, a modification can be done to the recently available devices for migraine treatment by using the near infrared radiations (probably red light) to block the pain transmission due to their proven use in other brain-related disorders diagnosis. It has been turned up in about a thousand scientific journals with potential harmless therapeutic efficacy for many human disorders.[22] It is depicted in upregulating the expression of reactive oxygen species (ROS), modulating the impression of genes in cDNA microarray studies and transcranial PBM, which can reduce the damage from experimentally induced strokes in rat models.[20-22] Recent advances have produced good focalization of stimulation in the brain centers, and selective stimulation of each brain area has also been reported. As the interaction between nerves and various biomedical fields has improved, it is essential to have a new design for the migraine treatment that can reach out to the patients hustle-free, hence providing them the treatment at the right time.

FUTURE RESEARCH APPROACH

Prototype Design

Key Requirements for Prototype Designing

Considering the above limitations, a more advanced form of this device is being made. Certain Standards of the International Organization for Standardization (ISO) 13485 and ISO 10993-1 are considered for designing and developing a medical device. These standards work on risk management and risk-based decision of medical devices.[3]

Working of the Device

Using all the requirements, a low-cost device is being designed to mitigate migraine and alleviate the symptoms associated with it.[3,4]

Proposition for theAabove Limitations

Based on the above specifications, we present a modified version of Nerivio device using near infrared radiations for clinical use in managing migraine headaches with aura. This is because Nerivio is a highly advanced device with more patient compliance than other devices and modification of just two to three factors in Nerivio could ultimately make it more advanced with improvised accuracy, hence increasing its spectrum of effectiveness.

No doubt, PBM has been the locus of research for many researchers, shedding light on its underlying mechanism for the use in prototyping the above-mentioned device may direct to a better conception of the effectiveness of Photo-Biomodulation.

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