A Review on

Migraine Management

A project submitted

by

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Dedicated to my parents

Certification Statement

This is to certify that the project titled “A Review on Migraine Management” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Sabrina Rahman Archie, Lecturer, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Counter signed by the supervisor

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Acknowledgement

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Abstract

Being one of the most occurring primary types of headache, migraine may occur at any age and to anyone. It is usually characterized by mild to severe throbbing pain that may be accompanied by photophobia, phonophobia, osmophobia and nausea. Even though the exact cause of migraine is unknown, it can be triggered by different types of behavioral, environmental, dietary, infectious, chemical and hormonal factors. Therefore, avoiding the triggers at any cost could be the simplistic way of reducing the headache recurrence. Many acute and preventative treatment plans have emerged in recent years to give relief from migraine attacks in patients. These pain management options may start from simple analgesics to the recent invention of electrical devices. All these treatment choices have tried to ease the pain in individual migraineurs. However, these options are unable to cure migraine, as of today. As a result, continuous research works and studies are going on to combat this chronic pain and it is very important to keep both the patients and physicians up to date about the recent advancements in this field. In fact, it can be said that this kind of advanced knowledge will help to manage migraine in a more successful manner indeed. So, the aim of this review paper is to assemble approximately all the migraine related pain management plans in one scientific report, including the novel approaches that are still in clinical trials. In addition to that, compilation of the potential side effects caused by each treatment option as well as the success rate of such treatment options are also included, so that can help to recommend some of the best suited and popular treatment options for different types of migraine sufferers.

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List of acronyms

AED= Anti-epileptic drug

ASA= Acetylsalicylic acid

APAP= Acetaminophen

CASP= China Association for the Study Pain

CGRP= Calcitonin gene-related peptides

CNS= Central nervous system

CNV= Contingent negative variation

COX= Cyclooxygenase

CYP 450= Cytochrome P450

DHE= Dihydroergotamine mesylate

ER= Extended-release

ET= Ergotamine tartrate

ETTH= Episodic tension-type headaches

FAD= Flavin adenine dinucleotide

FDA= Food and Drug Administration

FMN= Flavin mononucleotide

GABA= Gamma-aminobutyric acid

HM= Hemiplegic migraine

HRT= Hormone replacement therapy

ICHD= International Classification of Headache Disorders

IHS= International Headache Society

MAO-A= Monoamine oxidase A

MELAS= Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

MM= Menstrual migraine

MOH= Medication-overuse headache

MRM= Menstrually related migraine

MRN= Migraine-related nausea

MwA= Migraine with visual aura

NIH= National Institutes of Health

NSAIDs= Nonsteroidal anti-inflammatory drugs

OTC= Over-the-counter

t-SNS= Transcutaneous supraorbital nerve stimulation

WHO= World Health Organization

5-HT= 5-hydroxytryptamine

Introduction

Globally, headaches are one of the most common diseases occurring in all ages from youth to advancing years and nearly everyone encounters headache in life (Steiner, Stovner, & Birbeck, 2013). It is a multifactorial disorder that includes various hereditary, biological, medical, neuropsychological, physiological and psyche attributes (Guidetti, Faedda & Siniatchkin, 2016). Headaches can be generally classified as the primary and the secondary headaches, cranial neuropathies and other headaches (International Classification of Headache Disorders, 3rd edition, 2013). Primary headaches demonstrate a prevailing and leading health problem worldwide that cutback patients' aspect of life remarkably (Lanteri-Minet, Duru, Mudge, & Cottrell, 2011; Raggi et al., 2012). Migraine and tension-headaches are the primary type of headaches (Jensen & Stovner, 2008).

1.1 What is migraine?

Migraine is a neurological sensory disorder that affects the vascular systems as well. It is basically a self-restricting dysfunction of the gray matter (Gupta, Gupta, & Fields, 2015). Migraines involve several brain structures, inclusive of the hypothalamus, cortex, trigeminal nerve, brainstem and meninges (Wood, Goadsby, Lipton, & Ferrari, 2002; Pietrobon & Moskowitz, 2013). The afferent nerves associates within the meningeal blood vessel and this causes head pain (Gupta et al., 2015).

Migraine is a complex, yet common disease which is identified by frequent headaches accompanied by certain autonomic symptoms including sensitivity to light and sound, nausea, vomiting etc. (Burstein, Noseda, & Borsook, 2015). It usually kicks off in childhood or around puberty, and women are more affected than men (Bigal & Lipton, 2009; Leonardi, Steiner, Scher, & Lipton, 2005). Upwards 20% of the world's population suffers from migraine at some point of their lives. This disease is so prevailing that, the collective burden has put it in the list of the top 40 disability causing disorders in the world, as reported by the World Health Organization's (WHO) 2012 global burden of disease figures. Yet it is referred to as just an inconvenience by many people (Welch & Goadsby, 2002).

1.2 Classification of migraine

According to the International Classification of Headache Disorders (ICHD) criteria **(Table 1.1)**, there are mainly two types of migraines- migraine with aura, and migraine without aura (ICHD, 2013). This classification system characterizes migraine based on attack frequency, and thus arranges the types giving prominence to most serious forms of headaches in the migraine spectrum (Antonaci, Ghiotto, Pucci, & Costa, 2016). Hemiplegic migraine, menstrual-related migraine (MRM), chronic migraine, complicated migraine are also some other types of migraine (Al-Quliti & Assaedi, 2016).

Table 1.1: Distinctive characteristics of migraine with and without aura

Migraine without aura	Migraine with aura (classic migraine)
A. Minimum 5 attacks B. Headache attacks lasts for 4-72 hours C. Headaches have any two of the following characteristics: - Headaches located in one side only - Throbbing pain - Mild or severe pain - Regular physical activity increases symptoms or the symptoms hamper routine physical activities D. Associated symptoms: - Nausea or vomiting - Sensitivity to light and sound	A. Minimum 2 attacks B. Aura (no muscle weakness): - Completely reversible visual symptoms - Completely reversible sensory symptoms - Completely reversible dysphasia C. Minimum two of the below listed characteristics: - Homonymous hemianopsia (visual field loss) - Unilateral sensory symptoms - Gradually developing aura symptoms for over 5 or more minutes D. Headache starts amid the aura or within 60 minutes following the aura

From all the types, hemiplegic migraine (HM) is an infrequent autosomal dominant type migraine that is represented by reversible hemiplegia with few other neural symptoms, essentially seizure and coma. It can occur either as a sporadic or as a familial disorder (Russel & Ducros, 2011).

Chronic migraine is a type of migraine that has uncertain pathophysiology, multiplex co-morbidities and dissatisfying response to feasible pharmacological treatments, thus is difficult to treat (Buse, Manack, Serrano, Turkel, & Lipton, 2010). As stated in the International Headache Society's (IHS) International Classification of Headache Disorders, chronic migraine can be defined as "migraine headache occurring on 15 or more days per month for more than three months in the absence of medication overuse".

On the other hand, migraine related to menstruation (MRM) or a menstrual migraine (MM) attack is usually pro-longed, causes more disabilities and shows limited response to medications than other type of migraines (Grazzi et al., 2016). Ironically, over 90% women suffering from migraine during menstruation have MRM (MacGregor, 2008). MM without aura can be defined as the migraines occurring exclusively at least on -2 to +3 days of menstruation in 2 to 3 menstrual cycles consecutively. Oscillating oestrogen levels are believed to be causing MM, whereas stable or increasing level of this hormone provides protective effect. Again, unanticipated withdrawal of oestrogen is a factor in migraine attacks (MaxGregor, 2008; Mathew, Dun, & Luo, 2013).

Lastly, complicated migraine is represented by certain individual clinical symptoms of migraine. It mimics conditions like stroke, transient ischemic attack, non-epileptic event, and may also trigger them (Gupta et al., 2015).

1.3 Migraine triggers

Migraine triggers or precipitants can be described as different internal and external stimuli that may induce migraine events in susceptive individuals (Park et al., 2016). A wide range of precipitating factors can "trigger" or "precipitate" migraine attacks where the sufferer generally is capable of identifying the precipitating factors and features associated with increased possibility of attacks (Mathew et al., 2013; Peroukta, 2014). Triggers such as stress, fatigue,

hormonal changes, sleep deprivation, weather, certain food, sunlight, different sensory stimuli are reported to cause migraine. **Table 1.2** lists the probable migraine triggers (Pavlovic, Buse, Sollars, Haut, & Lipton, 2014; Hougaard, Amin, Hauge, Ashina, & Olesen, 2013; Hoffmann & Recober, 2013). It is important to identify, minimize and avoid these triggers to reduce the severity, frequency and span of attacks. Most of the migraineurs encounter the triggers daily but do not suffer from migraine attacks; whereas only few people go through a migraine attack resulting from a precipitating factor (Hougaard et al., 2013).

Table 1.2: Potential triggers for migraine

Potential migraine triggers	
Behavioral	- Sleep deprivation/ sleep disturbances - Skipping meals/ fasting - Emotions
Environmental	- Visual stimuli/ flushing lights - Changes in weather - Certain smell/ odors
Infectious	- Respiratory tract infections
Dietary	- Aged cheese - Alcohols - Caffeine - Citrus fruits
Chemicals	- Nitrates - Monosodium Glutamate - Tyramine
Hormonal	- Menstrual cycle

1.3.1 Behavioral triggers

Imaging studies show activations in regions of the hypothalamus, which is a prime appetite center during and prior to migraine headache in humans (Maniyar, Sprenger, Monteith, Schankin, & Goadsbby, 2013; Denuelle et al., 2008). Moreover, many studies and clinical investigations highlighted noticeable association among migraine, feeding habits and metabolic disorders. Migraineurs have been consistently reporting fasting and skipping meals as one of the prominent triggers of migraine (Martins-Oliveira et al., 2017). Disturbed sleep and/or heavy work load along with fasting around the day may precipitate migraine attacks by the night, which is mainly related to dehydration and hunger (Al-Shimmery, 2010). On the other hand, woman affected by bulimia or anorexia nervosa has more chances of getting migraine attacks associated with eating disorders (D'Andrea et al., 2012).

A recent study reported deep emotions and stressful life events as the most frequent triggers in migraine (Iliopoulos et al., 2015). As a matter of fact, more than 80% patients recognize stress as a precipitant in headache and 60% of them describe it as the main trigger (Martin, 2010; Houle et al., 2012). It is to be noted that the stress-aggravation of migraine shows a particular temporal pattern and attacks usually develop during the mitigation state after stress (Sauro & Becker, 2009). The proposed mechanism behind this condition is the increased sensitivity of migraine cortex due to acute stress affecting the neuromodulation pathway (Radat, 2013).

Similarly, physical exercise has also been reported as a migraine factor by some migraineurs. Upwards 22% of patients report the history of having at least one migraine attack triggered by exercise, as suggested by retrospective surveys (Kelman, 2007; Koppen & Veldhoven, 2013).

1.3.2 Environmental triggers

Bright sunlight, flickering light, certain odors are constantly being reported as ordinary triggers of migraine (Schulte & Jurgens, 2015). Individuals suffering from migraine with visual aura (MwA) are particularly susceptible to vivid visual stimuli and consider them to be aversive as these stimulates account for perceptual illusions and discomfort (Wilkins, Huang, & Cao, 2007).

Again, hypersensitivity to odors is common among migraineurs. Olfactophobia has been proven to be a highly distinguishing finding in migraine (Lima, Sapienza, Giraud, & Fragoso, 2011). Fragranced products, especially perfume may prompt migraine attacks within minutes of exposure (Steinemann, 2016).

In addition, weather is also predominantly mentioned as one of the environmental triggers of migraine (Spierings, Ranke, & Honkoop, 2001). Weather-related variables, for instance, temperature, barometric pressure and humidity are reported to be triggers of headache by many researchers, although this fact is poorly documented (Pavlovic et al., 2014).

1.3.3 Infectious triggers

In recent years, the impact of infectious diseases, digestive system disorders and the immune responses have been noted (Hosseinzadeh, Khosravi, & Ranjbar, 2011). The role of Helicobacter pylori infection is studied in many experiments and it is found to be a common factor in migraine headache (Su, Zhou, & Zhang, 2014). Furthermore, a recent study aimed to find out the association between Chlamydia pneumonia IgG antibodies and migraine, showed 59.2% migraine sufferers and 21.27% controls were C. pneumonia IgG antibody-seropositive (QiHong, Jinzh, HongYan, 2009).

1.3.4 Dietary triggers

Since 1930, relation between migraine and different concealed allergic reactions to food has been questioned. Even various studies showed observable improvement in patients who were going through an elimination diet (Alpay et al., 2010). From 12 to 60 percent of the patient reported food as a triggering factor in migraine, where many patients identified more than one food component as a trigger (Finocchi & Sivori, 2012). In addition, many evidences pointed out that food intake might be capable in altering calcitonin gene-related peptides (CGRP) levels, which apparently suggest a potential mechanistic link between migraine and diet. Again, few food components may help in expression or release of CGRP (Slavin, Bourguignon, Jackson, & Orciga, 2016).

Distinct potential dietary triggering factors including alcohol and cheese have been proposed for migraine (Finocchi & Sivori, 2012). Specifically for migraine with aura, different unique food triggers have been observed in one study. They found out that beer, citrus fruits and vegetables may induce migraine with aura, but has no effect on migraine without aura. Arguably, high consumption of caffeine and caffeinated beverages is also associated with migraine development and chronification, but there is no strong evidence for that (Lee, Choi, & Chung, 2016).

Migraine pathophysiology may be influenced by dietary triggers at one or several phases of the attack and the triggers may possibly affect the brainstem or limbic pathways, cerebral cortex, thalamus, brainstem trigeminal nuclei and the trigeminal nerve (Millichap & Yee, 2003).

1.3.5 Chemical triggers

Glutamate releasing from 5-HT1B/1D/1F receptors expressing neurons in the trigeminal ganglion is associated with migraine aura and migraine pathophysiology. It is implicated in cortical spreading depression, central sensitization and trigeminovascular activation (Andreou & Goadsby, 2009; Ramadan, 2003).

Food preservatives and also some nitrate-containing compounds are constantly identified headache triggers for people suffering from migraines (Sun-Edelstein & Mauskop, 2009). Reportedly, artificial sweeteners including aspartame, which are included in various foods and beverages, can prompt headaches in susceptible people (Newman & Lipton, 2001). Abnormal serotonin levels are observed in both migraine sufferers and in tension-type headaches and several studies have concluded that aspartame inhibits brain serotonin and dopamine (Aggarwal & Puri, 2012).

1.3.6 Hormonal triggers

Lastly, another important factor in migraine is hormonal triggers. Incidentally, more women than men suffer from migraine without aura (Parashar et al., 2014). Women are more vulnerable to migraine than men, which can be demonstrated by the fact that the usual migraine ratio among adults is 1:2 to 1:3 for male: female (Leonardi et al., 2005). In experimental studies, almost 60% migraineous women proclaimed links between migraine attacks and menstruation. Many of them

even claimed that menstruation causes more serious, longer lasting and hard to treat pain than non-menstrual ones (Granella et al., 2004). Migraine recurrences may be affected by women's changing hormonal status through menarche, menstruation, pregnancy, and menopause, and also by oral contraceptive usage and hormone replacement therapy (HRT) (Sacco et al., 2015). Investigations proved that a withdrawal state in either exogenous or endogenous estrogen concentration is a powerful trigger of migraine in women (Sulak, Scow, Preece, Riggs, & Kuehl, 2000). Although the association between sex hormones and migraine has been repeatedly established, the specific pathophysiology of the association has not yet been fully explicated (Chai, Peterlin, & Calhoun, 2014).

1.4 Burden of migraine: impacts

Migraine crises affect the day-to-day actions of patients and results in individual hardship along with economic losses resulting from decreased attendance and productiveness in workplaces. Due to other indirect and direct costs it ultimately impacts the quality of life. Furthermore, epidemiological studies have shown its high predominance and high socio-economic impact.

1.4.1 Socio-economic effects

On a personal level, a migraineur may be affected in numerous ways due to the disabling force of migraine (Freitag, 2007). Studies documented that the occurrence of migraine peaks in the ages between 25 to 55 years, when maximum individuals are supposedly employed (Lipton, Stewart, & VonKorff, 1997).

Assessment of the migraine burden in the United States suggests that migraine causes approximately 4 workdays loss in worker productivity every year (Burton, Landy, Downs, & Runken, 2009). Whereas in the United Kingdom, the population skips 25 million days each year in work due to migraine (Steiner et al., 2003). Additionally, American employers lose over $13 billion per year because of migraineurs lost work days (Migraine Research Foundation, 2017).

In 2011, migraine or chronic headache was named as the second most often identified (47%) source of short-term absence in case of non-manual employees. Consequently, migraine causes

lost wages, decreased productivity due to absence, and also reduced productivity while at work (Serrano, 2013).

1.4.2 Effects on family life

Undoubtedly chronic condition like migraine is also associated with consequential burden even on the family (Holmes & Deb, 2003; Lieberman & Fisher, 1995). A US-based survey that included 350 migraine patients, reported that about 60% of the respondents stated migraine to be affecting their family members, as well as their relationships with the children (Smith, 1998).

A global web-based audit conducted among 866 migraineurs and 162 people who have been living with a migraineur reported that migraine has a moderate to great effect on leisure/social activities and on family life (Macgregor, Brandes, Eikermann, & Giammarco, 2004). Another US web-based long-term study conducted among 16,789 migraineurs, 4022 spouses and domestic partners, and 2140 children also reported substantial impact of migraine on family life (Adams et al., 2015).

1.4.3 Effects on education

Headaches have a subtle impact on school performance of university students, where the impact is especially noticeable amid migraineous students than in students suffering from episodic tension-type headaches (ETTH). Compared to students with ETTH, students with migraine headaches are found to be more absent in school (Bigal, Betti, Bordini, & Speciali, 2001). However, different studies conducted around the world showed different results in this regard. Few studies were done in Turkey focusing on migraine prevalence among university students. Demirkirkan reported a predominance of 12.4%, whereas Bicakci showed a prevalence of 21.9% and Kurt reported 17.9% among 1029, 1256 and 2023 students respectively (Demirkirkan, Ellidokuz, & Boluk, 2006; Bicakci et al., 2008; Kurt & Kaplan, 2008). In a Croatian study conducted among 314 students, 8.9% were reported to have migraine. On the other hand, migraine prevalence is found to be 7.0% among 5847 Norwegian university students and 6.4% among 376 Nigerian university students (Zwart *et al* 2004; Ojini, Okubadejo, & Danesi, 2009).

According to a recent study conducted in Brazil, children with migraine do not perform as good as their peers. As a matter of fact, the migraineur students were 30% more likely to perform below average when compared to their healthy peers. Along with the frequent analgesic uses and abnormal mental health scores, migraine's recurrence, intensity and duration also had effect on the poor academic performance (Arruda & Bigal, 2012).

1.4.4 Effects on health/ co-morbidities

All types of headaches, specifically migraine is correlated with depression and anxiety disorders, ranging from 17- 47% for depression and 18- 58% for anxiety (Zebenholzer et al., 2016). Likewise, migraine has been associated with other conditions such a resting leg syndrome, several cardiovascular disorders, obesity etc. (Wang, Chen, & Fuh, 2010). Again, primary headaches supposedly increase the risk of ischaemic stroke with age- specific, time and gender dependent characteristics (Tsai et al., 2016). In addition, a recent Taiwan based cohort study concluded that migraine patients are more likely to have erectile dysfunction when compared to patients who were non-migraineurs (Wu et al., 2016).

Research Methodology

Thorough literature review was done to obtain all the information used in this review paper. Information were collected from various credible sources including different peer-reviewed journals, online scholarly database, books, newspapers and magazines. Following are the list of some of the many journals that were searched extensively for the present study:

- The Journal of Headache and Pain
- Headache: The Journal of Head and Face pain
- The Lancet Neurology
- The Journal of Neuroscience
- JAMA: The Journal of the American Medical Association
- Current opinion in Neurology
- Cephalalgia
- Neurological Sciences
- Journal of Neurology
- Frontiers in Neurology

Proper management of one of the most common headache disorders, migraine is a crucial matter in the current world. Researchers are persistently operating various studies and trials to find a perfect migraine management plan. Many acute and preventative migraine controlling therapy have come into use over the years. The objective of this review paper is to compile nearly all migraine management options including the ones that have been invented recently and help find the tailored management plan for individuals with migraine.

Migraine Management

Migraine management should accentuate identification of various trigger factors, control of pain during headache attack, and prophylactic medication (Matarese & Mack, 2010). Once being diagnosed, the initial management of migraine should start with assessing potential exacerbating factors or triggers. As migraine can have compelling impact on patient's family life as well, the next step should involve educating their families along with the patients themselves (DeMaagd, 2008). Although recognition of migraine triggers has been proved to be helpful, the patient must have realistic expectations as identification and avoidance of these factors might reduce headache frequency in migraine but does not completely eliminate headaches (Matarese & Mack, 2010).

Traditionally the pharmacological therapy for managing migraine is grouped into acute or abortive and preventive treatments (Silberstein & Goadsby, 2002). Acute treatment helps in relieving the pain and attack-associated potential disability, while preventive treatments aim to decrease attack severity and frequency in the longer term. Thus, an effective migraine management plan must consist of both acute and preventive treatments (Miller, 2012).

3.1 Acute (abortive) migraine treatments

Acute treatment is dedicated towards countering attacks while they have commenced, limiting disability and reducing pain and associated migraine symptoms (Silberstein & Goadsby, 2002). Migraine patients who undergo fewer than two attacks each month or who needs abortive medications not more than two days a week, the use of only abortive therapy alone in migraine management may prove to be convenient for them. The effectiveness of the used abortive medications, patient's tolerance to those agents, migraine's disabling outcomes, interference with day to day routines, are some other critical factors that need to be considered in acute migraine management (Diamond et al., 2006).

The objectives of abortive treatment are-

- Restoration of function
- To prompt treatment of attacks without recurrence
- To reduce the use of acute medical services or rescue medications
- Cost-effectiveness
- To encourage self-care
- Lessen side effects (Miller, 2012).

Table 3.1 lists common pharmacological therapies used in the acute management of migraine, comprising the simple and different combination of analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), 5-HT receptor agonists (triptans), ergot derivatives, antiemetic agents and few others. Some patients may need more than one of these listed agents in combination to mitigate a migraine attack (Lipton et al., 2001; Diamond, Wenzel & Nissan, 2006; Silberstein, 2000; Dipiro et al., 2005; Koda-Kimble, 2005).

Table 3.1: Medications used in the acute management of migraine

Analgesics and NSAIDs
• Aspirin/ Acetylsalicylic acid(ASA): 650- 1,000 mg/ 4-6 hours, up to 4,000 mg/ day (e.g., Bayer Aspirin) • Paracetamol/ Acetaminophen (APAP): 325- 1,000 mg/ 4-6 hours, up to 4,000 mg/day (e.g., Tylenol) • Ibuprofen: 200- 400 mg/ 4-6 hours, up to 1200 mg/ day (e.g., Advil) • Naproxen Sodium: 220 mg/ 6-8 hours, up to 660 mg/ day (e.g., Naprosyn) • Others: Ketorolac (e.g., Toradol), Diclofenac potassium (e.g., Cataflam)
Some combination of over-the-counter products
• Anacin (ASA 400 mg + Caffeine 32 mg) • Vanquish (ASA 227 mg + APAP 250 mg + Caffeine 33 mg) • Bayer Extra Strength (APAP 500 mg + Caffeine 32.5 mg)
Triptans (serotonin receptor agonists)
• Sumatriptan (e.g., Imitrex) • Rizatriptan (e.g., Maxalt) • Zolmitriptan (e.g., Zomigoro) • Naratriptan (e.g., Amerge) • Frovatriptan (e.g., Frova) • Almotriptan (e.g., Axert) • Eletriptan (e.g., Relpax)
Ergot alkaloids
• Dihydroergotamine mesylate (DHE): Nasal Spray, Injection (e.g., Migranol) • Ergotamine Tartrate: various combination with other agents (Caffeine, Belladona Alkaloids, Phenobarbital) available (e.g., Migergot)

Barbiturates combination products
• Fiorinal: Butalbital 50 mg + ASA 325 mg + Caffeine 40 mg, 1-2 tablets/ 4-6 hours • Fioricet: Butalbital 50 mg + APAP 325 mg + caffeine 40 mg, 1-2 tablets/ 4-6 hours *Drug rebound is possible, thus should not be used for more than 2 days/ week
Opiate combination products
• Percodan: Oxocodone + ASA • Percocet: Oxocodone + APAP • Darvocet : Propoxyphene + APAP
Others
• **Sympathomimetics:** Midrin (Isometheptene 65 mg + Dichloralphenazone 100 mg + APAP 325 mg) • **Anti-convulsants:** Depacon (Intravenous Valproate) • **Phenothiazines:** Compazine (Prochlorperazine), Thorazine (Chlorpromazine)

When compared to the preventive therapies, abortive therapies are capable of providing complete and rapid relief with minimum or no side effects and thus they are usually recommended to promptly alleviate the migraine symptoms (Holland et al., 2012). Acute treatment choices have been differentiated into non-specific and specific medications. Non-specific medications include NSAIDs and analgesics; and migraine-specific medications include triptans and ergot derivatives (Antonaci et al., 2016).

3.1.1 Non-specific drugs

Simple analgesic agents and NSAIDs

In mild to moderate migraine attacks, analgesics (aspirin, paracetamol or ibuprofen) are recognized as first choice of drugs, especially when they are taken in combined doses with an anti-emetic agent and early in the attack (Rapoport, 2008). Other than these three, opiate and

barbiturate combination products containing acetaminophen or aspirin are also used commonly (DeMaagd, 2008).

As supported by limited clinical data, APAP can be used as migraine management mono-therapy. In mild-moderate migraine 1,000 mg of APAP has been reported to be beneficial in one placebo-controlled trial, while NSAIDs are more effective as reported in comparison trials with NSAIDs (Larsen, 1990; Hamalainen, Hoppu, Valkeila & Santavuori, 1997). According to Cochrane reviews, 1000 mg paracetamol is beneficial for moderate migraine attacks and it has short-term efficacy in combination with 10 mg metoclopramide, which is equivalent to 100 mg sumatriptan (Derry, Moore & Mcquay, 2010). The anti-migraine action of this analgesic is possibly obtained by a central mechanism that is related to inhibition of central prostaglandin. For patients who fail to tolerate NSAIDs, a trial of APAP can perhaps be considered for them (Silberstein, 2000).

NSAIDs still remain the most frequently used acute treatment for migraine regardless of the increasing use of the lately introduced triptans (Antonaci et al., 2016). They are generally used as a primary approach to abort migraine attacks (Pringsheim et al., 2016). The probable mechanism of action of this group of drugs is achieved by anti-inflammatory effects on vasoactive peptide–induced inflammation that may arise during migraine (DeMaagd, 2008). However, a fixed combination of aspirin (250 mg), paracetamol (200 mg) and caffeine (50 mg) has been proved to be better choice than the agents administered alone (Diener et al., 2005).

Aspirin mono-therapy may also help some patients, even though the required doses might not be tolerated in patients suffering from concurrent GI symptoms (DeMaagd, 2008). Aspirin at 1000 mg dose eases pain within 2 hours in about 52% people and the dose is well tolerated (Kirthi, Derry, Moore, & McQuay, 2010; Lipton et al., 2005). Cochrane reviews suggested that high dose of aspirin (900-1000 mg) is effective for adults (18 to 65 years old) in the treatment of migraine. Whereas the combination of metoclopramide with ASA reduces the chances of nausea and vomiting, but does not offer any significant benefit in easing headache or pain (Inglidue & Mounsey, 2014). The mechanism of action of ASA is apparently comparable to that of the other NSAIDs acting on the anti-inflammatory action in migraine (DeMaagd, 2008).

Another NSAID, ibuprofen also relieves pain in up to 57% migraineurs at 400 mg dose, but cannot completely relief pain in most of the patients, as suggested by Cochrane reviews (Rabbie, Derry, Moore & McQuay, 2010). A promising NSAID formulation for treatment of migraine is the intravenous ibuprofen (800 mg), whose efficacy is still being investigated (Antonaci et al., 2016).

Barbiturate analgesics

Barbiturate combination products have been used for a long time in migraine treatment (see **Table 3.1**). They contain an intermediate-acting barbiturate, butalbital and other agents such as ASA (Watson) or APAP (Fioricet) and sometimes codeine is added with them. Although helpful in many cases, barbiturates produce central nervous system (CNS) confusion and depression. They can even affect cognition and cause paradoxical excitation (DeMaagd, 2008; Charney, Mihic & Harris, 1990). Because of these reasons barbiturate containing products have been banned in non-Western countries and Eastern Europe and expert panels all around the world have noted its probability to be abused (Silberstein & McCory, 2001). Considering all the negative effects of this drug, patients administering barbiturates on a routine basis should be assessed and provided with a substitute therapy (DeMaagd, 2008).

Opiate analgesics

Medications containing opiate have fewer evidence backing their use in migraine management (Oleson et al., 2006). Just like the barbiturate combinations, the use of opioid analgesics should be avoided or at least limited in the acute management of migraine, since they have similar concerns with abuse, tolerance, overuse and the danger of medication-overuse headache (Capobianco, Swanson & Dodick, 2001). The concept of hyperalgesia induced by opioid usage is also a concern which may be exclusive in migraineous patients only. This event supports an acceleration of the using of these agents in some patients and the lack of utility of them (Biondi, 2003). However, opiates may be prescribed to the patients who are pregnant or have ischaemic heart disease and have contraindications with triptans (Miller, 2012). Patients taking opioid analgesics should be monitored vigilantly by their family members and the health care professionals (DeMaagd, 2008).

Analgesic overuse (medication overuse headache)

Redundant use of OTC analgesics and pain medications can result in occasional migraine attacks converting to rebound headaches or analgesic-abuse headaches (Matarese & Mack, 2010). It is caused by the excessive use of analgesics, barbiturate combinations and opiates. Other than that, triptans and ergot derivatives may also cause this type of headaches (Copobianco et al., 2010; Bigal et al., 2004; Ferrari et al., 2006).

In accordance with IHS, "medication overuse" can be defined as the use of simple analgesics for at least 15 days/ month and the use of ergots, triptans, barbiturates, or their combination medicines for at least 10 days/ month (DeMaagd, 2008). Though the mechanism of medication-overuse headache (MOH) is questionable, it is presumed to be interrelated with dysregulation in serotonergic transmission (Biondi, 2003; Olesen, Goadsby & Steiner, 2003; Diener & Katasarva 2001). MOH can result into chronic daily headaches which need thorough supportive care including various treatment protocols, inpatient-management programs, and some preventive therapy. However, treating MOH is often a complicated task and the withdrawal of the respective overused agents is the primary choice of treatment (Evers & Jensen, 2011). Patients and their family members along with the health care professionals should involve themselves in the monitoring and evaluation process of medications use to analyze the frequency of use and effectiveness by keeping diaries (Freitag et al., 2004; Smith, 2002).

3.1.2 Migraine specific drugs

Triptans (5-HT 1B/1D receptor agonists)

Introducing triptans is quite an innovation in the acute management of migraine. Ever since it has come into use, this group of drugs has become the first choice in most cases of abortive migraine management, especially in migraineurs who cannot tolerate or have not responded to NSAIDs or simple analgesics (DeMaagd, 2008). Third edition of the International Classification of Headache Disorders (ICHD-3 Beta) has led to a distinct algorithm for migraine treatment where NSAIDs and triptans have been pointed as the first line of drug choice for treating migraine (**Figure 3.1**) (Evers & Lisotto, 2013).

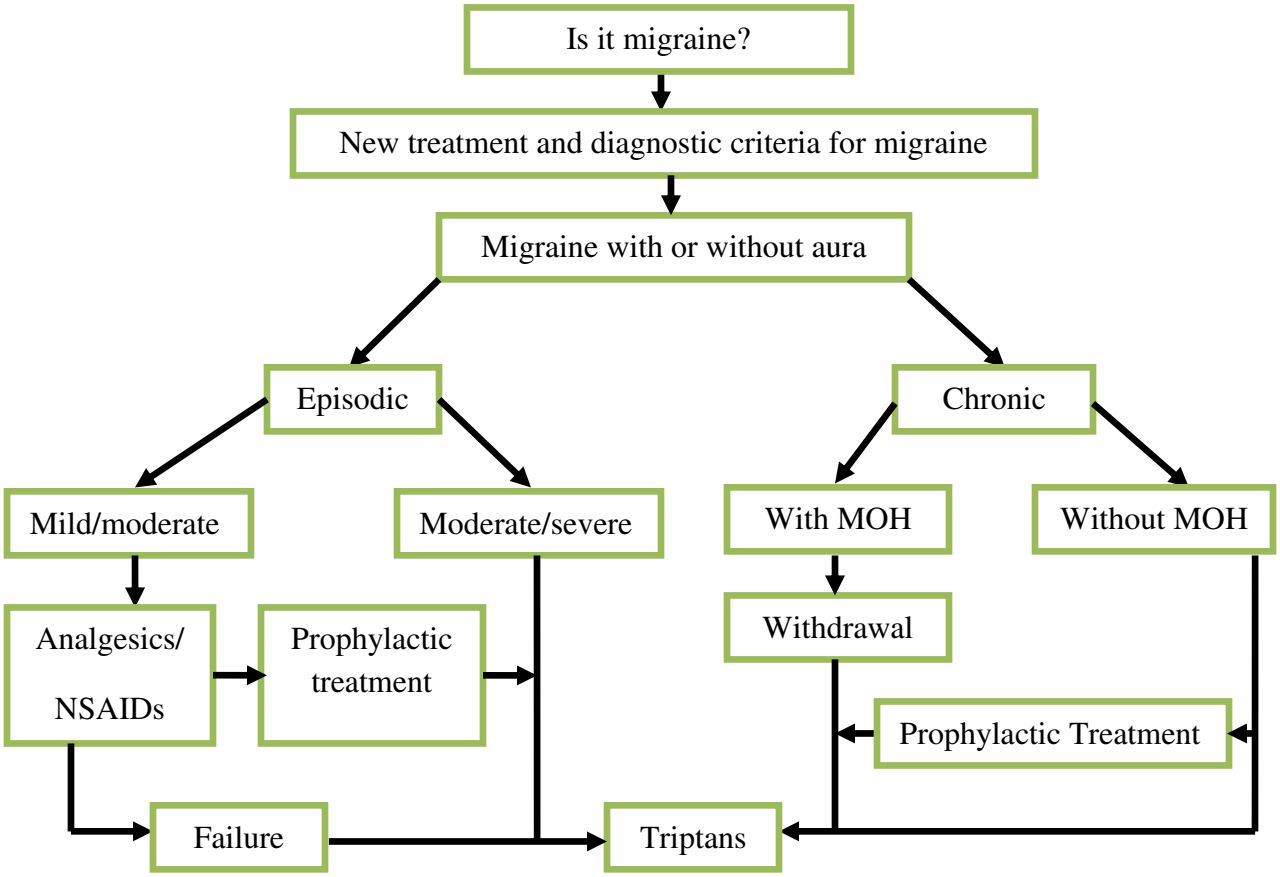

Figure 3.1: Treatment algorithm for migraine

It is projected that triptans work in 60% of patients who do not respond to NSAIDs and the efficacy of these agents has been verified in considerable number of comparative and randomized control studies (Miller, 2012; Linde, 2006).

Potent vasoconstrictors triptans seem to act by three main mechanisms on migraine: inhibition of both central and peripheral trigeminal nociceptive terminals neurotransmitter release, primarily via 5-HT1B/1D receptors (trigeminal nucleus caudalis and trigeminovascular afferents), and intracranial extracerebral vasoconstriction (Antonaci et al., 2016).

Till now a total of 7 triptans have come into use, though their availability from country to country differs (Miller, 2012). Various dosage forms and many delivery options are available for them. Their strengths differ from formulation to formulation and are available as oral tablets,

orally dispersible tablets, nasal sprays and injections. As the pharmacokinetic properties of these drugs deviate, every distinctive feature should be paired as the needs of the patients (DeMaagd, 2008; Miller, 2012).

The first introduced triptan in 1991, sumatriptan is still considered to be the touchstone of this class, although it has many drawbacks; it has a short plasma half-life, low bioavailability and low lipid solubility (McCory & Gray, 2003; Winner, Landy, Richardson, & Ames, 2005). The other six triptans (zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan) are called the second-generation triptans as they have entered more recently in the market and they have better pharmacokinetic profile than the first generation sumatriptan (**Table 3.2**) (Antonaci et al., 2016; Bigal, Bordini, Antoniazzi & Speciali, 2003; Derry, Derry & Moore, 2012; Kunka et al., 1997).

Table 3.2: Pharmacokinetic properties of the 7 triptans

Drug	Formulation	Dose (mg)	Maximum 24 hour dose (mg)	Time of peak levels, t_{max}	Elimination half life, $t_{1/2}$ (hour)	Bioavailability (%)
Sumatriptan	OT	50-100	200	2-3h	2	15
	SI	6	12	12 min	2	97
	NS	20	40	1 h	2	17
	S	25		2.5 h	2	
Zolmitriptan	OT	2.5-5	10	3h	2.5-3	40-48
	ODT			3.3 h	2.5-3	40-48
	NS			2 h	2.82	42
Naratriptan	OT	2.5	5	2-3 h	5-6.3	63 (men) 74 (women)
Rizatriptan	OT	10	30	1-2 h	2	45
	ODT		30	1.6-2.5 h		
Almotriptan	OT	12.5	12.5	1.4-3.8h	3.2-3.7	70-80
Eletriptan	OT	40	80	1-2 h	3.6-5.5	50
Frovatriptan	OT	2.5	7.5	2-4	25	24-30

OT (Oral tablet), SI (Subcutaneous injection), NS (Nasal spray), S (Suppository), ODT (Orally dispersible tablet), h (Hour), min (Minute)

The use of triptans in clinical practice is influenced by the pharmacokinetic difference among them (**Table 3.3**) (Antonaci et al., 2016; Lisotto & Zanchin, 2012).

Table 3.3: Use of triptans in clinical practice

Drug	Formulation	Use
Sumatriptan	OT	
	SI	Fast attack onset- if nauseous/ vomiting
	NS	If nauseous/ vomiting
	S	If nauseous/ vomiting
Zolmitriptan	OT	
	ODT	If nauseous/ vomiting
	NS	If nauseous/ vomiting
Naratriptan	OT	Previous adverse effects If attack lasts for long time
Rizatriptan	OT	
	ODT	Rapid acting, if nauseous/ vomiting
Almotriptan	OT	Rapid onset
Eletriptan	OT	Rapid onset
Frovatriptan	OT	If attack lasts for long time

Oral triptan trials have shown that they all are well tolerated and effective at marketed doses (Evers et al., 2009). Various systemic meta-analyses and systemic reviews have shown the efficiency of subcutaneous and intranasal sumatriptan preparations in randomized and placebo-

controlled trials in acute migraine therapy. Likewise, the novel transdermal formulation of this drug was also reported to be effective in a single placebo-controlled trial (Derry, Derry & Moore, 2012; Goldstein et al., 2012). However, subcutaneous sumatriptan at a dose of 6 mg is more effective and has the most rapid onset of action when compared to oral sumatriptan administered at a dose of 100 mg, but it also produces more adverse events than the oral formulation. Again, oral sumatriptan at a 100 mg dose is most effective, although the dose of 50 mg may give the best combination when it comes to efficacy and tolerability (Evers et al., 2009).

A novel delivery option for sumatriptan is the more recently marketed transdermal patch which delivers the dose by skin penetration through an electrical gradient system (Schulman et al., 2010; Smith, Pierce & Griesser, 2011). The iontophoretic transdermal system of sumatriptan is well tolerated and effective and may particularly be convenient for patients who suffer from different migraine-induced gastrointestinal symptoms including nausea (Goldstein et al., 2012; Vikelis, Mitsikostas & Rapoport, 2012). Furthermore, a lingual spray containing sumatriptan as the active ingredient is also under development and it has shown similar bioequivalence to 50 mg oral sumatriptan (Dilone et al., 2009).

A number of meta-analysis, randomized and placebo-controlled trials have demonstrated the efficiency of zolmitriptan as an abortive migraine therapy and the optimum starting dose of this agent appear to be 2.5 mg (Bird, Derry & Moore, 2014). Naratriptan, rizatriptan and eletriptan has also shown to be effective for abortive migraine treatment by several randomized and placebo-controlled studies (Antonaci et al., 2016).

In three randomized, double-blind crossover studies, frovatriptans have shown sustained effect and favorable tolerability, with a significantly low relapse rate over 48 hours compared to other triptans (Allais & Benedetto, 2016). This drug is recommended by many national guidelines for the avoidance of menstrual attacks during perimenstrual period in women who have menstrually related migraine or pure menstrual migraine (MM) (MacGregor, 2014).

Over the years of use, the comparisons made and the clinical evidence collected found almotriptan to be one of the rapid acting and more effective triptans available and its tolerability profile is similar to placebo (Antonaci, De Cillis, Cuzzoni & Allena, 2010; Pascual, Vila &

McGown, 2010). There is also a possibility of developing an iontophoretic transdermal patch to administer almotriptan (Calatayud-Pascual et al., 2011).

Triptans are most effective when they are administered just at the onset of headache (Belvis, Mas & Aceituno, 2014). Individual patient's characteristics, features of headache, patient's preference, and convenience, cost considerations etc. are the factors that need to be considered while choosing the right triptan (Antonaci et al., 2016).

The cytochrome P450 (CYP 450) system and also the monoamine oxidase A (MAO-A) system can metabolize the triptans; therefore, assessment of probable drug interactions and adjustment of doses is a must for those patients who have hepatic disease (DeMaagd, 2008). Again, dose adjustments are needed for patients with renal impairment also, as renal elimination takes place in some triptans (almotriptan, naratriptan) (Tfelt-Hansen, De Vries & Saxena, 2000).

Triptans are reported to be safe and well tolerated by studies done in healthy young patients and the selective pharmacological therapy suggests that they have acceptable side-effect profile. Nausea, vomiting, problems in digestion and other GI effects are common with triptans, but they possibly can be a consequence of the migraine itself. Other than these, different neck and chest symptoms may also appear and require follow-up (DeMaagd, 2008). Paraesthesias, tingling, neck pain, flushing and mild transient chest pressure are the most common side effects with triptans and they are recognized as 'triptan sensations'. As triptans can trigger the (5-HT2A) receptor in the peripheral arteries, few cardiovascular complications may also show up rarely. However, turning to a different triptan or changing the route of administration may mitigate the side effects (Antonaci et al., 2016).

Triptans are contraindicated in various conditions. This group of drugs should be avoided in the presence of coronary heart disease, untreated arterial hypertension, Raynaud's disease, hemiplegic migraine and severe kidney or liver failure. The administration of ergotamine or its derivatives and other vasoconstrictors and other triptans as well are contraindicated within 24 hour of administering a triptan (Antonaci et al., 2016; DeMaagd, 2008).

Triptans can cause potential drug-drug interaction with other serotonergic agents (**Table 3.4**), increasing the chances of serotonin syndrome that enhances serotonergic activities in the body (Gardner & Lynd, 1998; Shapiro & Tepper, 2007; Eadie, 2001).

Table 3.4: Common drugs having serotonergic properties

Monoamine oxidase inhibitors (MAOIs)	Antidepressants	Others
• Selegiline (Emsam) • Phenelzine (Nardil) • Tranylcypromine (Parnate) • Isocarboxazid (Marplan)	• Tricyclic: amitriptyline, nortriptyline etc. (Elavil) • Selective serotonin reuptake inhibitors (SSRIs): Fluxetine (Sarafem) • Miscellaneous: Venlafaxine (Effexor), Nefazodone (Serzone)	• Buspirone (BuSpar) • Lithium • Dextromethorphan • Cocaine • Amantadine (Symmetrel)

Ergot alkaloids (ergotamine and dihydroergotamine)

Though the first specific agents used for the acute management of migraine were the ergot alkaloids, their use have been limited by the invention of more selective triptans (Bigal & Tepper, 2003). Like the triptans, the ergot alkaloids also exert their anti-migraine effect by activating the serotonin (5-HT) receptors. Additionally, they interact at both dopaminergic and alpha-adrenergic systems which may contribute to their anti-migraine action but this also result in greater side effects (DeMaagd, 2008). Ergotamine tartrate (ET) and dihydroergotamine mesylate (DHE), these two ergot alkaloids are available as injections and nasal spray for using as migraine abortive (Silberstein, 2000). The oral ET formulation is available as combination products containing belladonna alkaloids, caffeine and phenobarbital (DeMaagd, 2008).

Ergotamine was introduced in 1926 and was the first agent used for abortive migraine treatment (Antonaci et al., 2016). Although it has been in use for treating acute migraine for over 80 years, there is little evidence for its use in a small group of patients (Miller, 2012). The oral dose starts from 0.5 mg to 2 mg, suppositories contain 1 to 2 mg and the inhalation formulations have the

maximum dose of 1.8 mg of ergotamine. Though it is used alone in some countries, the suppository formulation generally contains a combination of caffeine and ergotamine.

The main problems of ergotamine are poor oral bioavailability and irregular absorption (Miller, 2012). Again, its vasoconstrictor effect contraindicates its use in peripheral vascular disease, coronary heart disease, impaired renal or hepatic function, stroke and pregnancy. Ergots should be reserved for patients who have not responded to triptans or who have prolonged attacks (Wood et al., 2002). Even in these patients, rectal ergotamine should not be used for more than once a week and at a dose of 0.5 to 2 mg (Saper, Silberstein, Dodick & Rapoport, 2006). Ergotamine must not be administered within 6 hour of triptans and likewise triptans must not be taken within 24 hour of ergotamine.

DHE is less effective than ergotamine due to its poor oral bioavailability, but normally is better tolerated. Clinical data for DHE and ET have mostly favored DHE, and reported their efficacy in 90% and 50% of patients respectively (Antonaci et al., 2016; DeMaagd, 2008). One systemic review reported that DHE has similar efficacy as ketorolac, valproate, opiates but sumatriptan and phenothiazines are more effective than it (Colman et al., 2005).

Intranasal DHE is relatively slow acting but its bioavailability (40%) is better than many other anti-migraine agents. Nasal DHE is recommended for moderate to severe attacks if the patient does not respond to other acute medications and IV is recommended for severe migraine attacks (Rapoport & Bigal, 2005). Though parenteral (IV or SI) solutions of DHE are more effective in the treatment of severe migraine, they also produce more adverse events (Bigal & Tepper, 2003). Thus, pre-treatment with antiemetics may be required if DHE is administered intravenously. The long lasting effect and lower recurrence rate of this agent is due to the longer half-life (10 hours) it has and it works well into migraine attacks for this reason (Antonaci et al., 2016).

The common side effects with ergot derivatives include nausea and vomiting, tingling in the extremities, muscle cramps, chest discomfort, difficulty in swallowing, nasal congestion, fatigue, and depression (Bigal & tepper, 2003). If headache recurrence increases, these side effects can be limited by switching to a preventive therapy. As ergots have vasoconstrictive properties, heart

disease are considered to be a contraindication and thus any chest discomfort should be evaluated appropriately (Bigal & Tepper, 2003; Sculman & Rosenberg, 1991).

However, ergotamine carries the risk of overuse at a great extent and so they are no longer a choice of drug for migraine treatment (Antonaci et al., 2016). Prolonged overuse may result in ergotism, a term used to describe ischemic complications of main body systems including the myocardium. Additional complications including fibrosis, retroperitoneal fibrosis, MOH is also seen with ergotamine overuse and these conditions need proper monitoring and care (DeMaagd, 2008; Bigal, 2003).

3.1.3 Other abortive agents

Antiemetic agents can be used in patients who face disabling nausea and vomiting with migraine; and many antiemetics are available for this purpose (Al-Quiliti & Assaedi, 2016). Butyrophenones, phenothiazines and metoclopramide have been reported to show efficacy in acute migraine management (DeMaagd, 2008). These agents probably exert their effect by the antagonist property with dopamine and hypersensitivity to dopamine during a migraine attack (King & Herndon, 2005).

IV chlorpromazine, prochlorperazine, promethazine, droperidol and haloperidol decanoate have shown efficacy in clinical trials as migraine-abortive drugs (Kabbouche et al., 2001; Seim, March & Dunn, 1998; Bigal, Bordini & Speciali, 2002; Richman et al., 2002). Among them, prochlorperazine shows extrapyramidal side effects, promethazine is sedating but effective, while ondansetron is effective but does not produce sedation. Metoclopramide is commonly used and is usually well tolerated (Al-Quliti & Assaedi, 2016). Metoclopramide combined with triptans or ergots may provide additional efficacy along with antiemetic benefits (Sculman & Dermott, 2003; Klapper & Stanton, 1991).

These medications must be administered with caution when given intravenously because they may cause arrhythmias (electrocardiogram is recommended before giving the dose), hypotension and dystonic reactions (Silberstein, 2000).

Other than these, IV valproic acid may also be used in the acute management of migraine. This was found to have comparable efficacy to DHE in refractory cases and was more effective than placebo (Reiter, Nickisch & Merritt, 2005; Norton, 2000; Edwards, Norton & Behnke, 2001).

Patients taking abortive anti-migraine medications should be advised to not use the medications for more than 2 days a week or 10 days a month. This will guard them against the development of MOH, which is more resistant to treatment than episodic migraine (Lipton & Silberstein, 2005).

3.2 Preventative treatments

Prophylactic or preventative drugs lessen the severity or recurrence of headache associated symptoms and headaches if they are administered daily where 50% reduction of frequency or severity is considered to be a satisfying response (Chuang et al., 2016). A patient should be advised to take preventative therapy if-

- In spite of abortive treatment, frequency of attack is not reduced.
- Infrequent but serious disability causing headache attacks are observed in the patient twice or more times in a month.
- Patient constantly suffers from two or more attacks in a week that escalate over time.
- Acute treatments are failing, contradicting or causing adverse effects.
- There is a risk of acute medication overuse.
- Special cases (hemiplegic migraine).
- Patient's choice of taking preventative medication (Miller, 2012).

According to The US Headache Consortium, preventative treatments have some goals:

- To reduce attack recurrence by 50% and cutback attack severity and duration.
- To enhance the feedback of acute therapy.
- To boost function and downturn disability.
- To halt medication overuse headache and chronic headache (Holland et al., 2012).

There are huge variety of convenient prophylactic treatment including beta-blockers, alpha antagonists, calcium channel blockers, antidepressants, anti-convulsants, botulinum-A, serotonin agonists and serotonin reuptake inhibitors (SSRIs) (Jackson et al., 2015). Angiotensin converting enzymes (ACE) and Angiotensin receptor antagonists (ARB) are also in use now for the prevention of migraine attacks (Rapoport, 1994). The major drugs recommended for migraine preventative therapy are listed in **Table 3.5** (Miller, 2012).

Table 3.5: Main drugs used in episodic migraine prevention

Drug	Therapeutic dose	Headache attack reduction	Common side effects	Positive co-morbidities	Contra- indications
Beta blockers					
Propranolol	40-240 mg/day	50%	Sleep disturbance Fatigue Bradycardia Depression Erectile dysfunction	Anxiety Hypertension	Asthma Diabetes Bradycardia Peripheral vascular disease Raynaud's disease
Tricyclic antidepressant					
Amitriptyline	25-150 mg/day	50%	Sedation Weight gain Dry mouth Blurred vision Constipation Mental confusion Suicidal tendency	Depression Anxiety Sleep disturbance Chronic/ neuropathic pain	Closed-angle glaucoma Urinary retention Prostatic hypertrophy Cardiac arrhythmia
Nortriptyline	25-150 mg/day		Urinary retention Anxiety Sleep disturbance Dry mouth Constipation		
Anti-epileptics					
Sodium valproate	800-1500 mg/day	30-50%	Tremor Weight gain Nausea Hepatitis Alopecia	Depression Epilepsy	Obesity Pregnancy Liver disease

Topiramate	50-100 mg/day		Weight loss Paraesthesia Sedation Mood change Visual disturbance Renal stone Acute glaucoma Sedation	Obesity Epilepsy Neuropathic pain	Pregnancy Renal stone Glaucoma
Gabapentin	1200-2400 mg/day	50-75%	Dizziness	Epilepsy Tremor	
Calcium channel blockers					
Flunarizine	5-10 mg/day	50%	Sedation Weight gain Parkinsonism Depression	Complicated aura Hemiplegic migraine Resistant attacks	Depression Parkinson's disease Heart failure Cardiac arrhythmia
5-HT_2 antagonists					
Pizotifen	1.5 mg/day	50%	Increased appetite Weight gain Drowsiness		Obesity
Methysergide	3-6 mg/day	50-75%	Nausea Peripheral vasoconstriction Retroperitoneal/ valvular fibrosis	Should only be used as 3rd line treatment under specialist follow up	Pregnancy Cardiac disease Peripheral vascular disease Impaired kidney/liver function

Although no robust and well-established benchmark is set to choose one preventative drug over another, different conditions and considerations are to be acknowledged while measuring the

risk-benefit scale: co-occuring diseases, drug interactions, possible adverse effects, contraception, patient prospects and expenditure (**Table 3.6**) (Antonaci et al., 2016).

Table 3.6: Critical points in migraine management

Monitoring attacks
By keeping a migraine diary to record different information on the migraine attacks. It will help the doctor to make a firm diagnosis.
Educational programs
Discussion with patients to make them aware about the migraine triggers, their treatment plan, the possible side effects of the chosen treatment options etc.
Disability and outcome evaluation
Self-administered questionnaire
Non-pharmacologic strategies
Relaxation Therapy: slow and deep abdominal breathing, visualizing positive images **Biofeedback Therapy:** reduces muscle tension in the neck and head, modify blood flow, generally by warming the hands **Cognitive behavioral techniques:** they teach how to recognize and cope with stress
Pharmacological therapy
Potential side effects, drug-drug interactions, co-morbidities, patient's expectations and cost of the treatment should be considered

Discussion with patient before starting all preventative medications are encouraged to aware the patient about the treatment plans, adverse effects and duration of the treatment (Miller, 2012).

Treatment should be initiated with low drug doses and gradually increase doses to get expected therapeutic effect. Doses can be increased until maximum dose is obtained or till side effects remain tolerable. Patient should continue with adequate dose of any drugs for a trial period of minimum 6-8 weeks before being deemed ineffective (Freitag & Shumate, 2014). In case of most of the patients, drug can be sequentially withdrawn after treating for minimum 6 months. In all cases, the patient must know that acute medications might be needed even while continuing with preventative drugs as they are not sufficient to prevent all attacks (Antonaci et al., 2016; Moja, Cusi, Sterzi, & Canepari, 2005).

Table 3.7: Take-home message for optimal prevention

- Enhance adherence by involving patients in patient care.
- Recognize co-morbidities and if possible, pick one medication to deal with multiple co-morbid disorders.
- Pregnant woman patients must get special considerations; contraception and different dangers of using medication during pregnancy must be discussed with them.
- Initiate with a low dose.
- Prophylactic medications should be given at adequate dose for adequate time of 6-8 months.
- Refrain from administration of interfering, contraindicated or overused medications.
- Re-evaluation and follow up is also important.

(Antonaci et al., 2016)

3.2.1 Beta-adrenergic blockers

Most extensively used prophylactic migraine medications are the Beta-blockers. According to several studies, they are 60-80% efficient in reducing attack recurrence (Silberstein & Goadsby, 2002). This class of drugs works by acting on the central catecholaminergic system which is

believed to modulate a negative and slow cerebral potential called contingent negative variation (CNV). Prophylactic therapy with beta-blockers normalizes CNV (Tfelt-Hansen & Rolan, 2006).

These agents are notably helpful for migraine patients with anxiety, angina and other cardiovascular disease (Miller, 2012). Although useful, they are linked with many side effects including sleep disorders, depression, fatigue, reduced exercise tolerance and sometimes with orthostatic hypotension, bradycardia and impotence (Antonaci et al., 2016). These drugs are contradicted in type 1 diabetes (insulin-dependent diabetes), Raynaud's disease, asthma and cardiac failure (Miller, 2012). There are some reports of patient with migraine with aura having strokes after taking beta-blockers, but there are no reported absolute or relative contraindications of their use in patients suffering from migraine with or without aura.

Table 3.8 lists beta-blockers used for the prevention of migraine (Silberstein, 2015).

Table 3.8: Beta-blockers in the preventive treatment of migraine

Agents	Daily dose	Comments
Atenolol	50-200 mg	Use 1 or 2 times/day Less side effects than propranolol
Metoprolol	100-200 mg	Use the short acting form 2 times/day Use the long acting form 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 form 2 or 3 times/day Use the long-acting form once daily 1-2mg/kg in children
Timolol	20-60 mg	Use 2 times/day Short half-life

Out of all the agents of this class, propranolol is prescribed most commonly, although it is not proved that propranolol is more efficient than the other beta-blockers (Rapoport, 2008). Propranolol is effective at 80-240 mg/day doses and exerts its effect by diminishing central catecholaminergic activity through inhibition of norepinephrine release (Holland et al., 2012; Ramadan, 2004). It decreases neural activity and excitability, provide membrane stability and suppress the production of nitric oxide (Ramadan, 2004). Due to its high lipophilic property, propranolol can easily penetrate into the CNS, thus causes more CNS adverse effects than

atenolol. Hence, atenolol can be used as an alternative to propranolol if CNS side-effects are seen, as atenolol has poor access to CNS owing to its hydrophilic property (Jackson et al., 2015). Other than these, timolol at a dose of 10-15 mg two times a day and metoprolol at 50-200 mg/day are also beneficial in migraine prophylaxis (Holland et al., 2012). Beta-blockers that have intrinsic sympathomimetic property are ineffective for migraine prevention (Silberstein, 2015).

A Meta-analysis comparing the effectiveness of beta blockers on migraine showed that acebutolol, pindolol, alprenolol, bisoprolol and oxprenolol are as effective as placebo, whereas atenolol, propranolol, timolol and metoprolol are better than placebo for episodic migraine attacks (Jackson et al., 2015).

3.2.2 Anti-epileptic drugs

Many placebo-controlled trials have proven the efficacy of anti-epileptic drugs (AEDs) in migraine prophylaxis and their use is increasing day by day (Moja et al., 2005; Bussone, Diener, Pfeil, & Schwalen, 2005). According to a Cochrane Review, people are twice more likely in having a 50% minimization in headache frequency when treated with AEDs than with placebo (Bussone et al., 2005).

Table 3.9: Selected anti-epileptic drugs in migraine prophylaxis

Agents	Daily dose	Comments
Gabapentin	600- 3600 mg	600- 3200 mg/ day dose
Topiramate	50- 200 mg	Start 15-25 mg at bedtime Increase 15-25 mg per week Attempt to reach 50-100 mg Increase further if necessary Associated with weight loss, not weight gain
Valproate/ Divalproex	500- 2000 mg	Start 250-500 mg Monitor valproic acid levels if compliance is an issue Maximum dose is 60 mg/ kg/ day

(Moja et al., 2005; Silberstein, 2015)

AEDs are specially recommended for those who suffer from migraine with epilepsy, anxiety or bipolar disease. One thing that the clinician needs to remember is that most antiepileptics except for valproic acid, topiramate, pregablin, levetiracetam, zonisamide and gabapentin may have major interference with the effectiveness of oral contraceptives (Silberstein, 2015).

The AEDs work in the brain by acting on multiple molecular sites. They alter neurotransmission by effecting neurotransmitter receptors, neurotransmitter metabolism and different ion channels and are referred as neuro-modulators (Fenstermacher, Levin, & Ward, 2011; Krymchantowski, 2011). This network of interaction among these sites reduces unusual nervous excitability and support vulnerable neurons in high-energy demand conditions like metabolic impairment and neuronal hyper-activity (Calabresi, Centonze, & Bernardi, 2000).

Valproate

Valproates are available as both valproic acid and divalproex sodium, where various forms of both the formulations have similar efficacy (Shahien & Karine, 2012). At a dose of 500-1000 mg/day valproate is efficacious in reducing migraine severity as well as frequency (Bussone et al., 2005). Several placebo-controlled studies demonstrated that treatment with valproate reduces 50% or more headache frequency in 40-50% of the patients (Mathew et al., 2001).

Valproate exerts its anti-migraine effect by working on both the central and peripheral nervous system (Shahien, Saleh, & Bowirrat, 2011). It raises the level of gamma-aminobutyric acid (GABA) in synaptosomes, as well as in the brain by the activation of GABA-synthetic enzymes. At the same time, it also inhibits different GABA-degradative enzymes (Cutrer, Limmroth, & Moskowitz, 1997). Along with that, it communicates with central serotonin receptors, reduces the inflammatory effects of serotonergic neurons and inhibits the T-type calcium channels. Valproate also reduces the activation of central trigeminal nerve and proved to minimize neurogenic inflammation of peripheral trigeminovascular system that is a result of $GABA_A$ receptor agonism (Shahien et al., 2011; Vikelis & Rapoport, 2010; Haut, Bigal, & Lipton, 2006).

Divalproex sodium, which is prepared by combining both sodium valproate and valproic acid is approved for use in migraine by the US Food and Drug Administration (FDA) (Silberstein, 2015). It shows effectiveness at a dose of 500-1000 mg/day and tolerable at this dose. The common side effects with divalproex sodium include weight gain, hair loss, trembling of body parts and skin rashes. Some major side effects like liver failure, inflammation of the pancreas, thrombocytopenia may also show up. The drug is contraindicated during pregnancy and hepatic disease (Antonaci et al., 2016). Extended-release (ER) divalproex sodium is also effective in migraine prevention. However, patient compliance and side effect profile is shown to be better with this formulation (Silberstein, 2015).

Gabapentin

The response rates of gabapentin vary among placebo-controlled studies ranging from 36% to 46% and it has been proved to be efficient in few single blind trials (Tflet-Hansen & Rolan,

2006, Rothrock, 1997; Diener et al., 2002). It is a chemical analog of GABA and accelerates GABA-mediated inhibition while inhibiting GABA metabolism. It has high affinity towards $\alpha_2\delta1$ and $\alpha_2\delta2$ subunits of voltage-gated calcium ion channels, thus it inhibits high-voltage-activated calcium currents resulting in reduced synaptic transmission (Silberstein, 2006).

Gabapentin does not bind to plasma proteins and has no significant drug interactions. Hepatic enzymes are not induced by it and also it is not metabolized. The oral bioavailability of the drug is 60% and the biological half-life is 6-8 hours (Shahien et al., 2011). In clinical practice, valproate and topiramate appear to be more effective than gabapentin. As this drug has positive consequence on neuropathic pain, it may be useful in patients that have co-existing neuropathy, trigeminal neuralgia or chronic pain. Gabapentin is effective at doses of 600-3200 mg/day (Miller, 2012; Moja et al., 2005). It has some possible side-effects- fatigue, somnolence, peripheral edema and dizziness, although it is well tolerated in general.

Topiramate

Topiramate, a sulfamate-substituted monosaccharide, is derived from the naturally occurring sugar D-fructose (Shahien et al., 2012). It is one more antiepileptic medication which is now FDA-approved to be used for migraine prevention (Tflet-Hansen & Rolan, 2006). Its anti-migraine potential is based on several possible mechanisms that include blocking of voltage-sensitive sodium channels which causes modification of nerves excitability; inhibition of carbonic anhydrase activity and inhibition of the excitatory glutamate pathway along with enhancing the GABA inhibitory effect (Calabresi et al., 2000; Shahien et al., 2011; Silberstein & Collins, 1999).

Topiramate is not related with significant estrogen exposure reduction at doses lower than 200 mg per day; a dose-associated reduction to the estrogen exposure may arise from doses above 200 mg per day (Silberstein 2015). The drug shows effectiveness at doses of 100 mg/day and this dose provides similar outcomes to propranolol for daily rescue medication use, migraine frequency and migraine days reduction according to a placebo-controlled trial where propranolol was the active control (Jackson et al., 2015; Diener et al., 2004). The recommended dose starts at 25 mg/day and is gradually raised by 25 mg a week up to the total dose of 100 mg a day (taken

as 50 mg twice a day) is reached (Brandes, 2005). It's likely side effects include behavioral or cognitive disturbances, renal stone formation, weight loss, impaired vision due to high intraocular pressure, fatigue, hypohydrosis–hyperthermia, metabolic acidosis, and a sensation of prickling or tingling in both hands and feet (Welch & Goadsby, 2002; Silberstein, 2005). Topiramate may be beneficial to patients who have obesity, idiopathic intracranial hypertension or diabetes along with migraine (Miller, 2012).

Other anti-epileptics

Zonisamide has an acceptable safety profile and this antiepileptic drug is well-tolerated as well (Baulac, 2006). It is a sulphonamide derivative, chemically and structurally different from other anti-epileptic drugs. Its specific mechanism in migraine prevention is reduction of ion flow through the T-type calcium channels (Kito, Maehara, & Watanabe, 1996; Bermejo & Dorado, 2009).

It has some very similar mechanisms to topiramate, including sodium channel blockage, carbonic anhydrase inhibition, potassium-mediated glutamate release inhibition and GABA release enhancement. However, the drug has lower side effects incidence than topiramate, thus is well tolerated and more effective in migraine patient refractory to topiramate (Bermejo & Dorado, 2009; Villani, Ciuffoli, Prosperini, & Sette, 2011).

Lamotrigine also blocks the voltage-gated sodium channels and is thought to aid in the cortical spreading depression process. Although it is not yet found to be active in migraine prevention, few studies have reported it to be beneficial in controlling troublesome migraineous auras (Miller, 2012).

3.2.3 Anti-depressants

Amitriptyline, which is a tricyclic antidepressant, is used as a prophylactic therapy for headache since 1968 (Magyar et al., 2015). Norepinephrine and serotonin reuptake is inhibited by amitriptyline and it is the only antidepressant of this class having established efficacy in prevention of migraine. Other potential mechanisms of this agent in migraine could be explained by its ability to block sodium-channels, increase GABA-mediated inhibition, increase effects of

endogenous opioids and intensify descending blockade on nociceptive pathways (Sawynok, Esser, & Reid, 2001). It can be particularly useful when co-morbid depression, peripheral neuropathy, or insomnolence is present. Usual side-effects include weight gain, constipation, hypersomnia, fatigue, and blurred vision in addition to other anti-cholinergic events.

Reviews of the limited clinical trials suggest that amitriptyline is at least as good as propranolol if not better, in reducing headache frequency (Silberstein & Goadsby, 2002). The usual starting dose is 10 mg and can be gradually increased by 10 mg per week up to 75 mg or 1 mg/kg body weight (Lance & Goadsby, 2005). When high doses are used, it can be divided in 1–3 doses.

An important metabolite of amitriptyline is nortriptyline, which has a more approving side-effect profile compared to the parent drug. The initial dose for this drug is 10 mg each night and the dose can be increased gradually if needed (Silberstein, Sapper, & Freitag, 2001). It has almost similar side effects, contraindications and precautions as amitriptyline.

Serotonin specific reuptake inhibitors (SSRIs), another group of antidepressants, may help in treating co-existent depression with migraine but no real proof of them being active as anti-migraine agent is reported in Cochrane Reviews (Ozyalcin et al., 2005). Fluoxetine (doses of 10–40 mg per day) and venlafaxine extended release (doses of 75–150 mg per day) however seem to be effective (Evers et al., 2009).

3.2.4 Calcium channel blockers

Although not FDA-approved for migraine, over 45 clinical studies report on the effectiveness of several different calcium channel blocking agents including verapamil, flunarizine (not available in the United States), nicardipine, nifedipine, nimodipine and cyclandelate (Gray et al., 1999). These agents have uncertain mechanism in preventing migraine. They inhibit Ca^{2+} dependent enzymes that help in prostaglandin formation and prevent contraction of vascular smooth muscles (Shukla & Sinha, 2010).

Verapamil is another calcium channel blocker that could particularly benefit patients with prolonged aura (Mathew, 2005). Although it is used in migraine prevention, no randomized control trial has proven its efficacy (Miller, 2012). The dose range starts at 80 mg a day and is

increased as tolerated up to 480 mg a day in two or three divided doses (Toda & Tfelt-Hansen, 2000). Common side-effects are hypotension, edema, constipation, dizziness, and nausea. Hypertensive migraineurs can potentially benefit from the hypotensive side-effect. Verapamil cannot be used in patients with bradycardia, cardiac conduction disorders, symptomatic hypotension and in those who simultaneously use beta blockers, as these conditions are contraindicated with this drug.

Flunarizine has constant tenacious evidence from eight placebo-controlled trials to be efficacious in migraine prevention. This evidence is reinforced by comparison trials with propranolol (Gray et al., 1999). It is reported to be of particular benefit in patients who have complicated or prolonged migraine aura. The normal dose is 5-10 mg a day at bedtime and weight gain is the most common side effect with this drug (Silberstein, 2015). The drug is frequently used in South America and Canada, although it is not approved for the USA (Bigal et al., 2003; Pringsheim et al., 2012).

3.2.5 Anti-serotonin drugs (5-HT_2 antagonists)

Methysergide was one of the first drugs to be used for in migraine prevention (Gray et al., 1999). It is a semi-synthetic ergot alkaloid and is efficient to reduce migraine frequency. Methysergide's efficacy is similar to propranolol, flunarizine and pizotifen (Ozyalcin et al., 2005). Neurogenic inflammation, as well as peptide release inhibition from perivascular sensory nerve endings have been invoked as a mechanism of action in migraine therapy (Diener, 2000). The daily dosage of methysergide is 3 to 6 mg given in three separate doses (Olesen, Tfelt-Hansen, & Welch, 2006). The administration of methysergide is somewhat restricted by its side effects profile. It is estimated that 1 out of 5000 patients on treatment with methysergide may develop pleural, retroperitoneal or heart valve fibrosis (Ozyalcin et al., 2005). Owing to the serious side effects it may cause, methysergide should be prescribed only to those patients who cannot respond to other prophylactic medications. In practice, after every 6 months patient should take a drug vacation from this agent to cut the risk of developing retroperitoneal fibrosis (Miller, 2012).

Another serotonin antagonist, pizotifen is used in many countries to prevent migraine attacks. Placebo controlled studies of this drug suggest clinical efficacy in 40 to 79% patients at a dose of

1.5-3 mg (Silberstein & Goadsby, 2002; Rapoport, 2008). It was found to be less effective than flunarizine and metoprolol in direct comparison studies (Ozyalcin et al., 2005). Moreover, pizotifen may cause tiredness and substantial weight gain which has limited the use of this drug (Miller, 2012).

3.2.6 Botulinum toxins (BoNTs)

There are 7 serotypes (A-G) of botulinum toxins; among them type A has been studied most extensively for therapeutic purposes and reported to be most potent and stable.

OnabotulinumtoxinA (botulinum toxin type A) is the exclusive agent particularly approved for preventing chronic migraine (Dressler & Adib, 2005; Bell, Vermeulen, & Sperling, 2000). The approval was based on 2 parallel, large phase III randomized, placebo-controlled clinical trials conducted in North America and Europe, named Phase III Research Evaluating Migraine Prophylaxis Therapy 1 (PREEMPT 1) and PREEMPT 2 (Silberstein et al., 2013).

OnabotulinumtoxinA has better side effect profile than topiramate and divalproex sodium and all of them have similar efficacies, as reported by comparative study conducted with these three agents (Schaefer, Gottschalk, & Jabbari, 2015). The exact mechanism of the agent in chronic migraine therapy is not clearly known, but it is proposed that this neurotoxin functions by more than one mechanism that involve the blockade of neurochemical release from motoneurons and sensory nociceptive neurons that are associated with the muscle fibers (**Figure 3.2**) (Durham & Cady, 2011).

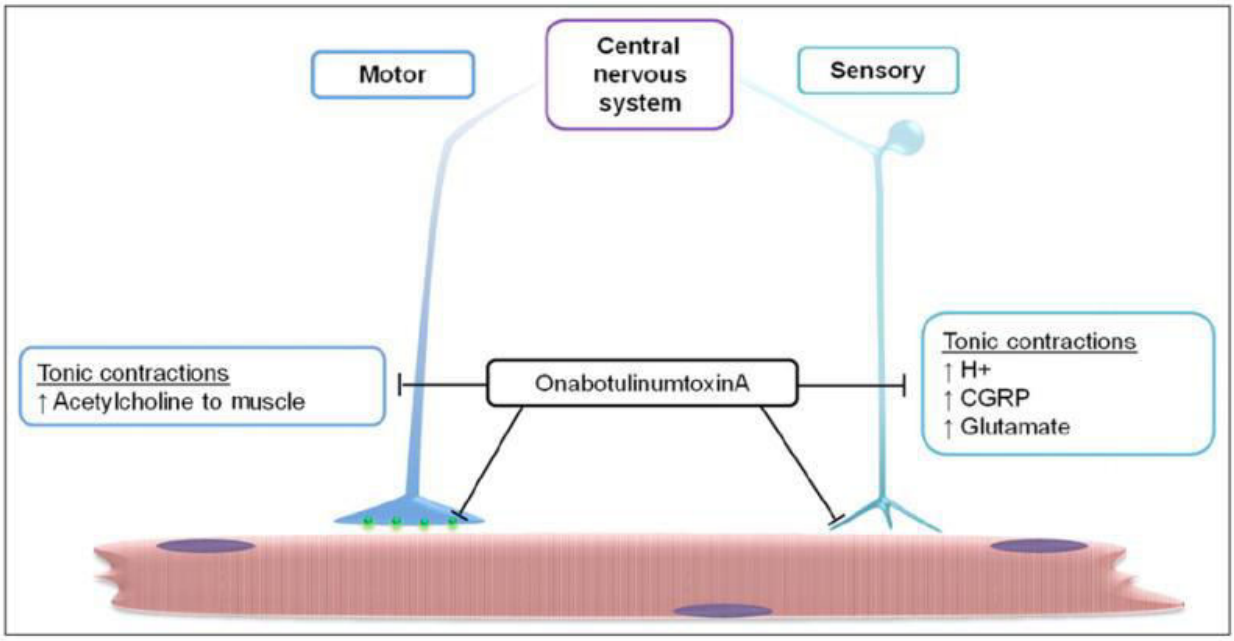

Figure 3.2: Proposed cellular targets of onabotulinumtoxinA

Optimum benefit from using injectable onabotulinumtoxinA relies upon the accurate dose delivered to the target, adherence to the proposed number of injections in each site and injections frequency (Ashkenazi & Blumenfield, 2013). Usually the drug is injected on the neck and head across 31 sites (injected muscles include the bilateral corrugators, procerus, temporalis, cervical paraspinal, superior trapezius musles and frontalis). Intramuscularly 155 units (5 units/ site) is the approved dose and retreatment is required every 12 weeks (Pringsheim et al., 2012). It is advised to use the minimal amount that is required to bring about the desired result while lessening possible adverse effects. Few reversible and temporary side effects like muscular weakness, bruises, pain around the injected area are common with this agent; xerostomia, fever, fatigue and ptosis may also show up after 1-2 weeks of injecting onabotulinumtoxinA (Sim, 2011).

3.3 Alternative medicines (non-traditional therapies)

Many patients face difficulties in administration of prophylactic drugs because of their side effects (Fenstermacher et al., 2011). Few patients have even reported tolerance to the favorable

effects of those drugs, after continuing a drug treatment. Non-pharmacological treatments are thus beneficial for them (Rizzoli & Loder, 2011; Zheng et al., 2015).

3.3.1 Acupuncture

Acupuncture has been globally used for treating migraine and a sound body of evidence is present to support its use in migraine prophylaxis (Du, Wang, Liu, & Liu, 2015; Molsberger, 2012). The method originating in China plays a vital role in traditional medicine there and it has a history of hundreds of years. Acupuncture is basically a method that treats disease by needling along specific meridians or pathways. It was suggested as an alternative headache treatment by the China Association for the Study Pain (CASP) and the National Institutes of Health (NIH) (Du et al., 2015; NIH consensus conference, 1998; Rapoport, 2012).

A recently published study demonstrated that reduction in migraine frequency and prevention of attacks are possible through acupuncture (Zhao, Chen, & Li, 2017). A German randomized controlled trial found that a total of 11 acupuncture sessions given within 42 days was as effective as a six-month period daily beta blocker administration. Another randomized controlled trial conducted in German also concluded that acupuncture is more efficacious than no acupuncture (Linde et al., 2005; Diener et al., 2006). A 2002 US survey claimed that 9.9% of the acupuncture users among the respondents had been taking acupuncture for migraine and other type of headaches (Burke, Upchurch, Dye, & Chyu, 2006). A Cochrane review in 2009 established a consistent evidence of acupuncture being beneficial in acute migraine treatments and other available studies show that it has fewer side effects (Linde et al., 2009).

The pain relieving mechanism of acupuncture is explained in some theories. According to few studies, acupuncture inhibits transmission of pain to the CNS by various types of afferent fibres stimulation (Zhao, 2008). It also improves the releasing of endorphins and some other pain suppressors within the CNS (Han, 2004; Griggs & Jensen, 2006). As claimed by the practitioners, a short time of acupuncture treatment (12 sessions in 3 months) can have a persisting impact on the intensity and frequency of headache episodes (Linde et al., 2009).

3.3.2 Natural remedies

Vitamins

The potential role of vitamin B_2 (riboflavin) in migraine prevention was investigated in several studies (Boehnke et al., 2004). Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) aids in the transfer of electrons in redox reactions. Migraine-like headaches experienced due to reduced mitochondrial metabolism in patients who have mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), are alleviated by riboflavin (Shaik & Gan, 2015).

A study report demonstrated that around 59% of migraineurs showed 50% reduction of symptoms at a 400 mg/day dose and showed only fewer adverse effects with riboflavin. It was also concluded that it is a convenient option for migraine prevention owing to its low cost, excellent tolerability and high efficacy (Schoenen, Jacquy, & Lenaerts, 1998). However, a dose of 200 mg/day failed to produce any noteworthy effect in alleviating migraine in 48 Australian children, when compared to placebo (MacLennan,et al., 2008). Other than these, several other studies were conducted in the USA, Germany, Italy and Netherlands; most of these studies concluded riboflavin to be an effective migraine prophylactic agent, although minor side effects including vomiting, appetite changes were reported (Shaik & Gan, 2015). One study reported both vitamin B2 and sodium valproate had similar impacts on relieving migraine pain. Since vitamin B2 resulted in minimum complications, it can be administered to patients who have sodium valproate-induced complications or those who are prohibited from taking it (Rahimdel, Zeinali, Yazdian-anari, Hajizadeh, & Arefnia, 2015).

Several clinical trials were also carried on among migraine patients using vitamins B_6, B_9, and B_{12} and found to reduce migraine severity when compared to placebo. Further research is thus needed incorporating varying doses of vitamin B_9, B_6 and B_{12} to find out the long term effects of these vitamin supplements on the migraine management (Menon et al., 2016).

Herbs and minerals

Since the 2000 US guidelines, several studies have assessed the efficacy of petasites (butterbur), MIG-99 (purified feverfew), coenzyme Q10, estrogen, magnesium etc. (Estemalik & Tepper, 2013). Among them, petasite extract may reduce migraine pain as it reduces CGRP through the

inhibition of COX-2 expression and leukotriene synthesis in cell models (Grossmann & Schmidramsl, 2000; Fiebich et al., 2005). The petasites plant also contains carcinogenic, mutagenic and hepatotoxic pyrrolizidine alkaloids (Aydin, Zerbes, Parlar, & Letzel, 2013).

Magnesium is also possibly effective for preventing migraine as demonstrated in one study (Maizels, Blumenfeld, & Burchette, 2004). A total of 21 studies concluded that Intravenous magnesium can alleviate acute migraine symptoms within 15 to 45 minutes, 2 hours and 24 hours subsequently the initial infusion; the intensity and frequency of migraine is also reduced by oral magnesium (Chen, Huang, Chiu, & Yeh, 2016).

3.4 Novel approaches

As mentioned earlier, sumatriptan iontophoretic transdermal patch is available now for treating migraine. The US FDA has approved this patch system (Zecuity) for acute care of migraine with or without aura in adults. Besides relieving migraine headache pain, this battery-powered, one time use patch also alleviate migraine-related nausea (MRN) (Barclay, 2013). The patch is beneficial for patients with small bowel absorption problems and gastroparesis as they cannot fully respond to oral treatments. Patients who suffer from intense nausea and vomiting, they will also find this patch helpful, so will the patients with triptan intolerabilities (Smith et al., 2011; Vikelis et al., 2012). However, the manufacturer has temporarily halted the sales of Zecuity as many users have reported to experiences severe redness, skin burn, discoloration, scar and blistering from using this patch system (FDA, 2016).

A more recent innovation in the treatment of migraine is the invention of an electrical stimulation patch that blocks the pain signals reaching the brain using electrical stimulation. The ability of controlling the device by a smart phone app and the wireless design adds more to its value. This device was tested for its efficacy among 71 patients and the non-painful stimulation of skin proved to reduce migraine pain significantly, especially if used early in an attack. However, more studies need to be conducted to examine the side effects of the device (Yarnitsky et al., 2017).

Another novel approach towards migraine management is the Cefaly device that works by transcutaneous supraorbital nerve stimulation (t-SNS). It has proved to be efficient and safe

method for self-delivered treatment sessions (Magis, Sava, D'Elia, Baschi, & Schoenen, 2013). Some mild and transient side effects like drowsiness, reversible forehead irritation, worsening of headache condition may appear after using Cefaly. The US FDA and the EU have approved this device for preventing episodic migraine (Vikelis et al., 2017; Miller, Sinclair, Davies, & Matharu, 2016).

Conclusion

As this review has demonstrated, migraine is a prevailing and complicated form of headache that might be present at any stage of a human life. Although both acute and preventative management options are available, complete recovery from this condition is not yet possible. Over the years there have been thousands of researches conducted to find one cure for this and researchers have come up with several innovative treatment options. Besides the traditional pharmacological management options, many non-pharmacological therapies have also emerged over the course of time. As individual patients show differing features of migraine, each of them needs separate treatment plans. Where many of them can ease their symptoms just by avoiding triggers and simple medications, some may need the most recent innovations to prevent migraine attacks. Since all the migraine management options have at least some side effects, both patients and health professionals seek to point out the best option to treat the migraine patients. Therefore, the final approach towards proper management of migraine symptoms needs to be based on various migraine variables. This paper has summarized mostly used migraine management alternatives that can be used to prevent or minimize migraine attacks in individual patients.

Recommendations

Clearly migraine is one of the pervasive causes of disability worldwide, but many of the migraineurs are not diagnosed properly and many of the diagnosed patients do not get appropriate treatment for managing the migraines. In order to mitigate or prevent migraine, it is a must that every person that suffers from any kind of headache or headache related symptoms, contact with a physician to diagnose their condition. As the reason behind migraine attacks are yet to be truly understood, everyone including those who do not have migraine should avoid all the migraine triggers as much as possible.

If a person is identified to have migraine, proper treatment options should be chosen based on the severity and frequency of migraine. If a patient is suffering from mild migraine, he can start their management plan with different home remedies and lifestyle changes. Identifying triggers and avoiding them, regular physical exercise, proper meal and sleep routine are strongly recommended for the patients. In terms of pharmacological therapies, the right medications must be selected according to patient profile. Potential side effects of each medication taken must be monitored and choice of drug must be changed if severe adverse events and dependence appears to rise from using them.

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