An overview of migraine disease with modern options for treatment and future aspects

By

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Brac University
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Declaration

It is hereby declared that-

1. I completed the project as part of our degree program at Brac University.
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Approval

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Ethics Statement

The study does not involve any kind of animal and human trail.

Abstract

Migraine is one amongst the most common primary headache kinds and can affect anyone at any age which is typically distinctive feature that moderate to intense and sudden pain that could be associated with phobic reactions to light, sound, or smell as well as nausea. Although the precise etiology of migraine is unknown, a variety of behavioral, environmental, nutritional, viral, chemical, and hormonal factors might cause it to occur. Therefore, the most straightforward method of limiting headache recurrence could be to avoid the triggers at all costs. In recent years, a variety of acute and preventative treatment programs have been developed to provide patients with relief from migraine attacks. Simple analgesics to more modern electrical gadgets are just a few of the possibilities for treating pain. All of these possibilities for treatment aim to reduce migraine sufferers' suffering. As of yet, these treatments do not, however, work to treat migraines. Therefore, ongoing research and studies are being conducted to find ways to treat this chronic pain, and it is crucial to keep both patients and doctors informed about the most recent developments in this area. Actually, it can be argued that having this level of sophisticated understanding will make managing migraines more effective. Therefore, the purpose of this overview paper is to compile nearly all migraine-related treatments for pain into a single academic study, including cutting-edge methods that are now in clinical testing. Additionally, a compilation of each treatment option's potential adverse effects and success rates is also provided. This information can be utilized to suggest some of the most effective and well-liked treatments for various sorts of migraine patients.

Keywords : Migraine suffering, Migraine treatment, Chronic pain, Migraine attack

Dedication

I dedicate this project to my loving and supportive parents.

Acknowledgement

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List of acronyms

AED = Anti-epileptic drug

ASA = Acetylsalicylic acid

CGRP = Calcitonin gene-related peptides

CNS = Central nervous system

FDA = Food and Drug Administration

GABA = Gamma-aminobutyric acid

HM = Hemiplegic migraine

ICHD = International Classification of Headache Disorders

MAO-A = Monoamine oxidase A

MOH = Medication-overuse headache

NIH = National Institutes of Health

NSAIDs = Nonsteroidal anti-inflammatory drugs

WHO = World Health Organization

5-HT = 5-hydroxytryptamine

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Chapter 01 : Introduction

Migraine is a complex neurovascular condition marked by recurrent headache attacks (Goadsby PJ, Lipton RB, Ferrari MD, 2002), affects 14% of the world's population and is more common in women (Lipton RB, Bigal ME, Diamond M, et al, 2007), making it the most common cause of disability in people under the age of 50. Unilateral, pulsing headaches of moderate to severe severity are the hallmark of migraine attacks, which are commonly accompanied by other symptoms such nausea, vomiting, photophobia, and phonophobia (Dodick DW. Migraine. Lancet, 2018). About half of migraineurs experience an aura, which consists of various sensory signs and signs that typically persist 5 to 60 minutes before a headache attack. However, when a patient reports having more than four attacks in a month, they are often given preventative medications which comprise both abortive drugs for acute attacks and preventive drugs (Lionetto L, Capi M, Curto M, et al. Rimegepant. Drugs Future, 2019). In order to cure acute episodes, migrants frequently self-prescribe NSAIDs, acetaminophen, and other generic medications (Lampl C, Voelker M, Diener HC, 2007, Hougaard A, Tfelt-Hansen P, 2015). However, these treatments have a history of producing unsatisfactory results. NSAIDs and triptans, the first-line specific migraine acute medication have equivalent efficacy, according to numerous randomized clinical trials (Lampl C, Voelker M, Diener HC, 2007, Hougaard A, Tfelt-Hansen P, 2015). Although 5-HT1B/1D receptors were later recognized to modulate neuropeptide release (Goadsby PJ, Edvinsson L, 1994; Haanes KA, Edvinsson L, 2019), the first identified migraine-specific therapeutic mechanisms were triptans' vasoconstrictive effect (mediated by the agonism of 5-HT1B/1D receptors) and modulation of neuroactive compound release (mediated by the agonism of 5-HT1F receptors). Triptans are ineffective for 30–40% of migraine sufferers, and their use is contraindicated in people with cardiovascular diseases who need other specific acute therapies (Kuca B, Silberstein SD, Wietecha L, 2018). In order to develop new and efficient antimigraine drugs, various molecular targets have been discovered in recent years. Since the late 1980s, it has been demonstrated that CGRP, a potent vasodilator produced by the trigeminal sensory nerves in response to vasoconstriction, has a significant role in the pathophysiology of migraines (Edvinsson L, Haanes KA, Warfvinge K, 2015; Edvinsson L, Haanes KA, Warfvinge K, 2012). It modulates pain transmission, participates in neuronal inflammation (a contentious aspect of migraine pathogenesis) and releases from the trigeminal ganglion when a migraine attack occurs (Goadsby PJ, Edvinsson L, Ekman R, 1990; Ramachandran R, 2018). It is expressed in sensory neurons, the trigeminal ganglion, and the dorsal root ganglia. Gepants, also known as CGRP receptor antagonists, have just recently been identified and are currently undergoing clinical trials to determine their safety and efficacy as novel acute migraine treatments.

1.1 Overview of migraine disease

A neurological sensory disease that also has an impact on the cardiovascular system is migraine. According to Gupta, Gupta, and Fields (2015), it is essentially a self-restricting gray matter defect. According to Wood, Goadsby, Lipton, and Ferrari (2002) and Pietrobon & Moskowitz (2013), the hypothalamus, cortex, trigeminal nerve, brainstem and meninges are all implicated in migraines. According to Gupta et al. (2015), the connection of afferent nerves within the meningeal blood artery is what causes headaches. According to Burstein, Noseda, and Borsook (2015), migraine is a complex, yet common illness characterized by recurrent headaches as well as autonomic symptoms such hypersensitivity to sound and light, nausea, and vomiting. Usually starting in adolescence or around puberty, it affects more women than men (Bigal & Lipton, 2009; Leonardi, Steiner, Scher, & Lipton, 2005). Around 20% of people worldwide will get migraines at some point in their lives. The World Health Organization (WHO) assesses the global burden of disease for 2012, and due to the disease's extreme prevalence, it has been ranked among the top 40 causes of disability worldwide. However, a lot of individuals disregard it as a bother (Welch & Goadsby, 2002).

1.2 Classifications of migraine

According to the International Classification of Headache Disorders (ICHD) criteria (Table 1.1), there are two types of migraines: migraine with aura and without aura (ICHD, 2013). According to the frequency of attacks, this classification approach classifies migraine and subsequently organizes the different migraine types, giving the most severe types of headaches priority (Antonaci, Ghiotto, Pucci, & Costa, 2016). Hemiplegic migraine, menstruation-related migraine (MRM), chronic migraine and complicated migraine are a few other types of migraine (Al-Quliti & Assaedi, 2016).

Table 1.1: Distinct traits of migraine either with or without aura

Migraine without aura	Migraine with aura
● At least 5 attacks Headache assaults last for four to seventy-two hours chronic headaches contain two of the following characteristics: ● Headaches that are only on one side ● Stabbing pain ● Moderate to severe pain ● Regular vigorous exercise exacerbates symptoms, or symptoms impede ordinary physical activity Related symptoms: ● Vomiting or nausea ● Light and sound sensitivity	● At least two attacks Aura (no muscle twitching): ● Totally visual symptoms which is reversible ● Totally reversible sensory symptoms ● Dysphasia is completely reversible At least two of these following traits must be present: ● Homonymous hemianopsia (loss of visual field) ● One-sided sensory symptoms ● Aura gradually growing ● Symptoms lasting 5 minutes or more ● Headache begins during the aura or within 60 minutes of the aura.

The rare autosomal dominant kind of migraine known as the "hemiplegic migraine" (HM) is marked by reversible hemiplegia and only a few additional neurological signs, including seizures and coma. As a sporadic or hereditary disorder, it may manifest (Russell & Ducros, 2011). It is challenging to treat chronic migraine because it has an unidentified pathophysiology, multiplex co-morbidities, and an inadequate response to existing pharmacological treatments. Serrano, Turkel, Buse, Manack, and Lipton (2010). The International Category of Headache Disorders (ICD) of the International Headache Society (IHS) defines chronic migraine as "migraine headache occurs on a minimum of fifteen days

per month for a period of time exceeding three months in an absence of medication overdose." On the other hand, menstrual migraine (MM) or migraine linked to menstruation (MRM) attacks usually cause more impairment, are more severe, and respond less to therapies than other types of migraines (Grazzi et al., 2016). Nearly 90% of women who experience migraines during their periods have MRM (MacGregor, 2008). Migraines that exclusively occur on days -2 to +3 of menstruation in 2 to 3 consecutive menstrual cycles are known as MM without aura. Estrogen levels are suggested to protect against MM while providing a protective effect when they are stable or increasing. According to MaxGregor (2008) and Mathew, Dun, and Luo (2013), sudden estrogen withdrawal can cause migraines. Finally, distinct clinical migraine symptoms are a sign of a complicated migraine. It imitates and may provoke disorders such as stroke, transient ischemic attack, and non-epileptic event (Gupta et al., 2015).

1.3 Migraine etiology

Emotional and physical stress can trigger migraines. Studies have shown that stress reduction techniques such as mindfulness meditation and relaxation techniques may help reduce the frequency and intensity of migraines. (Buse, S. D., et al. (2019). Certain foods such as aged cheese, chocolate, and red wine have been identified as common triggers of migraines. Avoiding these foods or limiting their intake may help reduce the frequency and intensity of migraines. (Gelfand, A. A., & Goadsby, P. J. (2019). Hormonal changes in women that occur during menstruation, pregnancy, and menopause can trigger migraines. Hormonal therapy may be prescribed to manage these triggers in some cases. (Marmura, M. J., & Silberstein, S. D. (2015). Changes in sleep patterns: Lack of sleep or changes in sleep patterns can trigger migraines. Maintaining a regular sleep schedule and getting adequate sleep may help reduce the frequency and intensity of migraines. (Noseda, R., & Burstein, R. (2020). **Table 2.1** list of the migraine etiology (Pavlovic, Buse, Sollars, Haunt & Lipton, 2014; Hougaard, Amin, Hauge, Ashina & Olesen, 2013; Hoffman & Recover, 2013). Environmental factors such as changes in weather, strong odors, and bright lights can trigger migraines in some people. Identifying and avoiding these triggers may help reduce the frequency and intensity of migraines. (Zhang, Y., et al. (2018).

Table 2.1 Potential etiology for migraine

Behavioral	● Lack of sleep ● Fasting ● Emotions
Environmental	● Visual stimulation ● Weather changes ● Particular smell
Infection	● Infections of the respiratory system
Nutritional	● Mature cheese ● Alcohols ● Caffeine ● Citrus fruits
Chemical	● Nitrates ● Tyramine
Hormonal	● Menstrual cycle

1.3.1 Behavioral etiology

Episodic migraine is a debilitating neurological disorder characterized by recurring attacks of moderate to severe headache pain, often accompanied by nausea, vomiting, and sensitivity to light and sound. While medication management is often the first line of treatment for episodic migraine, behavioral management strategies can also be effective in reducing the frequency and severity of attacks. One such strategy is cognitive-behavioral therapy (CBT), which aims to change negative patterns of thought and behavior that may contribute to migraine episodes. In a randomized controlled trial of 232 adults with episodic migraine, participants who received

CBT reported significantly fewer migraine days per month than those who received only headache education (Houle et al., 2019). Another behavioral management approach for episodic migraine is relaxation training, which involves teaching patients to reduce muscle tension and promote relaxation in response to stressors that may trigger migraine attacks. In a randomized controlled trial of 67 patients with episodic migraine, participants who received relaxation training reported a significant reduction in headache frequency and intensity compared to those who received only medication management (Mehdizadeh et al., 2019). These studies suggest that behavioral management strategies, such as CBT and relaxation training, can be effective in reducing the frequency and severity of episodic migraine attacks. Health care providers may want to consider incorporating these approaches into their treatment plans for patients with this debilitating condition.

1.3.2 Environmental etiology

Migraine is a complex neurological disorder that can have multiple etiologies, including environmental factors. Some of the most commonly reported environmental triggers for migraines include weather changes, bright lights, strong smells, certain foods, and stress. Research studies have suggested that exposure to air pollutants, such as nitrogen dioxide (NO2), can also increase the risk of migraines. A study conducted by Hanigan et al. (2016) found that people living in areas with high levels of NO2 were more likely to experience migraines than those living in areas with low levels of NO2. The study also suggested that exposure to other air pollutants, such as particulate matter, could contribute to the development of migraines. In addition to air pollution, other environmental factors such as noise, temperature changes, and barometric pressure fluctuations have also been linked to migraines. A study by Grazzi et al. (2013) found that changes in barometric pressure were the most commonly reported environmental trigger for migraines in a sample of migraine patients. Overall, the evidence suggests that environmental factors play an important role in the etiology of migraines, and that reducing exposure to these triggers may help to prevent or reduce the frequency and severity of migraines in susceptible individuals.

1.3.3 Infectious etiology

A neurological condition called migraine is characterized by repeated headaches that range in intensity from mild to severe and are frequently accompanied by other symptoms like nausea, vomiting, and sensitivity to sound and light. Infectious agents have been proposed as a potential migraine trigger, despite the fact that the precise origins of migraine are not entirely understood. One study that looked into the connection between infectious agents and migraine concluded that illnesses brought on by specific bacteria, viruses, and parasites may help some individuals acquire migraine (Ozturk et al., 2017).

1.3.4 Nutritional etiology

The complex neurological condition known as migraine has been linked to a number of dietary factors. Bic Zorman et al. (2020) looked into the connection between dietary habits and migraine in a group of 178 adults and published their findings in the journal Nutrients. The authors found that a diet high in omega-3 fatty acids, magnesium, riboflavin, and coenzyme Q10 was associated with a lower frequency and intensity of migraines. On the other hand, a diet high in sodium, caffeine, alcohol, and saturated fats was associated with a higher frequency and intensity of migraines. These findings suggest that a balanced and healthy diet can play an important role in the prevention and management of migraines.

1.3.5 Chemical etiology

Migraine is a neurological disorder that is characterized by severe headache, often accompanied by symptoms such as nausea, vomiting, and sensitivity to light and sound. The exact causes of migraine are not clearly known disease but it is believed to involve a combination of genetic and environmental factors, as well as chemical imbalances in the brain. Several chemical etiology have been identified that can contribute to the development of migraine attacks. These include: Serotonin is a neurotransmitter that is involved in the regulation of mood, appetite, and sleep, as well as the constriction and dilation of blood vessels. Imbalances in serotonin levels have been implicated in the development of migraines, and many migraine medications target serotonin receptors to alleviate symptoms (Holland PR, Goadsby PJ, 2018). Histamine is a chemical that is involved in the immune response and

allergic reactions. It is also present in the brain and has been shown to play a role in the development of migraines. Histamine can cause the dilation of blood vessels and stimulate the release of other chemicals that contribute to inflammation and pain (Vgontzas A, Cui L, Merikangas KR, 2017). Calcitonin Gene-Related Peptide (CGRP) which is CGRP a neuropeptide that is involved in the regulation of pain and inflammation. Elevated levels of CGRP have been found in individuals experiencing a migraine attack, and drugs that target CGRP have been developed to treat migraines (Edvinsson L, 2015). Nitric oxide is a gas that is produced by cells in the body and is involved in many physiological processes, including the regulation of blood flow. Nitric oxide can cause the dilation of blood vessels, which can contribute to the development of migraines (Edvinsson L, Tfelt-Hansen P, 2008).

1.3.6 Hormonal etiology

Migraine is a neurological disorder characterized by recurrent headaches, often accompanied by visual disturbances, nausea, and sensitivity to light and sound. Hormonal changes have been identified as one of the possible triggers of migraine headaches. A study by MacGregor and colleagues (2018) investigated the role of hormones in migraine and found that estrogen withdrawal, such as during the menstrual cycle or with the use of hormonal contraceptives, can trigger migraines in some women. The study also found that hormonal fluctuations during pregnancy and menopause can affect migraine frequency and severity. Furthermore, a review article by Pavlovic and colleagues (2018) suggested that fluctuations in other hormones, such as progesterone, testosterone, and cortisol, may also play a role in the pathophysiology of migraine. Overall, the evidence suggests that hormones, particularly estrogen, play a significant role in the etiology of migraine headaches.

1.4 Consequences of migraine : Impact

Migraine is a neurological disorder that affects approximately 15% of the global population. The impact of migraine can be quite significant, as it is associated with significant disability, lost productivity, and reduced quality of life. According to a systematic review and meta-analysis of the global burden of migraine published in the Journal of Global Health in 2018, migraine was found to be the second leading cause of years lived with disability (YLDs) globally, accounting for 45.1 million YLDs in 2016. The study also found that migraine was

connected to a high burden of disability-adjusted life years (DALYs), with an estimated 1.2% of total DALYs attributed to migraine in 2016.

1.4.1 Socio-economic effect

Migraine disease is a debilitating neurological condition that affects millions of individuals worldwide. The socio-economic impact of migraine disease is significant, as it can lead to decreased productivity, increased healthcare costs, and reduced quality of life. According to a study published in the Journal of Headache and Pain, the direct and indirect costs of migraine disease in the European Union (EU) in 2019 were estimated to be € 111 billion ($126.1 billion USD). This covered both medical expenses and missed wages resulting from presenteeism and absenteeism (i.e., decreased productivity at work) caused by migraine. Furthermore, individuals with migraine disease often experience reduced quality of life, including increased levels of anxiety and depression, decreased social functioning, and a higher likelihood of disability. This can have a significant impact on their personal relationships and employment opportunities. In conclusion, migraine disease has a significant socio-economic impact on individuals and society as a whole. Further research and resources are needed to improve the migraine evaluation, therapy, and control disease to reduce its burden on individuals and the economy.

1.4.2 Effects on health

Migraine disease can have a significant impact on an individual's health, including physical, emotional, and social consequences. According to a study by Buse et al. (2019), individuals with migraine have higher rates of comorbidities such as depression, anxiety, sleep disorders, and chronic pain conditions. Migraine also increases the risk of cardiovascular disease, stroke, and other neurological conditions. Furthermore, migraine can significantly impair an individual's quality of life, affecting their ability to work, socialize, and participate in daily activities. Migraine attacks can be debilitating, lasting for several hours to days, and are often accompanied by symptoms such as nausea, vomiting, and sensitivity to light and sound. Overall, migraine disease can have a significant impact on an individual's physical and mental health, as well as their social functioning and overall quality of life.

Chapter 02 : Methodology

To gather all the information included in this review study, a comprehensive literature review was conducted. Information was gathered from a variety of reliable sources, including books, newspapers, periodicals, online scholarly databases, and several peer-reviewed publications. The following is a selection of a few of the many articles that were exhaustively searched for the current study. The Pain & Headache Journal, Headache, migraine, and facial pain. Current Neurology Opinion, The Journal of Neuroscience, The Journal of the American Medical Association and The Lancet Neurology. One of the most common headache illnesses, migraine, requires adequate management in today's society. To come up with the ideal strategy for managing migraines, researchers are consistently conducting several experiments and studies. Several acute and preventive migraine treatment options have become common through time. The objective of this review paper is to synthesize almost all migraine treatment options, including those that have recently been established, and to support the creation of a specialized treatment plan for migraine patients. Investigating the Relationship between Migraine Frequency and Sleep Quality in Adults by Stam, A. H., Louter, & Ferrari (2019). 100 adults with a clinical diagnosis of migraine illness were the participants. Age range: 18-65 years both male and female participants will be included. To procedure there's recruitment of participants will be recruited from neurology clinics and through advertisements in local newspapers and online forums. For screening participants will be screened to ensure that they meet the diagnostic criteria for migraine disease as outlined by the International Classification of Headache Disorders (ICHD-3). In addition, for data collection Participants will complete a questionnaire that includes demographic information, medical history, migraine characteristics (frequency, duration, intensity), and sleep quality (measured using the Pittsburgh Sleep Quality Index). Lastly, for data analysis, statistical analyses will be conducted to examine the relationship between migraine frequency and sleep quality, as well as any potential moderating factors (e.g., age, gender, medication use). These are the methodology for migraine disease. It is important to have a clear idea about migraines or neurological disorders.

Chapter 03 : Migraine management

Identification of numerous trigger variables, pain control during headache attacks, and preventative medicine are all important aspects of migraine care (Matarese & Mack, 2010). Assessing potential exacerbating variables or triggers should be the first step in the therapy of migraine once it has been diagnosed. Since migraine can have a significant impact on a patient's family life as well, the next step should involve educating both the patients' relatives and themselves (DeMaagd, 2008). Although it has been demonstrated that identifying migraine triggers is helpful, patients must have realistic expectations because doing so will only reduce the incidence of migraine headaches is not completely eradicate them (Matarese & Mack, 2010). Acute or abortive and preventative drugs have historically been used in the pharmaceutical therapy of migraines (Silberstein & Goadsby, 2002). Acute therapies help to alleviate discomfort and potential disability associated with attacks while preventative treatments try to reduce attack intensity and frequency over the long term. As a result, both acute and preventive medications are necessary for an efficient migraine management strategy (Miller, 2012).

3.1 Acute migraine treatment

Acute migraine treatment typically involves the use of abortive medications, such as triptans and nonsteroidal anti-inflammatory drugs (NSAIDs). The goal of these medications is to relieve pain and other symptoms associated with migraines as quickly as possible. One study published in the Journal of Headache and Pain found that a combination of sumatriptan (a triptan medication) and naproxen (an NSAID) was more effective in treating acute migraines than either medication alone (Cady, 2013). Another study published in the Journal of the American Medical Association found that the use of intranasal lidocaine (a local anesthetic) was effective in reducing pain associated with migraines (Lipton, 2014).

3.1.1 The objectives of acute migraine disease

The objectives of acute migraine disease can vary depending on the individual patient and the severity of their condition. However, some common objectives of treating acute migraine disease include relieving pain and associated symptoms, preventing recurrence, improving function and quality of life, and minimizing medication side effects. One study by Lipton et al. (2018) aimed to develop a patient-centered definition of successful acute migraine treatment. The authors found that patients prioritize pain relief and the ability to return to normal activities as the most important treatment outcomes. They also identified a set of secondary outcomes, including freedom from symptoms such as nausea and sensitivity to light and sound, and a rapid onset of action of the medication.

Table 3.1 A frequent mix of analgesics, NSAIDs, 5-HT receptor agonists (triptans), ergot derivatives, antiemetic medicines, and a few more pharmaceuticals are listed in **Table 3.1** as common pharmacological therapy utilized in the acute management of migraine. To reduce a migraine attack, some people may require a combination of more than one of the following medications (Lipton et al., 2001; Diamond, Wenzel & Nissan, 2006; Silberstein, 2000; Dipiro et al., 2005; Koda-Kimble, 2005).

Table 3.1 : Drug used in the immediate treatment of migraine

Analgesics and NSAIDs
● Acetylsalicylic acid (ASA) and aspirin: 650–1,000 mg every 4–6 hours, up to 4,000 mg per day (e.g., Bayer Aspirin). ● Acetaminophen/Paracetamol: 325–1,000 mg/4-6 hours up to 4,000 mg/day (Tylenol, for example). ● Ibuprofen: 200–400 mg every 4–6 hours, up to 1200 mg per day (Advil, for example). ● Naproxen Sodium: 220 mg every 6 to 8 hours with a daily maximum of 660 mg (example: Naprosyn). ● • Other: diclofenac potassium (Cataflam), ketorolac (Toradol, etc.)

Some combination of over-the-counter products
● Anacin (ASA 400 mg plus 32 mg of caffeine) ● Vanquish (227 mg ASA, 250 mg APAP, and 33 mg caffeine) ● Bayer Extra Strength (APAP 500 mg with 32.5 mg of caffeine)
Triptans (serotonin receptor agonists)
● Sumatriptan (e.g., Imitrex) ● Eletriptan (e.g., Relpax) ● Rizatriptan (e.g., Maxalt) ● Zolmitriptan (e.g., Zomigoro) ● Naratriptan (e.g., Amerge) ● Almotriptan (e.g., Axert)

Barbiturates combination products
● Fiorinal: 1-2 pills every 4-6 hours, butalbital 50 mg, ASA 325 mg, and caffeine 40 mg. ● Fioricet: 1-2 pills every 4-6 hours, butalbital 50 mg, APAP 325 mg, and caffeine 40 mg ● Drug use should not exceed two days per week because drug rebound is possible.
Opiate combination products
● Percodan: ASA and oxycodone ● Percocet: APAP and oxycodone ● Darvocet: APAP and oxyphene
Others
● Midrin (sometheptene 65 mg, dichloralphenazone 100 mg, and APAP 325 mg) is a sympathomimetic. ● Depacon (intravenous valproate), an anticonvulsant ● Phenothiazines, such as Thorazine (Chlorpromazine) and Compazine (Prochlorperazine).

Abortive therapies are typically advised to quickly relieve the migraine symptoms since they are superior to preventative therapy in that they can offer complete and quick relief with little to no side effects (Holland et al., 2012). There are two types of drugs available for acute treatment: non-specific and specific. Triptans and ergot derivatives are migraine-specific medicines, while NSAIDs and analgesics are non-specific (Antonaci et al., 2016).

3.2 Non-specific drugs

3.2.1 Simple analgesic agents and NSAIDs

Simple analgesic agents and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of acute migraine attacks. Simple analgesic agents, such as acetaminophen and aspirin, are often used as first-line treatments for mild to moderate migraine attacks. They work by inhibiting the production of prostaglandins, which can cause inflammation and pain. NSAIDs, such as ibuprofen and naproxen, are also effective in treating migraine attacks. They work by inhibiting the production of prostaglandins and reducing inflammation. NSAIDs are often used when simple analgesic agents are not effective, or when the migraine attack is more severe. One meta-analysis by Derry et al. (2013) compared the efficacy and safety of different NSAIDs for the treatment of acute migraine attacks. The authors found that naproxen was more effective than other NSAIDs, such as ibuprofen and diclofenac, in achieving pain relief and reducing migraine-associated symptoms. They also found that the incidence of adverse events was similar among the different NSAIDs studied. Despite the growing usage of the recently launched triptans, NSAIDs continue to be the most popular acute treatment for migraine (Antonaci et al., 2016). Typically, they serve as the major method of stopping migraine attacks (Pringsheim et al., 2016). The anti-inflammatory effects on vasoactive peptide-induced inflammation that may develop during migraine are the likely mechanism of action for this class of medications (DeMaagd, 2008). However, it has been discovered that a set dosage of aspirin (250 mg), paracetamol (200 mg), and caffeine (50 mg) is a better option than the drugs given alone (Diener et al., 2005). Even though the necessary doses may not be tolerated by individuals experiencing concurrent GI symptoms, aspirin monotherapy may still be beneficial for some people (DeMaagd, 2008) About 52% of persons have pain relief from aspirin at a dose of 1000 mg in under two hours, and the dose is good tolerated (Kirthi, Derry, Moore, & McQuay, 2010; Lipton et al., 2005). For adults (18 to 65 years old), Cochrane reviews claimed that a high dose of aspirin (900–1000 mg) is beneficial in the treatment of migraine. While metoclopramide and ASA together lessen the likelihood of nausea and vomiting, they do not significantly improve headache or pain relief (Inglidue & Mounsey, 2014). According to DeMaagd (2008), the pharmacological action of ASA is reportedly similar to that of the other NSAIDs operating on the anti-inflammatory activity in migraine. According to Cochrane studies, ibuprofen, another NSAID, also reduces pain in up to 57% of migraineurs when taken at a dose of 400 mg (Rabbie, Derry, Moore & McQuay,

2010). However, it does not entirely eliminate pain in the majority of patients. The effectiveness of intravenous ibuprofen (800 mg), a potential NSAID formulation for the treatment of migraine, is still being studied (Antonaci et al., 2016).

3.2.2 Barbiturates analgesics

Barbiturates have been historically used for the treatment of migraines, but their use has decreased in recent years due to their potential for abuse and addiction. A study by McAlpine et al. (2019) found that the use of barbiturates in the treatment of migraines was associated with a higher risk of developing medication overuse headaches, which can exacerbate the underlying condition. Therefore, barbiturates are no longer recommended as first-line treatment for migraines.

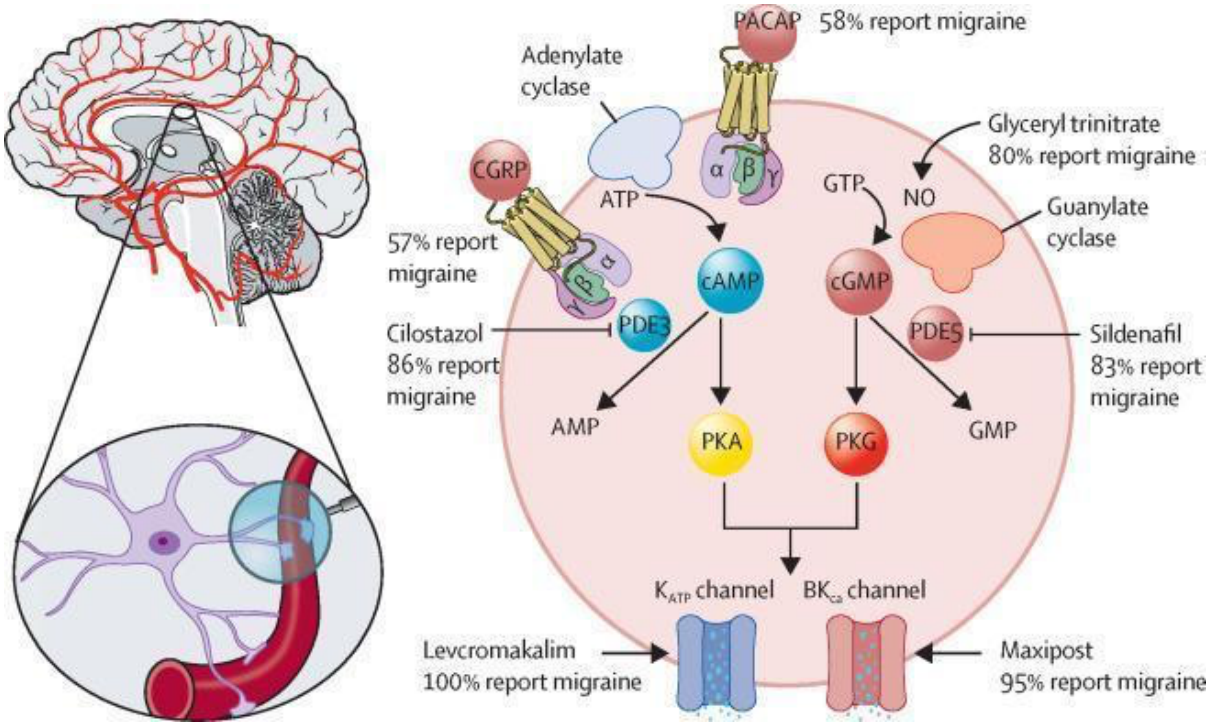
3.2.3 Opiate analgesics

Studies have shown that opioid analgesics can be effective in the acute treatment of migraine headaches, but their use is limited due to potential adverse effects and the risk of developing medication overuse headaches. One such study is "Opioid Use in the Management of Migraine: Insights and Strategies" by Minen and colleagues (2019), published in Pain Medicine. The study reviewed the use of opioids in the management of migraine, including their efficacy, safety, and potential risks. The authors concluded that while opioids can provide relief for acute migraine attacks, they should be used with caution and only when other treatments have failed or are contraindicated.

Figure 1.1 : Diagnosis of migraine

Clinical criteria are used to diagnose migraine, a neurological condition that can be quite debilitating. These criteria fall short because they do not adequately account for the genetic and neurological underpinnings of migraine's heterogeneity. This complexity has sparked a surge in biomarker research to better characterize diseases and find new treatment targets. In this article from the Series, we outline the developments in the fields of genetics, provocative modeling, biochemistry, and neuroimaging research related to the hunt for migraine biomarkers. We also describe problems and potential future developments for each biomarker method. Additionally, we go through the developments in collecting and integrating data from

several biomarker modalities. These initiatives help to produce precision medicine that will benefit future migraine patients. Ashina, M., Terwindt, G. M., Al-Karagholi, M. A., De Boer, I., Lee, M. W., Hay, D. L., Schulte, L. H., Hadjikhani, N., Mollan, S. P., Ashina, H., Schwedt, T. J., & Goadsby, P. J. (2021.



Here are the details about migraine disease in this figure. It shows the mechanism of migraine disease. According to a study by Buse et al. (2012), overuse of acute medications, including analgesics, is common in patients with migraine disease and can lead to medication overuse headache (MOH), a condition characterized by increased headache frequency and severity.

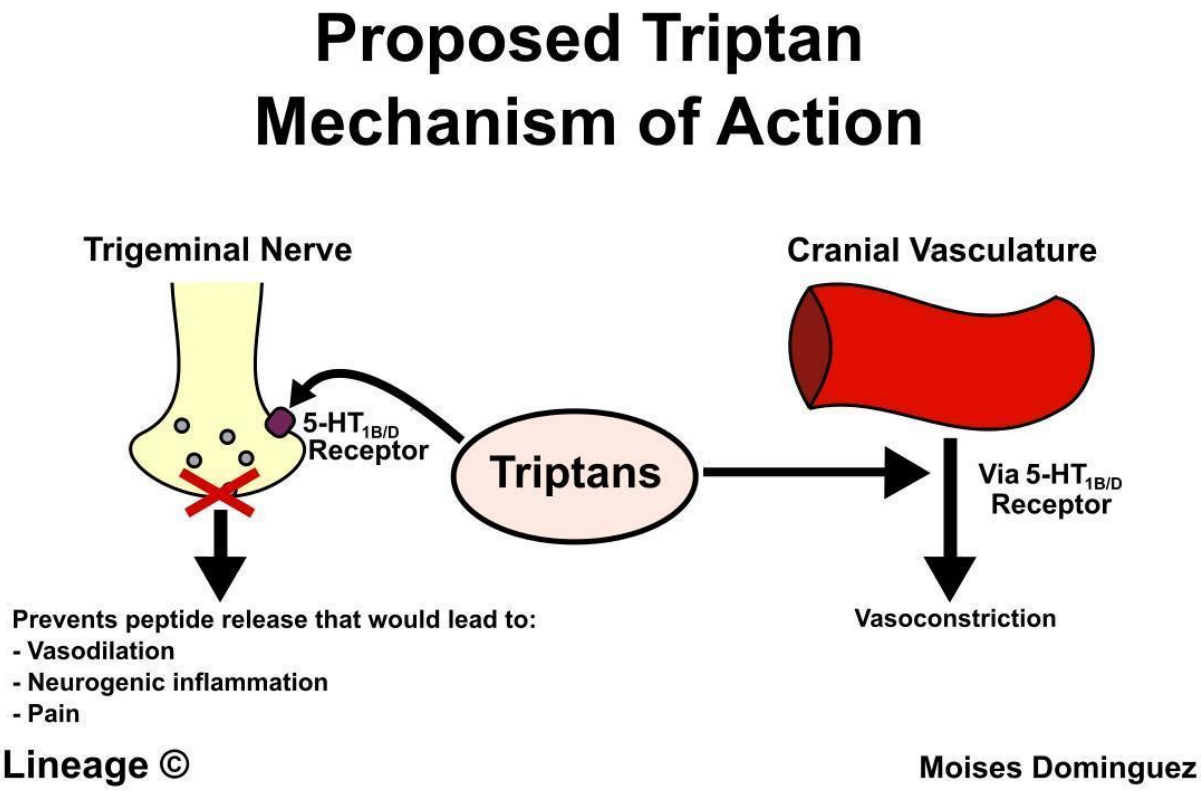
3.3 Migraine specific drug :

3.3.1 Triptans drug

The introduction of triptans represents a significant advancement in the acute treatment of migraine. Since its introduction, this family of drugs has become the first choice for managing abortive migraines, especially for migraineurs who cannot tolerate or do not respond to NSAIDs or simple analgesics (DeMaagd, 2008). The International classification of headache has designated NSAIDs and triptans as the first line of pharmacological treatment for managing migraine disorders (ICHD-3 Beta) third edition treatment algorithm. Central sensitization is a key component of a model of migraine pathogenesis in which neurons in the trigeminal nucleus caudalis (TNC) with dural receptive fields are both excited and sensitized by peripheral stimulation of vascular and dural afferents by electrical, chemical, or mechanical stimuli (Goadsby and Zagami, 1991; Strassman et al., 1996). According to this concept of peripheral and central sensitization, as a migraine attack progresses, spinal and supraspinal nociceptive responses are sequentially recruited, leading to the development of cutaneous allodynia in cranial and non-cranial parts of the body (Burstein, 2001). There is little question as to the existence of triptan receptor mRNA and tripan binding sites inside the central nervous system (CNS), particularly in the dorsal raphe and periaqueductal gray of the midbrain (Bonaventure et al., 1998). The triptans may have CNS effects. The question if CNS effects were indeed necessary for sumatriptan's antimigraine efficacy was raised, however, by the drug's comparatively poor brain penetration (Humphrey et al., 1991). Sumatriptan's potential CNS activities were investigated using hyperosmolar mannitol infusion to disrupt the blood-brain barrier. Only in those circumstances did systemically sumatriptan infusion block the single-unit evoked responses of the TNC (Kaube et al., 1993) and suppress the production of the neuronal activity marker Fos protein (Shepherd et al., 1995). In line with these findings, triptan iontophoresis in the TNC also potently reduced the activity of neurons with dural fields of reception under both evoked and spontaneous stimulation (Storer and Goadsby, 1997). It should come as no surprise that the arrival of more lipophilic triptans increased awareness of the potential advantages of triptan activation in the CNS. For instance, in both electrophysiological and c-fos experiments, zolmitriptan and rizatriptan inhibit the dura-evoked activation of TNC neurons (Cumberbatch et al., 1997; Hoskin and Goadsby, 1998). The greater lipophilicity and better brain penetration of the various triptans are remarkable, but

they do not necessarily translate into much higher clinical efficacy than sumatriptan (Ferrari et al., 2002), despite the evidence for their central modulatory effects.

Figure 2.1 Andrew H. Ahna,b,c and Allan I. Basbaumb,c, (2005)



3.3.2 Triptans efficacy for migraine disease

Cameron, C., Kelly, S., Hsieh, S., Murphy, M. E., Chen, L. S., Kotb, A., Peterson, J., Coyle, D., Skidmore, B., Gomes, T., Clifford, T., & Wells, G. A. (2015) mentioned in article the although triptans are frequently used to treat acute migraines, it is unknown how effective they are compared to other triptans and to non-triptan migraine treatments. To compare the relative effectiveness of triptans (alone or in combination with other medications) for the acute treatment of migraines against other triptan agents, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or anti-emetics, we conducted systematic reviews and network meta-analyses.We looked for randomized controlled studies that contrasted triptans with placebo-controlled or active migraine medications in the Cochrane Library, MEDLINE, and EMBASE databases. Multiple reviewers independently selected the studies, extracted the data, and evaluated the studies' quality. A Bayesian network meta-analysis was used to integrate the outcome data and examine it. Odds ratios, relative hazards, and the absolute probability of response were computed for each outcome. The inclusion criteria were satisfied by 133 randomized controlled trials in total. Triptans at a standard dose reduced headaches in 42 to 76% of patients after two hours, and in 18 to 50% of patients, pain relief lasted for two hours. Triptans at a standard dose gave sustained headache relief after 24 hours to 29 to 50% of patients and long-term pain relief to 18 to 33% of patients. Utilization of rescue drugs ranged from 20 to 34%. Standard dose triptan produced comparable to or better results for 2-hour headache alleviation than ergots (38%) and in comparison to NSAIDs, ASA, and acetaminophen, combination treatment had equal to better results (46 to 52%) and somewhat worse results (62 to 80%). The best results were seen with the individual triptans sumatriptan subcutaneous injection, rizatriptan ODT, zolmitriptan ODT, and eletriptan tablets. Triptans are useful for treating migraines. The majority of triptans are associated with equal or better outcomes when compared to NSAIDs, ASA, and acetaminophen, and regular doses of triptans are linked with better outcomes than ergots. Alternative methods of administration, such as injectables, or the administration of triptans in combination with ASA or acetaminophen may produce slightly better results than conventional dose triptan tablets.

Table 4.1 Triptans may interact with other serotonergic drugs in a negative way (Table 4.1), promoting the risk of serotonin syndrome, which heightens serotonergic activity in the body (Gardner & Lynd, 1998; Shapiro & Tepper, 2007; Eadie, 2001).

Table 4.1 : Common drugs having serotonergic properties

Monoamine oxidase inhibitors (MAOIs)	**Antidepressants**	**Others**
● Selegiline (Emsam) ● Phenelzine (Nardil) ● Tranylcypromine (Parnate)	● Tricyclic: amitriptyline ● Selective serotonin reuptake inhibitors (SSRIs): Fluoxetine (Sarafem)	● Buspirone (BuSpar) ● Lithium ● Dextromethorphan ● Cocaine

There are three types of common drugs that have serotonergic properties.

3.4 Preventive treatment

Migraine disease is a neurological disorder characterized by recurrent episodes of severe headaches, often accompanied by sensitivity to light and sound, nausea, and vomiting. Preventive treatment of migraine disease is important for individuals who experience frequent or disabling attacks. Several preventive treatments have been shown to be effective, including medications, behavioral therapies, and lifestyle modifications. According to a systematic review and meta-analysis conducted by Sun et al. (2021), various pharmacological treatments have been shown to reduce the frequency of migraine attacks, including beta-blockers, antiepileptic drugs, antidepressants, and botulinum toxin. Non-pharmacological interventions, such as cognitive behavioral therapy, biofeedback, and relaxation techniques, have also been found to be effective in preventing migraine attacks. Preventive treatment of migraine disease is important to improve quality of life for individuals with this condition. A combination of pharmacological and non-pharmacological interventions may be the most effective approach for some patients. It is important to discuss preventive treatment options with a healthcare provider to determine the best approach for each individual. American Headache Society. (2019) Migraine is a neurological disease that affects approximately 1 billion people worldwide, with a significant impact on quality of life and economic burden. Preventive treatment is a critical aspect of migraine management and involves pharmacological and non-pharmacological approaches. According to the American Headache Society (AHS), people who encounter four or more headache days per month or who have headaches that seriously lower their quality of life should think about getting preventive treatment for migraine. Beta-blockers, anticonvulsants, antidepressants and monoclonal antibodies are examples of pharmacological preventive therapy. Cognitive-behavioral therapy, biofeedback, relaxation exercises, and dietary changes are examples of non-pharmacological preventive interventions. Only a few of the numerous easily accessible preventive medicines offered are beta-blockers, alpha antagonists, calcium channel blockers, antidepressants, anticonvulsants, botulinum-A, serotonin agonists, and serotonin reuptake inhibitors (SSRIs) (Jackson et al., 2015). To stop migraine attacks, people currently take drugs called angiotensin convert enzymes (ACE) and angiotensin receptor antagonists (ARB) (Rapoport, 1994). **Table 3.2** lists the main medications that have been suggested for use in migraine prevention therapy (Miller, 2012).

Table 5.1 : Important drugs used in episodic migraine prevention

Drug	Dose	Headache attack reduction	Common side effects
Beta blockers ● Propranolol	40-240 mg/day	50%	● Sleep disturbance ● Fatigue ● Depression ● Erectile ● Dysfunction
Tricyclic antidepressant ● Amitriptyline	25-150 mg/day	50%	● Sedation ● Weight gain ● Dry mouth ● Blurred vision ● Constipation ● Mental ● Confusion ● Suicidal ● Tendency
● Nortriptyline	25-150 mg/day		● Urinary retention ● Anxiety ● Sleep disturbance

Anti-epileptics ● Sodium valproate	800-1500 mg/day	30-50%	● Tremor ● Gaining weight ● Nausea
Calcium channel blocker Flunarizine	5-10 mg/day	50%	● Sedation ● Gaining weight ● Depression
Gabapentin	1200-2400 mg/day	50-75%	● Dizziness

These are some main drugs that have been widely used in episodic migraine prevention.

Table 6.1 Some home-message for optimal prevention

- Integrating patients in patient care, we can increase adherence.
- Be aware of co-morbidities and, if at all possible, choose a single medicine to treat a variety of comorbid diseases.
- Patients who are pregnant should receive extra concern, they should be informed of the risks of using contraceptives and other medications during pregnancy.
- Start with a small doses of drug
- Prophylactic drugs must be administered at the recommended dose for 6 to 8 months.
- Avoid administering any interference-causing, contraindicated, or over-the-counter drugs.
- Again evaluation and follow up are also crucial.

(Antonaci et al., 2016) [Table 4.1]

These are some instructions for patients to take good care and for optimal prevention from migraine disease. Keeping a consistent sleep schedule, managing stress through relaxation techniques or therapy, and avoiding trigger foods and beverages can help prevent migraines. Additionally, regular exercise and staying hydrated may also be beneficial.

Chapter 04 : Modern options of treatment for migraine

4.1 Beta adrenergic blockers

The Beta-blockers are the preventative migraine drugs that are most commonly utilized. They are 60-80% effective at reducing attack recurrence, according to various studies (Silberstein & Goadsby, 2002). The central catecholaminergic system, which is what this family of medicines targets, is management of migraines hypothesized to affect the contingent negative variation (CNV), a sluggish and negative brain potential. Beta-blocker preventive treatment normalizes

CNV (Tfelt-Hansen & Rolan, 2006). These medications are especially beneficial for migraine sufferers who also have anxiety, angina, or other cardiovascular conditions (Miller, 2012). Despite being helpful, they have a number of negative side effects, including impotence, sleep difficulties, depression, exhaustion, and impaired exercise tolerance (Antonaci et al., 2016). Contradictions between these medications and Raynaud's disease, asthma, type 1 diabetes (insulin-dependent diabetes), and cardiac failure (2012) Miller. Beta-blockers have been linked in some cases to strokes in migraine patients with aura, but there are no either relative or absolute contraindications to their usage in migraine patients with or without aura. (Linde, M., Dahlof, C., & Dahlof, P. (2004) stated that he uses beta-blockers as a preventative treatment for migraines. The authors explore the rationale behind using beta-blockers in migraine treatment and review the available evidence for their efficacy. They also discuss the potential adverse effects of beta-blockers and suggest patient selection criteria for their use. Overall, the authors conclude that beta-blockers can be an effective prophylactic treatment for migraines, especially in patients with comorbid hypertension or anxiety. (Linde, M., Mulleners, W, Chronicle, E., McCrory, D. C. (2013) Beta-adrenergic blockers are commonly used in the prophylactic treatment of migraine. One study published in the Journal of the American Medical Association found that beta-blockers were effective in reducing the frequency and severity of migraine attacks in patients with a history of migraine.

(**Table 7.1**) Lists beta-blockers used for the prevention of migraine (Silberstein, 2015)

7.1 Beta-blockers in the treatment of migraine

Agents	Regular dose	Comments
Atenolol	50-200 mg	Use half times/day. Side effects are less compared to propranolol.

Metotprolol	100-200 mg	Use the short acting from 2 times/day Use the long acting from once daily
Nadolol	20-160 mg	Use once daily Fewer side effects than propranolol Long half life
Propranolol	40-240 mg	Use the short acting from 2 or 3 times/day Use the long acting from once daily 1-2 mg/kg in children
Timolol	20-60 mg	Use 2 times/day Short half/life

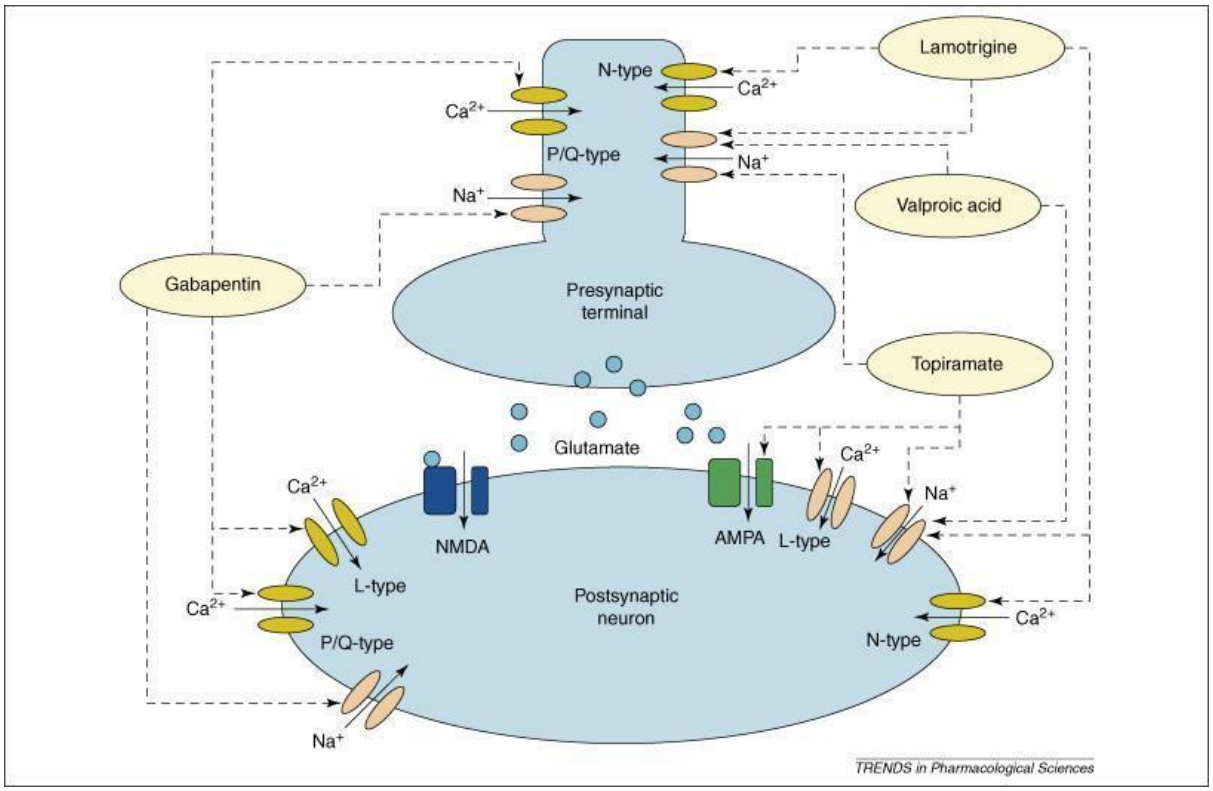
Propranolol is the most often prescribed medication in this class, despite the lack of evidence to support its superior efficacy to other beta-blockers (Rapoport, 2008). According to Holland et al. (2012) and Ramadan (2004), propranolol is effective at doses of 80–240 mg per day and works by reducing central catecholaminergic activity by inhibiting norepinephrine release. It provides membrane stability, reduces neuronal activity and excitability, and inhibits the formation of nitric oxide (Ramadan, 2004). Because propranolol has a strong lipophilic characteristic and may quickly enter the CNS, it has greater negative effects on the CNS than atenolol for migraine treatment. Since atenolol has poor access to the CNS due to its hydrophilic characteristic, it can be used as a substitute for propranolol if CNS adverse effects

are observed (Jackson et al, 2015). In addition to these, metoprolol at a dose of 50-200 mg/day and timolol at a dose of 10-15 mg twice daily are also helpful in the prevention of migraines (Holland et al., 2012). According to Silberstein (2015), beta-blockers with intrinsic sympathomimetic properties are ineffective for preventing migraines. Acebutolol, pindolol, alprenolol, bisoprolol and oxprenolol are all as effective as a placebo in treating migraines, but atenolol, propranolol, timolol and metoprolol are superior to a placebo in treating episodic migraine attacks (Jackson et al., 2015).

4.1 Anti-epileptic drug

Anti-epileptic drugs (AEDs) are a class of medications that have been found to be effective in preventing migraines in some patients. According to a systematic review and meta-analysis published in the journal Neurology, AEDs such as topiramate, divalproex sodium, and gabapentin have been shown to be effective in reducing the frequency of migraines in patients with episodic or chronic migraine (Diener HC et al., 2018). Topiramate, in particular, has been extensively studied and is considered one of the first-line medications for migraine prevention (Silberstein SD et al., 2012). Divalproex sodium has also been found to be effective in preventing migraines, especially in patients with comorbid psychiatric disorders such as bipolar disorder or anxiety (Silberstein SD et al., 2012). Gabapentin, on the other hand, may be more effective in patients with comorbid neuropathic pain (Silberstein SD et al., 2012). Other AEDs such as carbamazepine and lamotrigine have been investigated for their effectiveness in migraine prevention, but the evidence is limited and conflicting (Diener HC et al., 2018). In summary, AEDs can be a useful treatment option for preventing migraines in some patients, particularly those with comorbid psychiatric disorders or neuropathic pain.

Figure 3.1 Antiepileptic drugs in migraine from clinical aspects to cellular mechanisms
Calabresi, P., Galletti, F., Rossi, C., Sarchielli, P., & Cupini, L. M. (2007)



Numerous clinical characteristics of both migraine and epilepsy are shared and epilepsy is a comorbid disease of migraine. Some antiepileptic medications have been found in clinical research to be useful at avoiding migraine attacks. The idea that migraine and epileptic share some common pathogenetic processes justifies their use in migraine prophylaxis. These two pathological disorders have been linked to an imbalance between GABA-mediated inhibition and excitatory glutamate-mediated transmission in particular brain regions. In addition, aberrant voltage-operated ionic channel activation has been linked to both migraine and epilepsy. In addition to producing the migraine aura, cortical spread pessimism has been revealed to play a role in the pathogenesis of epilepsy.

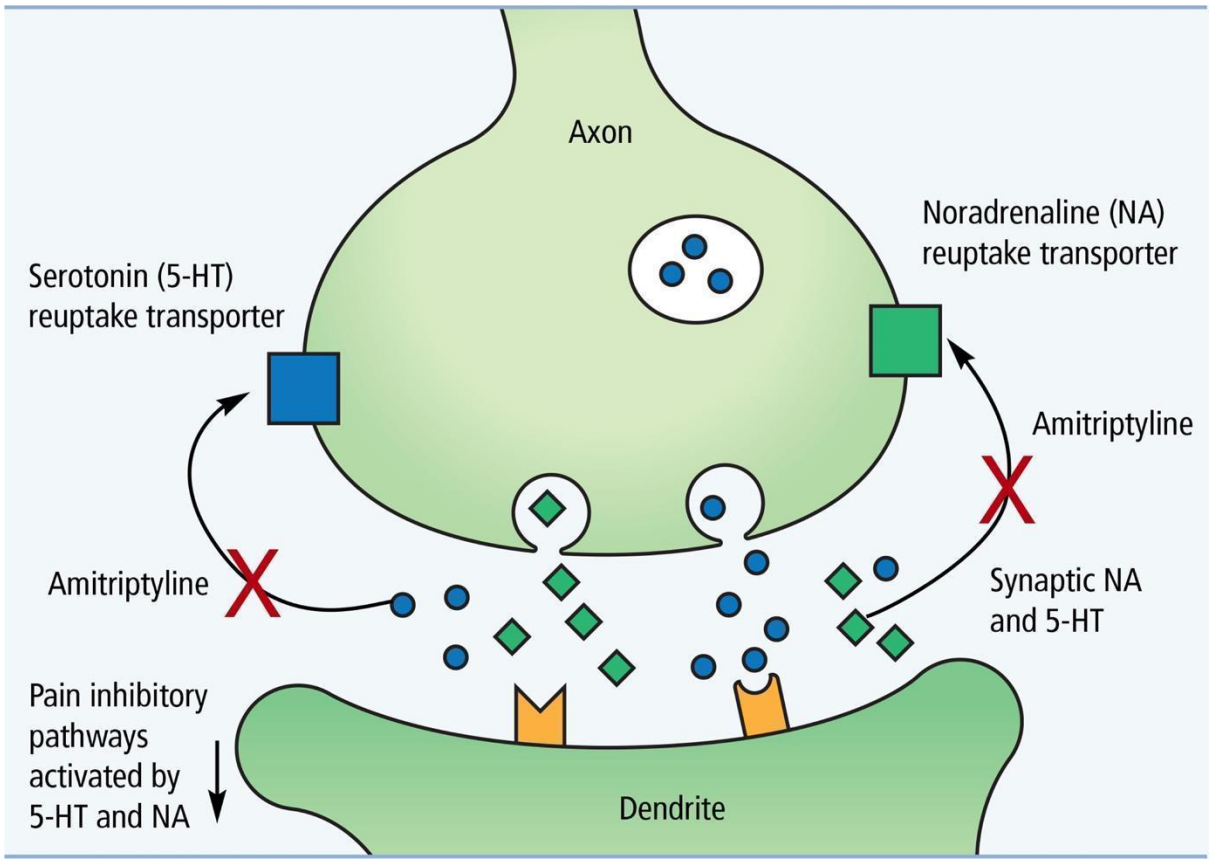
4.1.1 Valproate

Valproates come in the forms of valproic acid and divalproex sodium, and they are equally efficacious in various formulations (Shahien & Karine, 2012). When taken at a dose of 500–1000 mg daily, valproate is beneficial in reducing migraine frequency and intensity (Bussone et al., 2005). Valproate medicine reduces headache frequency by 50% or more in 40–50% of patients, according to a number of placebo-controlled studies (Mathew et al., 2001). Shahien, Saleh, and Bowirrat (2011) claim that valproate works to treat migraines by having an impact on both the central and peripheral nervous systems. It raises the content of gamma-aminobutyric acid (GABA) in synaptosomes as well as in the brain by activating GABA-synthetic enzymes. Concurrently, a number of GABA-degrading enzymes are blocked (Cutrer, Limmroth, & Moskowitz, 1997). Furthermore, it inhibits T-type calcium channels, interacts with central serotonin receptors, and reduces the inflammatory effects of serotonergic neurons. Valproate has been demonstrated to reduce neurogenic inflammation of the peripheral trigeminovascular system as a result of GABAA receptor agonism (Shahien et al., 2011; Vikelis & Rapoport, 2010; Haut, Bigal, & Lipton, 2006). Valproate also lowers activation of the central trigeminal nerve. Divalproex sodium, a medication created by combining sodium valproate with valproic acid, has been approved by the US Food and Drug Administration (FDA) for use in the treatment of migraines (Silberstein, 2015). At dosages of 500 to 1000 mg per day, it is effective and well-tolerated. Bloating, hair loss, trembling of body parts, and skin rashes are some of the side effects of divalproex sodium. There could potentially be serious adverse effects including thrombocytopenia, pancreatic inflammation, and liver failure. If you are expecting or have liver disease, you shouldn't use the drug (Antonaci et al., 2016). Extended-release (ER) divalproex sodium is also effective at preventing migraines. The adverse effect profile and patient compliance, however, have been demonstrated to be superior with this formulation (Silberstein, 2015). In short, Valproate is an antiepileptic drug that has been used in the prevention of migraine attacks. It is believed to work by regulating the neurotransmitter gamma-aminobutyric acid (GABA) and inhibiting the release of the neurotransmitter glutamate, both of which are involved in the development of migraine.

4.1.2 Anti-depressant

Antidepressant drugs are commonly used as prophylactic treatment in patients with migraine, especially in those with comorbid depression or anxiety. They have been shown to be effective in reducing the frequency and severity of migraine attacks. The two most commonly used antidepressant drugs in migraine prophylaxis are amitriptyline and venlafaxine. Amitriptyline is a tricyclic antidepressant that works by increasing the levels of certain neurotransmitters in the brain, including serotonin and norepinephrine. It has been shown to be effective in reducing the frequency and severity of migraine attacks, and is often the first-line treatment for migraine prophylaxis in patients with comorbid depression. A systematic review and meta-analysis of randomized controlled trials found that amitriptyline was more effective than placebo in reducing migraine frequency with a mean difference of -0.91 attacks per month (95% CI -1.27 to -0.54) (Bendtsen et al., 2015). Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that works by increasing the levels of serotonin and norepinephrine in the brain. It has also been shown to be effective in reducing the frequency and severity of migraine attacks. A systematic review and meta-analysis of randomized controlled trials found that venlafaxine was more effective than placebo in reducing migraine frequency, with a mean difference of -1.14 attacks per month (95% CI -1.52 to -0.76) (Jackson et al., 2015). Finally, antidepressant drugs such as amitriptyline and venlafaxine are effective in reducing the frequency and severity of migraine attacks, especially in patients with comorbid depression or anxiety. They are often used as first-line treatment in migraine prophylaxis and can provide significant relief to patients suffering from this debilitating condition. Here is the figure below (Figure 4.1) Devine, K. (2016) pharmacological action of amitriptyline drug that is usually used for migraine disease which is an antidepressant.

Figure 4.1 : Amitriptyline pharmacological action



Devine, K. (2016) mentioned in this figure that after imipramine, amitriptyline was the second tricyclic antidepressant created by Merck in 1960. Although it has a considerably smaller impact on dopamine, its main effect is to raise the activity of serotonergic and noradrenergic neurons by decreasing central serotonin and noradrenaline absorption at the synapse (Figure 4.1). It additionally demonstrates blockage at adrenergic (1), histaminergic (H1), muscarinic (mCh), and NMDA receptor sites, as well as sodium and L-type calcium channels, which may result in a variety of unexpected and severe clinical consequences. Nortriptyline, which has extra therapeutic effects, is produced by substantial first-pass metabolism of amitriptyline in the liver by the cytochrome p450 enzymes CYP2D6 and CYP2C19. Nortriptyline has a stronger effect on noradrenaline while amitriptyline is more effective at the serotonin receptor. Amitriptyline is firmly protein bound in plasma and has a bioavailability of 45%.

4.2 Calcium channel blockers

Wang SJ, Fuh JL, Lu SR, Juang KD, (2006) & Gupta R, Khan S, Kothari P, et al, (2016) Calcium channel blockers (CCBs) are a class of drugs that have been used in the treatment of migraine disease. They work by blocking the entry of calcium ions into smooth muscle cells, causing relaxation and widening of blood vessels. This leads to a reduction in the frequency and severity of migraine attacks. One study published in the journal Headache evaluated the efficacy of CCBs in the treatment of migraine disease. The study found that CCBs, such as verapamil and nimodipine, were effective in reducing the frequency and intensity of migraine attacks in some patients, particularly those with a history of aura. Additionally, another study published in the journal Cephalalgia evaluated the use of calcium channel blocker in the prophylactic treatment of migraine. The study found that calcium channel blockers such as flunarizine and verapamil, were effective in reducing the frequency and severity of migraine attacks in patients who had not responded to other prophylactic treatments. Overall, while calcium channel blocker may not be effective for all patients with migraine disease, they can be a useful option for those who have not responded to other treatments or who have a history of aura. Here is the (figure 5.1) given below in details of showing how it pharmacologically be active and how it works in migraine disease. Ferrari, A., Tiraferri, I., Neri, L., & Sternieri, E. (2014) the authors conducted a meta-analysis of randomized controlled trials evaluating the use of calcium channel blocker in migraine prophylaxis. They found that CCBs were effective in reducing the frequency and severity of migraines in patients who experienced at least two attacks per month. The authors also noted that calcium channel blockers were generally well-tolerated, with few reported side effects. Overall, this study suggests that CCBs may be a useful prophylactic treatment option for patients with migraine disease.

Figure 5.1 : Calcium channel blocker mechanism

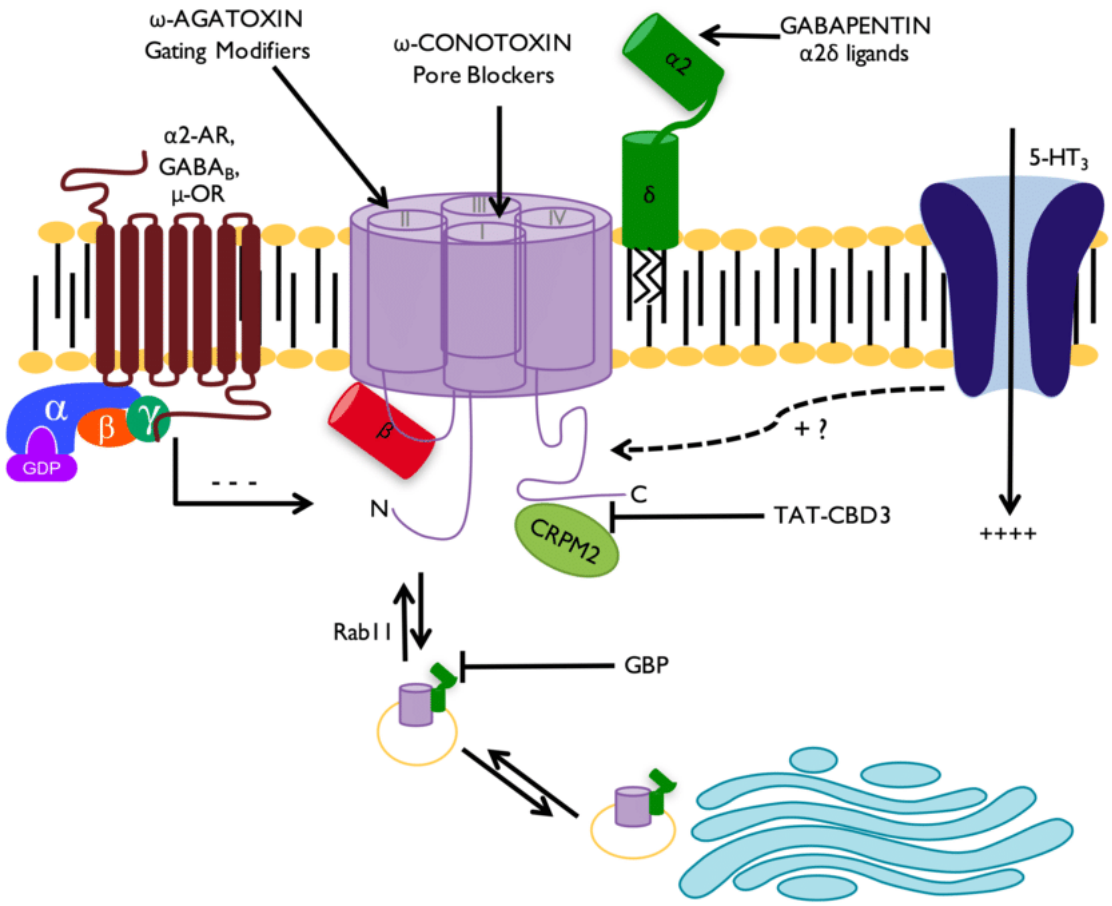


Figure 5.1 Methods for modulating calcium channels in chronic pain. To date, the preferred method for modifying channel activity has been to target VGCC trafficking. (Bauer et al., 2009) Tran-Van-Minh and Dolphin, (2010) The gabapentinoids (GBP) bind to an arginine motif of the 2 subunit of 2-1 and 2-2 and impede axonal trafficking of 2-1 and Rab11-dependent recycling of endosomal channels to the synapse. Utilizing CBD3 peptides to prevent the interaction between VGCCs and CRMP2 is one of the novel methods to decrease trafficking. Inhibitory GPCRs, such as 2 adrenoreceptors, GABAB, and -opioid receptors, can control channel activity. According to Bourinet and Zamponi (2016), peptide blockers can change gating by directly blocking the pore (-conotoxins) or by targeting voltage-sensitive domains (such as -agatoxin).

4.3 Side effects, adverse effects of migraine medications

According to “American Migraine Foundation” Migraine is a neurological disorder that causes recurring headaches, often accompanied by sensory disturbances and other symptoms. There are several drugs available for the treatment of migraines, each with its own set of potential side effects, adverse effects, and contraindications. One common class of drugs used for migraine treatment is triptans. Triptans work by constricting blood vessels in the brain and reducing inflammation. However, they can also cause several side effects, including dizziness, nausea, and fatigue. In rare cases, triptans can also cause more serious adverse effects, such as heart attack or stroke. In addition, Triptans drug can also cause side effects such as paresthesia. Adverse effects include serotonin syndrome, myocardial infarction, and cerebrovascular events. Contraindications include ischemic heart disease, uncontrolled hypertension and hemiplegic or basilar migraine (Lampl et al., 2016). Another class of drugs used for migraine treatment is ergots. Ergots work by constricting blood vessels in the brain, but they can also cause several side effects, including nausea, vomiting, and muscle pain. Ergots are contraindicated in patients with cardiovascular disease, liver disease, or kidney disease. Finally, nonsteroidal anti-inflammatory drugs (NSAIDs) are also commonly used for the treatment of migraines. NSAIDs work by reducing inflammation and pain, but they can also cause several side effects, including stomach upset, heartburn, and dizziness. NSAIDs are contraindicated in patients with a history of gastrointestinal bleeding or ulcers. However, Migraine affects approximately 1 in 7 people worldwide. Various drugs are used to prevent or treat migraines but they can have side effects, adverse effects or contraindications that need to be considered. One of the commonly used drugs for the prevention of migraine attacks is Topiramate. It can cause side effects such as fatigue, dizziness, and cognitive impairment. Adverse effects include metabolic acidosis, renal stones, and angle-closure glaucoma. Contraindications include hypersensitivity to topiramate, liver or kidney disease, and metabolic acidosis (Lampl et al., 2015).

Chapter 05 : Conclusion and future aspects

As this overview has shown, migraine is a common and complex type of headache that can strike at any point in a person's life. Although there are options for both acute and preventative care, full healing from this illness is not yet attainable. Numerous cutting-edge therapy alternatives have been developed as a result of the thousands of studies that have been undertaken over the years in an effort to find a cure for this. In addition to the conventional pharmaceutical therapy choices, a large number of non-pharmacological therapies have also developed over time. Every patient requires a different treatment strategy because their migraine symptoms vary from person to person. Many patients may be able to control their symptoms by avoiding triggers and using simple medications. Some medications could need the most recent developments in order to stop migraine attacks. Both patients and medical professionals search for the best migraine treatment option because all available methods to treating migraines have at least some unfavorable side effects. As a result, the ultimate strategy for effective migraine symptom treatment must be based on multiple migraine characteristics. In order to avoid or lessen migraine attacks in specific people, this study has outlined the most popular migraine therapy approaches. Some potential advancements in migraine research and treatment that are currently being explored. Personalized Medicine, like one approach being explored, is the use of personalized medicine to treat migraine, where treatment is tailored to an individual's specific symptoms, triggers, and genetic makeup. This approach may help to identify more effective treatments and reduce side effects. Furthermore, New Preventive Treatments researchers are developing new preventive treatments for migraine that target different pathways in the brain. These treatments include CGRP inhibitors, monoclonal antibodies, and calcitonin gene-related peptide (CGRP) receptor antagonists. However, Neurostimulation is a technique that involves the use of electrical or magnetic impulses to stimulate specific areas of the brain. Researchers are exploring the use of neurostimulation as a potential treatment for migraine, including transcranial magnetic stimulation (TMS) and vagus nerve stimulation. Moreover, Telemedicine or remote healthcare is becoming increasingly popular in the treatment of migraine. Telemedicine allows patients to receive care and support from healthcare providers without having to leave their homes, which can be particularly beneficial for individuals with mobility or transportation issues.. It's important to note that these potential advancements in migraine research and treatment are still being studied and may not be available for widespread use for some time.

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