Migraine and quality of life

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Abbreviations

CGRP - Calcitonin Gene Related Peptide

CCB – Calcium Channel Blockers

DALY – Disability Adjusted Life Years

GABA - Gamma-Aminobutyric Acid

ICHD - International Classification of Headache Disorders

IL - Interleukin

MDD – Major Depressive Disorder

MIDAS - Migraine Disability Assessment Scale

MIBS - Migraine Interictal Burden Scale

MSQ - Migraine Specific Quality of Life Questionnaire

NSAIDS - Nonsteroidal Anti-inflammatory Drugs

TCA - Tricyclic Antidepressants

Contents

1. Abstract

Migraine is a prevalent debilitating neurological condition that affects over 1.1 billion around the world and it is 2 to 3 times more common in females than in males. Migraine is characterized by intense, pulsating unilateral headaches usually lasting between 4-72 hours that tend to recur, often accompanied by symptoms such as nausea, vomiting, photophobia and phonophobia where it can significantly impair daily functioning and overall well-being of those who suffer from it. Migraine lowers the quality of life in many different domains in life, including emotional health, social interactions, occupational and financial burdens. This thesis focus on migraine in general and specifically detailed the effect of migraines on disruption daily living and to explore the different domains of life which are affected by this condition and how to assess the migraine impact with different scales such as Migraine Interictal Burden Scale (MIBS-4), Migraine Specific Quality of Life Questionnaire V2.1 (MSQv2.1) and Migraine Disability Assessment Scale (MIDAS) in order to accomplish better management of the disease to achieve a better quality of life for those who suffer for migraine.

2. Sažetak

Migrena je prevalentna neurološka bolest koja pogađa više od 1,1 milijardu ljudi širom svijeta, s dvostruko većom učestalošću kod žena. Obilježava je intenzivna, pulsirajuća, jednostrana glavobolja koja, ukoliko se ne liječi, traje između 4 i 72 sata te se često ponavlja. Uz glavobolju, simptomi migrene uključuju mučninu, povraćanje, fotofobiju i fonofobiju, što može značajno ometati svakodnevno funkcioniranje. Migrena značajno umanjuje kvalitetu života u raznim aspektima, uključujući emocionalno zdravlje pojedinca, društvene interakcije i profesionalni život, te predstavlja značajan financijski teret. Ovaj diplomski rad pruža pregled migrene s posebnim naglaskom na njezin utjecaj na kvalitetu života. Analizirane su različite sfere života koje su pogođene ovim stanjem te su detaljno opisane različite skale za procjenu migrene, kao što su MIBS-4, MSQv2.1 i MIDAS. Cilj ovog rada je unaprijediti prepoznavanje migrene i poboljšati kvalitetu života oboljelih.

3. Introduction

The term "migraine" originates from Greek which means "hemicranias", which is "half of the head." This term highlights one of the condition's most notable characteristics of migraine, which is that pain frequently affects one side of the head, although bilateral discomfort is in fact equally prevalent, and less frequently can also be felt in the front or back of the head. The pain usually last between 4-72 hours and is throbbing pain which means pulsating in nature that is usually moderate to severe and can be disabling and is worse with movements and can be accompanied by photophobia, phonophobia, nausea and vomiting (1). Migraine affects about 15% of the general population which accounts for 1.1 billion people and can causes significant personal suffering and impairment of the quality of life with a substantial socioeconomic effects, family relationships, and work and school activities. Migraine is the second biggest to disability adjusted life years(DALY) lost due to neurological disorder in 2016, accounting for 16.3% of attributable DALY (2,3).

Migraine is a cyclic disorder that consists of different phases: premonitory phase, aura phase (which consists of transient neurological symptoms), intense headache phase and postdrome phase. Among the common risk factors assumed to be associated with migraine are lower socioeconomic status, caffeine, medication overuse, sleep disorders, and obesity. In addition, risk factors that suggested to be associated with chronic migraine including ineffective treatment of acute migraine and the overuse of medication (3). Factors which are associated to trigger the migraine attack are stress, hormonal changes in women, not eating, sleep disturbance, perfume or odors, light, alcohol, smoke, heat, and certain foods (4).

Migraine treatment is divided into abortive treatment in acute setting and preventive treatment. Acute treatment includes specific drugs such as triptans and Gepants and non-specific drugs such as analgesics, antiemetics, and opioids. Preventive treatment can be divided into non-pharmacological which include lifestyle modification and pharmacological with variety drugs. While these therapeutic medications are effective in many patients, they may still not work

perfectly to all patients and may not be appropriate for some due to their side effects of due to contraindications (5).

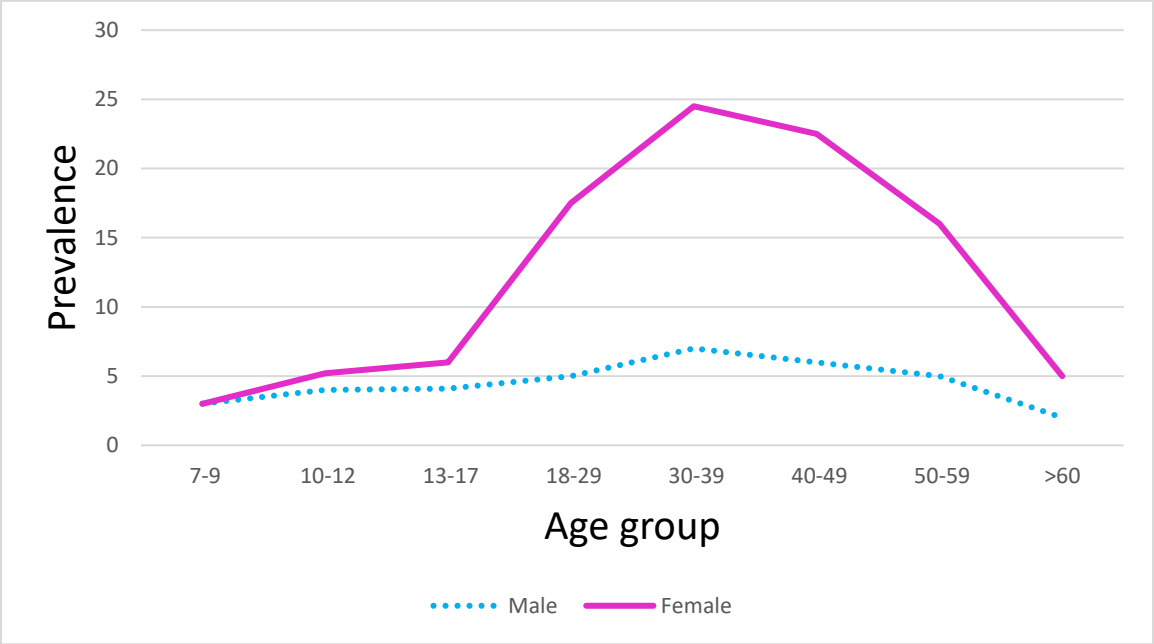
4. Epidemiology of migraine

4.1. General Incidence and prevalence

Migraine is among the most prevalent neurological conditions in the world. Over the past three decades, migraine prevalence has significantly grown with global prevalence grew from 722 million patients in 1990 to 1.1 billion patients globally in 2019. According to Global Burden of Disease Study estimations show that Italy and Belgium having the highest age-standardized point prevalence rates, whereas Ethiopia and Djibouti had the lowest rates. Incidence rate was estimated to be 14,100 people yearly where national age-standardized incidence rates show the highest in Italy and Norway, where on the other hand again Ethiopia and Djibouti have the lowest rates (6,7).

Over the years between 1990 to 2019, East Asia and Andean Latin America showed the largest increase in the age-standardized prevalence per 100,000 people, where the High-income North America and Southeast Asia have shown the largest decreases. Migraine is being more common in women than men in each age group. The incidence of migraine is the highest at adolescent, especially at the age group of 10-14 years old in both sexes, where the prevalence keep increasing during puberty until reaching the peak in the age group between 35 to 39 and then decreasing later in life, significantly after menopause in women (4,6).

Figure 1. Migraine prevalence by age sex (8).



Migraine accounts for 3% of all emergency hospitalization that stands for the fifth most frequent cause, and account for the second most common cause of years living with disabilities after back pain (4).

4.2. Socioeconomic level on prevalence of migraine

National Health Interview Study has shown the effect of employment on migraine prevalence. It was shown that people who worked full-time jobs reported the least number of migraines and then people who are working part time with and then people who were unemployed or never worked before and then the highest among those who were unemployed but were employed. Migraine prevalence was also the highest among the people who are living below the poverty level. Reduced access to treatment and medical resources combined with greater exposure to migraine triggers might account for such results, where it is also postulated that low socioeconomic can also be related with higher stress and other factors that can contribute for developing migraine (9,10).

4.3. Major depressive disorder(MDD) on prevalence of migraine

Epidemiological researches have consistently shown that those having history of migraine are more likely to experience depression. Patients with migraine have 3.4

times more the likelihood to experience depression, particularly in the age group between 18 to 38. Moreover, MDD and demonstrate dose-response-type which is bidirectional, indicating that the exacerbation of one condition is linked to a later worsening of symptoms in the other condition as well (11).

It is assumed that both migraine and MDD share some genetic and environmental variables that are common for both conditions, such as stress, poor life habits, avoidance behavior and genes belonging to the serotonergic, dopaminergic, and gamma-aminobutyric acid (GABA)ergic systems (11,12).

5. Pathophysiology of migraine

The pathogenesis of migraines is becoming more well understood, where migraine is now considered to be more than just a vascular headache, but rather a complex and varied disease of nervous system due to improved characterization and identification of its symptoms (13). The earlier vascular hypothesis of migraine stated that vasoconstriction causes aura and vasodilation causes headache, however this hypothesis is no more supported. These days, theories of the pathogenesis of migraine propose number of fundamental neuronal abnormalities result in a cascade of extracranial and intracranial alterations that result in a migraine (6).

5.1. Effects of pro-inflamantory mediators during aura phase

The secretions of pro-inflammatory mediators with the propagation of this inflammatory signal to trigeminal nerve fibers near pia mater vessels are the mechanisms by which trigeminal afferents are activated. Such pro-inflammatory cytokines that are suggested to be involved in the pathogenesis including interleukin(IL-1β), IL-6, and tumor necrosis factor-α, that may be involved in the activation and sensitization of both meningeal and muscle nociceptors. The involvment of these pro-inflammantory mediators are suggested to account for prolonged activation of trigeminal nociception that causes headache and the cerebral depression that forms the aura. The aura is thought to be caused by the cortical spreading depression of Leão, which propagates a wave of neuronal and

glial depolarization and starts a cascade, which activates trigeminal afferents and changes the permeability of the hematoencephalic barrier by activation of matrix metalloproteinase. The discomfort in the anterior area of the head may be explained by the fact that the ophthalmic division of the trigeminal nerve innervates this specific area. This pathogenesis can be supported by the fact that non-steroidal anti-inflammatory drugs can help in abortion of the migraine attacks (6,14).

5.2. Vasoactive neuropeptides role

Vasoactive peptides such as substance P, vasoactive intestinal peptide(VIP), and Calcitonin gene related peptide(CGRP) are released upon activation of the trigeminal ganglion and showed association by being increased during migraine attacks (15). CGRP specifically plays a significant role in the pathogenesis and started being used as part of the treatment against migraine targeting it. Patients with migraine were found to be triggered by an intravenous infusion of CGRP, where healthy volunteers were not affected by this injection. CGRP is encoded by calcitonin gene which is neuropeptide that acts in digestive, sensory, and cardiovascular systems. The development of neuronal sensitization and the production of pain, particularly in migraine, have been linked to its somatosensory function. CGRP behaves differently on the central nervous system and on the peripheral nervous system. CGRP is found in the afferents nerves that innervate the meningeal blood vessels where it facilitates vasodilation and induce pain. In addition, it is also believed that CGRP acts at several locations along the trigeminovascular system. In addition to causing arterial vasodilatation, peripheral release of CGRP in the meninges can also induce sterile inflammation and meningeal nociceptors to become activated. Furthermore, CGRP has been linked to trigeminal ganglion neuronal-glial cell signaling, which may aid in peripheral sensitization (16,17).

it was first found that CGRP was elevated in jugular outflow during the episode of the migraine and was found to elevated in more body fluids, including saliva, plasma and tears (18).

6. Clinical picture and diagnosis of migraine

The migraine attack usually last between 4-72 hours and can be divided into 4 phases:

- **Premonitory phase:** Usually starting hours to even days before the headache symptoms begin. Neuroimaging show evidence of hypothalamus involvment in this phase. The symptoms of this phase include mood swings, difficulties with concentration, stiff neck, yawning, fatigue, increased micturition frequency, and thirst (17,19).
- **Aura phase:** This phase precedes the headache pain. This phase does not occur in all individuals with migraine but in about third of the patients, where it is more common in female patients. Aura is a focal neurological deficit where the most prevalent symptoms are visual symptoms in over 90% of patients, sensory symptoms with up to 50% of patients, and language symptoms with about 30% of patients. Symptoms of motor, brainstem, and retinal symptoms are can also appear but are much less common (17,19).
- **Headache phase:** The classic symptom of throbbing pain of a migraine is produced during this phase through the activation of the trigeminal sensory pathway. The headache intensity can progress over time or starts at maximum intensity. Movement of the head usually makes a headache intensity worse. This phase typically accompanied with vomiting, nausea, and aversions to light (known as photophobia), sound (known as phonophobia), touch (known as allodynia) and smell (known as osmophobia) (17,19).
- **Postdrome phase:** This is defined as the time between headache resolution and the return to feel completely back to normal. This phase contains symptoms such as fatigue, drowsiness, difficulties with concentration, and increased sensitivity to noise are among the most common symptoms that occur during this phase. The intensity and duration of these symptoms are usually correlated with the intensity of the pain during the headache phase, individuals with greater intensity of headache usually will have greater intensity of the symptoms of postdrome phase. Due to its symptoms, this phase is also known as "migraine hangover" (19,20).

Migraine is classified into migraine with aura or without aura, although many patients can have both conditions. Migraine with aura and migraine without aura are suggested to have different etiologies. Patient with migraine with aura are at elevated risk for ischemic stroke while there is no relation for those with migraine without aura. According to imaging studies, those who experience migraines are more likely than controls to have structural brain alterations, some of which are particularly noticeable in patients with aura rather than those without aura, as well as there is difference in blood flows during the migraine attack for those with aura and those without aura. Therefore, it is still unclear if migraine with aura is a separate condition or is a subset of migraine spectrum (21).

Migraine is diagnosed clinically based on the patient's history using the criteria of International Classification of Headache Disorders(ICHD-3) that states that there must be at least five untreated headache attacks lasting 4–72 hours with at least two of the following: unilateral, pulsating, moderate to severe in intensity, and aggravated by routine physical activities. Each attack must be associated with nausea and/or vomiting, and/or photophobia, and/or phonophobia (22,23).

The need for neuroimaging in the diagnosis of is when there is a need to confirm or exclude causes of secondary headache that are suspected on the basis of red flags such as unexplained fever, impaired memory and focal neurological symptoms, neck stiffness, weight loss, or altered consciousness or personality. Where MRI is preferred over CT due to higher quality of imaging and not exposing the patient to ionizing radiation (24).

Although migraine symptoms have some more suggestive symptoms it is still misdiagnosed in many cases. There are a number of reasons why diagnosis of migraine is sometime inadequate, including poor patient awareness, lack of biological migraine indicators, and the use of patient history as the only basis for diagnosis. Furthermore, research has shown that neurologists do not find headache sub-specialization to be particularly attractive. This insufficient diagnosis can have many negative effects of patient quality of life (25).

6.1. Migraine without aura

This type is the most common form of migraine in both pediatric and adults. Presenting with three phases: prodromal phase, headache phase, and post-dromal phase. The symptoms are diverse and heterogenic (26). These headaches recur and continue between four and 72 hours and are the hallmark of migraine without aura. Symptoms including pain that is unilateral location, pulsating in nature, and worsening by ordinary activity. However, about 40% of the people are experiencing pain that is bilateral during the episodes, therefore bilateral discomfort is not uncommon. The most frequent accompanying symptoms include nausea, vomiting, photophobia, and phonophobia (24).

Table 1. ICHD-3 diagnostic criteria for migraine without aura (23).

Migraine without aura
A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

6.2. Migraine with aura

This subtype is experienced in about third of patients with migraine which can be either during every episode or during part of these episodes of migraine attacks.

ICHD-3 farther subdivide into migraine with typical aura, migraine with brainstem aura, hemiplegic migraine, and retinal migraine (23).

Aura is a transient localized neurological symptoms which occur before, but occasionally also accompanying, the phase of the headache. Aura manifest visual symptoms in more than 90% of the cases and divided into positive and negative, where positive are more common and include flash hallucinations, flash scotoma, visual distortion and sense of heat wave, where the negative symptoms include dark spots, blurred vision and homonymous hemianopia (24,27). Almost third of the cases showing sensory symptoms, which are mostly unilateral paresthesia that eventually extends to the arm or face. Less common symptoms of aura including aphasic speech, dysarthria, vertigo, motor weakness in hemiplegic migraine, and retinal symptoms such as monocular vision abnormalities (24). Visual and sensory symptoms are mostly unilateral, while speech aphasia is mostly Broca aphasia like, which means the patient can comprehend but cannot speak (28). It's important to notice that migraine with and without aura can often coexist and therefore both should be diagnosed in such circumstances. Transient ischemic attack and aura symptoms share many similarities, however aura symptoms can be distinguished by the fact that TIA symptoms generally begin abruptly and occur simultaneously, whereas aura symptoms generally occur gradually in a period of more than five minutes (24). For better distinguishing migraine aura from transient ischemic attack, aura symptoms have to fulfill three of the following: at least one aura symptom that progress over at least 5 minutes, more than two aura symptoms that occur in succession, last for 5-60 minutes, one or more aura symptom that is unilateral, and accompanied by a headache either immediately after the or within 60 minutes after it occurs. The previous term basilar artery migraine is now known as migraine with brain stem aura which is likely involving the basilar artery in the pathogenesis (29).

Migraine with brainstem aura features include the following: vertigo, dysarthria, diplopia, tinnitus, ataxia, and consciousness disturbances. The duration of

migraine with brain stem aura is usually short and level of consciousness generally return to normal within about 30 minutes (30).

Table 2. ICHD-3 diagnostic criteria for migraine with aura (23).

Migraine with aura
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal
C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis

6.3. Episodic migraine

Episodic migraine is defined as migraine headaches that occur on less than 15 days per month. Episodic migraine is much more common than chronic migraine. Patients with episodic migraine can remit, stay the same, or progress into chronic migraine over time (31). Episodic migraine can be further differentiated to low-frequency episodic migraine and high-frequency episodic migraine, where there is no clear defintion but in general 8 to 14 or 10 to 14 migraine headaches days per month are used to characterize the high frequency (32).

6.4. Chronic migraine

Chronic migraine impacts around 2% of people in the population which is far less than episodic migraine. These patients experiencing headaches for at least 15 days per month, with a minimum of 8 days exhibiting headache related symptoms that are consistent with a migraine. Such patients suffer from frequent headaches, vomiting, nausea, and high sensitivity to visual, auditory, and smell stimuli. It usually develop after gradual rise in the frequencies of the migraine headaches in period of months to years (33). Chronic migraine accounts for about eight percent of all patients with migraine. Chronic migraine develops from episodic migraine with year progression rate of 3%, indicating that chronic migraine might be neurological condition that progresses over time. However, although this suggest that episodic and chronic migraine are disorders within the same spectrum where episodic progress into chronic migraine, there are other suggestions that claim that chronic migraine is a separate clinical entity where episodic migraine is only a predisposition for developing chronic migraine later on (34). Chronic migraine mostly occur simultaneously with medication overuse headache, with medication overuse headache developing in more than half of the patients suffering from chronic migraine (35).

Table 3. ICHD-3 diagnostic criteria for chronic migraine (23).

Chronic migraine
A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C. On ≥8 days/month for >3 months, fulfilling any of the following: 1. criteria C and D for Migraine without aura 2. criteria B and C for Migraine with aura 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

7. Migraine treatment

7.1. Acute treatment

Acute treatment is considered as an abortive treatment and is used once the attack has started with the goal to abort the symptoms associated with the migraine attack. The drugs used in acute treatment can be classified into specific and non-specific (36).

7.1.1. Specific acute treatment drugs

- **Triptans**

  Triptans are the most effective migraine specific drugs thus used as first line among these drugs and being used in moderate to severe attacks of migraines. 7 different triptans can be used in different dosages and different routes of administration. Triptans are effective in 60% of patients with migraine who didn't respond to NSAIDS. Using triptans in oral routes are suitable for patients who do not experience associated nausea, where subcutaneous and nasal spray can be used for those that experience nausea and vomiting. Triptans are administrated at the onset of the headache phase and are contraindicated during the aura. Triptans can be repeated after 2 hours as needed but should not be used more than twice a week and can cause medications overuse headache if used more than 10 days a month.

  - **Sumatriptan –** Oral tablets 25-100 mg, Nasal spray 5-20 mg, Subcutaneous injection 4-6 mg.
  - **Rizatriptan –** Oral tablets 5-10 mg.
  - **Zolmitriptan –** Oral tablets 2.5-5 mg, Nasal spray 2.5-5 mg.
  - **Frovatriptan –** Oral tablets 2.5 mg
  - **Eletriptan –** Oral tablets 20-40 mg.
  - **Naratriptan –** Oral tablets 1-2.5 mg.
  - **Almotriptan –** Oral tablets 6.25-12 mg.

The choice of the specific triptan is individualized. If there is no response to one of the triptans after 3 trials, it should be considered to increase the dose or using another triptan (36,37).

- **Gepants**

  Gepants are non-peptide small molecules that act as CGRP antagonists taken orally. Rimegepant and ubrogepant are used for acute treatment for both migraine with aura and without aura, where rimegepant can be used in preventive treatment for episodic migraine as well. Rimegepant is used in 75 mg per day and ubrogeptant used in 50 or 100 mg per day. Clinical trials show that gepants seem to be safe in patients with history of cardiovascular diseases and thus can be preferred over triptans in such patients in acute treatment (38,39).

7.1.2. Non-specific acute treatment drugs

- **Simple analgesics**

  Simple analgesics are used as first line in mild to moderate migraine attacks. They should be administrated early in the migraine attack usually combined with the antiemetics such as with 10 mg of the D2 antagonist metoclopramide especially if the patients having nausea at that time. These medications include Paracetamol in 1000 mg and different NSAIDS such as:

  - Acetylsalicylic acid – 500-1000 mg
  - Ibuprofen – 200-800 mg
  - Naproxen – 500-825 mg
  - Diclofenac – 50 mg

  Usually combinations of acetylsalicylic acid or paracetamol with caffeine make them more effective in treating the acute migraine, however this increases the risk for medication overuse headache. In order to prevent medication overuse headache, their usage should be no more than 15 days a month and use of combined analgesics to no more than 10 days a month (36,40–42).

- **Antiemetic**

  Dopamine receptor antagonists are used alone or in combination with other acute treatment to manage the associated nausea and vomiting with the migraine attack and to increase the absorption and thus the bioavailability of the triptans and analgesics taken along. Doses recommended are 10 mg of metoclopramide and 10 mg of domperidon, where metoclopramide is

considered the primary agent in the treatment of acute migraines in settings of emergency (40,43).

- **Opioids**

  Opioids are rarely used in acute migraine treatment because they are less effective than all other drugs for treating acute migraine and also due to their side effects. They can be used in patients who cannot use triptans such as patients with ischemic heart disease (36,40).

7.2. Preventive pharmacological treatment

Prophylactic treatment should be started for:

- Recurrent migraine attack that is disabling regard being acutely treated.
- 2 or more severe disabling migraine attacks in a month.
- When acute treatment did not respond or contraindicated or risk for causing overuse.
- Very disabling symptoms even if infrequent (including brainstem aura, hemiplegic migraine, syncope)

7.2.1. Non-specific preventive treatment

The non-specific prophylactic drugs for migraine are drugs which were developed for different conditions such as hypertension, epilepsy, and depression. The choose for the exact medication is based on evidence for efficacy, adverse effect or contraindications to the medications, costs, availability, patient preference, drug interactions, and patient comorbidities such as patients with asthma should not receive beta blockers or patients with comorbidity of depression could benefit from tricyclic antidepressants. Medications should initiate as low dose and slowly increased until reaching therapeutic effect and could be considered ineffective only after a perioid of at least 8-12 weeks of therapeutic dose. Most prophylactic treatment last at least 6 months where after this perioid the medications can be withdrawn slowly (36,44).

Prophylactic treatment usually does not stop all migraine attacks but reducing the headache frequency with goal to reduce the frequency in about 50%, and acute treatment is still needed. Although monotherapy is preferred, it is often not enough

to achieve the desired therapeutic effect, thus combination of different preventive medications is usually desired (36,45). The medications that can be used include the following:

- **Beta blockers**

  These are the most used preventive migraine drugs and are considered as first line treatment. Effective in reducing the migraine frequency attacks in half or more for up to 60-80% of the patients. Beta blockers also reduce the severity and the duration of the migraine headaches. They are especially used in patients with comorbidities such as hypertension and angina, and are contraindicated in patients with asthma, heart failure, insulin dependent diabetes and Raynaud's disease. Among them propanolol is the most widely used in a dosage of 40-240 mg per day. Other beta blockers such as atenolol and bisoprolol can also be prescribed (36,46).

- **Anti-seizure drugs**

  Most widely used anti-seizures drugs for prevention of migraine are valproate, topiramate and gabapentin. These medications are also considered as first line and are especially useful in patients with comorbidities of epilepsy, anxiety, and bipolar disorders. Valproate can be sodium valproate, or divalproex sodium (a mixture of the two) and is used in a dose of 500-1000 mg per day. Valproate shows to reduce both the migraine headaches frequency and severity. Valproate should be avoided in pregnant patients. Topiramate should be given at a dose of 50-100 mg per day, as clinical trials have shown that there is not significant difference in the efficiency above this dose. Gabapentin can be given in a dose of 600-3200 mg per day and is considered the least effective among the anti-seizure drugs for chronic migraine but due to its effect on neuropathic pain, gabapentin may be advantageous in patients with co-existing neuropathy, chronic pain or trigeminal neuralgia (36,47).

- **Calcium channel blockers (CCB)**

  Mainly include flunarizine in a dose of 5-10 mg per day and was proved to prevent migraines in randomized control trial(RCT) especially in patients with complicated or prolonged migraine aura, Although verapamil is also sometimes

used in migraine prevention even though there is no RCT evidence to support this. CCB are considered as first or second line treatment in different countries (36,48).

- **Antidepressants**

  These drugs are considered as second line and used for migraine prevention especially with coexisting depression and include amitriptyline which is a tricyclic antidepressants(TCA) that is used in a dose of 25-150 mg per day and also help for coexisting insomnia (48,49).

- **Botulinum toxin**

  Botulinum toxin is a very cost effective drug which is an exotoxin produced by the bacteria clostridium botulinum which cause blockage of acetylcholine release at the nerve endings. It is used as intramuscular injection route in different areas around the head and neck every 3 months by a physician. Patients should try other treatments for migraine prevention before initiating this treatment (50,51).

7.2.2. Specific preventive treatment

- **Anti-CGRP antibodies**

  Usage of anti-CGRP antibodies as preventive treatment for migraine is relatively new treatment. They have relatively long half-lives that allow injection every 1 month or every quarterly which means every 3 months. Showing high efficacy in migraine prevention. They target CGRP itself such as eptinezumab, fremanezumab, and galcanezumab, or CGRP receptor such as erenumab. Due to their molecular size they can only be administrated in injection route mostly subcutaneously and can be self-injected unlike botulinum toxin that must be injected by a physician (50,52–54).

Table 4. anti-CGRP antibodies doses and administartion routes (52).

Name	Route	CGRP target	Frequency	Dose
Eptinezumab	Intravenously	Ligand	Quarterly	100-300 mg
Erenumab	Subcutaneously	Receptor	Monthly	70-140 mg
Fremanezumab	Subcutaneously	Receptor	Monthly	225 mg

			Quarterly	675 mg
Galcanezumab	Subcutaneously	Receptor	Monthly	120 mg

- **Gepants**

  As previously mentioned, Gepants are CGRP antagonist administrated orally. Rimegepant is used for prevention of episodic migraine in a dose of 75 mg per day, where atogepant is used for prevention of both episodic and chronic in a dose of 10, 30, or 60 mg per day depends on the severity, frequency, and comorbidities (38,55).

7.3. Non-pharmacological preventive treatment

This approach of treatment include lifestyle modification and avoiding of recognized triggers are important in order to reduce the frequency and the intensity of migraine. For example these include weight loss in case of obesity, reducing the amount of alcohol, reducing or quitting smoking, regular exercises, and drinking enough water in order to keep hydrated (56).

Exercise in addition might also decrease the migraine duration, severity, and the need for abortive treatment. Red wine and chocolate are associated with triggering migraines as well, even though identifying the exact food triggers in migraine is difficult to identify, many “migraine diets” including elimination diets are reported to help in some patients. Sleep comorbidities such as sleep apnea and insomnia are reported to be associated with migraine as well and poor sleep was reported to trigger migraine, therefore better sleep schedule can improve the condition of migraine as well (57).

Acupuncture, especially the Chineese acupuncture is found to be beneficial in both acute and preventive treatment of migraine. Studies suggest that it is as effective as the prophylactic drugs for migraine with the benefits of safety, long lasting, and cost effective (58).

8. Migraine and quality of life

Migraine was identified by World Health Organization in the top 20 causes of disabilities and defined as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (59,60).

Living with a migraine is difficult because it causes many disabilities on the daily life, which are exacerbated by anxiety of constantly thinking about the future attacks and a sense of helplessness over the condition, making plans and carrying out actions are impacted by this condition due to the uncertainty. Moreover, as in other chronic diseases, the quality of life is also affected by the fact that its negative effect also on the social life, family of the patient and career of the patient with financial consequences (59)**.**

Migraine accounts for 1.3% of years with disability in the world which is half all headaches together (61). Global Burden of Disease identify migraine as the seventh leading cause of years lived with disability generally and first among those under the age of 50. Between 50-73% of people with migraines report negative impact on their family not only during the attack but also in between the attacks. Furthermore, migraine is linked to significant impairment in function, which impact on social, professional, and academic performance with over of ninety percent of people report that during the migraine episode they are either unable to work effectively or are unable to work at all. In order to effectively treating migraines, patients' quality of life assessments is crucial by assessing the activity limitations and any disabilities (60).

The burden of disability is approximated to be twice higher in chronic migraine than episodic migraine and also with higher incidence of comorbidities than episodic migraine (34)**.** Another study has shown that there was a moderate to severe impairment in disease-specific quality of life and associated disability among patients with migraine who sought therapy. Predictors of migraine-related impairment include headaches with a significant to severe effect, headaches with longer durations, and headaches that are more frequent. Coexisting mental

illnesses increase the impairment caused by migraines and lower quality of life, where not just the migraine themselves are associated with emotional and mental effects impairing the quality of life, but frequent coexisting conditions that we found associated such as anxiety and depression that increase the effect on quality of life and disabilities even further, therefore a thorough examination of must also involve an assessment of the patient's mental health as well in order to provide management and reach a higher quality of life (62).

According to another study, just 13% of patients with migraine had little to no disability related to migraines, where more than fifty percent of patients with migraine had severe disability. The prevalence of disability was considerably greater in women, healthcare professionals, and people with lower incomes. It was also shown that most patients with migraine experienced a highly significant impairment that had a negative effect on their quality of life in all domains (63).

8.1. Effect on family

Number of studies have evaluated the influence of migraines on family life and found that they negatively affect social and recreational activities as well as family life, particularly affecting patient's spouses and children. Individuals who suffer from migraine, especially chronic migraine, together with their partners and spouses, have reported several detrimental implications on family members. For instance, adolescent children for patients with chronic migraine, reported to miss big events, social gatherings, and group activities much more often than adolescent children of individuals with episodic migraine. It is suggested that higher incidence of migraine attacks of the parents was linked to a bigger negative effect on the general well-being and personal future of the adolescents. Individuals with migraines reported feeling less active in their children's home and school life and arguing more frequently with their spouses and children. In a global study About 50% of participants have reported negative effects such as missing social occasions, avoiding to commit, and negative influence in their sexual lives, where almost half of them felt guilty on their family members (64). About 80% of patients with migraines report delay cooking, cleaning, shopping, and yard chores,

and around 65% postpone activities with their children and spouse. Another study has shown that 85% of patients with migraine at decrease in capability to do household work and almost 40% of spouses of patient with migraine reported a considerably lower capacity to conduct household tasks due to their spouse. According to reports about forty percent of people with migraine postponed social events with friends and family, about 30% canceled birthday or anniversary celebrations, about 20% canceled vacations, and another twenty percent canceled holiday events. It was reported that 20% of people with migraine are missing one or more days of family or social events on average every month. It was also indicated that their migraines had an influence on their sexual interactions in about 25% of cases, that they needed marital therapy in about five percent of cases, and that their migraines caused them to separate or divorce in five percent of the cases. There appears to be a difference in views and higher levels of anxiety between patients with migraines and their spouses, as those with migraines expressed more concern about the financial burden of their condition than did their spouses, especially those with chronic migraine. Additionally, study participants stated that they thought they would be better parents if they were migraine-free (65).

8.2. Effect on career

Migraine is also linked to unfavorable effects financially as it has effects on both education and career. According to a cross-sectional study carried out in several headache centers in Austria, roughly 34% report negative effect on their careers, and twenty one percent report a negative effect on their earnings.

It's interesting to note that only half of the people with migraine feel their coworkers accepted their headaches. According to this study, there is a negative correlation between headache frequency and financial, professional, and other outcomes (64).

8.3. Economic effects

In research was done in the UK, migraines account for over 25 million of days loss at work or school each year (60). The yearly medical expenses of patients with

chronic migraine is approximated to be about three times more than patients with episodic migraine, which include long term medications, diagnostic tests, hospitalization, and visits in the emergency ward. A research that was done in Australia has estimated the yearly economic cost of chronic migraine in this country was 8 billion dollars, almost 3 billion dollars for the health system costs, and around 4 billion dollars for the loss of productivity (34). Another research that was conducted in the United States in 2016, Both direct costs (including medical and pharmaceutical expenditures) and indirect costs (including loss of productivity, and related disability) was estimated to be 36 billion dollars. The average difference in healthcare expenses between patients with migraines to people without migraines were estimated to be 6,575 dollars more for the patients with migraine. The cost of migraine medications has drastically increased in the recent years due to the recent new, branded, and pricy medications both for acute and prophylactic treatment, but especially the introduction of anti-CGRP monoclonal antibodies medications (66).

8.4. Migraine as a stigma

Stigma is defined as a mark, condition, or status that is devalued by the society. Stigma around migraines is a common issue which exacerbates the discomfort associated with the disease, which arise mostly from the lack of knowledge and awareness of this disorder. Several terms that are being used to characterize patients with migraine for example as pill poppers, histrionic, drug seekers, lazy, or incapable of handling stress. One of the social effects of this distortion of migraine is that people who don't fit this stereotype often won't identify their own migraine symptoms, which may cause them to put off seeking any medical help. It may result in prejudice in personal relations, in healthcare settings, and the workplace. People who suffer from migraine can find it uncomfortable to discuss about their illness in the workplace because the fear of judgment. In one survery that was done on 4,000 people, about 50% of people with migraines reported they did not tell their boss the reason for the days they were absent. Additionally, it may result in emotions of shame, remorse, and isolation. Decreasing the stigma of migraine

is an important in order to improve the quality of life of the people suffering with migraines (67).

Another study which was conducted on 60,000 people with migraine, has shown that approximately third of the people experienced stigma related to their migraine either as minimizing the burden suffering from migraine or in a way of thinking of these people using it in order to get a secondary gain. This study has found that those who experienced migraine related stigma were more associated with increased disability and decrease in the quality of life (68).

9. Scales

9.1. Migraine Interictal Burden Scale

Interictal mean between the migraine attacks, which means this scale measure the burden associated with migraine in the perioid in between the attacks, which is used as questionnaire that is used clinically. This scale is using 4 domains including impairment at work or school, impairment at family and social life, difficulty making plans or commitments, and emotional and cognitive distress. MIBS-4 specifically asks about migraine effect in a period of the last 4 weeks on days without any migraine attack. Each domain has 5 option to answer (don't know/not applicable, never, rarely, some of the time, much of the time, or most or all of the time) and getting a numerical score. With score ranging from minimum of 0 points to maximum 12 points. where 0 is no burden, 1–2 is mild burden, 3–4 is moderate burden, and 5 or more is severe burden (68–70). Example of using MIBS-4 in research**:** One epidemiological study conducted in Japan in 2020, used MIBS-4 as part of migraine to assess the interictal burden of migraine. This study has shown that 19% responded that the headaches affected work or school at times when they did not have a headache, about 27% responded that they worried about planning social activities. Approximately 22% reported that headaches impacted their lives at times they did not have headaches and another 22% reported that they feel helpless at times when they did not have a headache (71).

9.2. Migraine-Specific Quality-of-Life Questionnaire

Glaxo Wellcome has created the first version of the MSQ in 1992. It was a 16-item test with three domains. The questions chosen were determined by means of 25 individual patient interviews, in which participants were requested to provide feedback regarding difficulty, comprehensiveness, and appropriateness of proposed response categories. The MSQ version 2.0 was revised as a consequence of additional development research performed on the first version which included input from doctors and patients engaged in five clinical trials. In the end 2 items were removed from the second version which was yielding the last version MSQ v2.1 (72).

MSQ v2.1 is a questionnaire which have 14 items about migraine attack in the previous 4 weeks that assesses the effects of migraine on quality of life in 3 domains:

1.Role Restrictive: Originally called Role Function Restrictive in MSQv1, which consists of seven items that demonstrate how the functional impact of migraine limits regular activities such working, productivity, regular daily activities, amount of energy, amount of tiredness, ability to concentrate, leisure, and relationships.

2.Role Preventive: Originally called Role Function-Preventive in MSQv1, which consists of four items that show how the impact of migraine prevents social and daily activities.

3.Emotional Function: Consists of three items that evaluate the emotional effect of migraine for example such as feeling frustration or helplessness due to the migraine.

Each question in the questionnaires has 6 options to answer ranging from 1 to 6 with relation the time that the migraine attack affected in relation to the question, where 1 is non, 2 is little bit, 3 is some, 4 is a good bit of time, 5 is most of the time, and 6 is all the time. The score is between 0 to 100 where sum of all scores from each domain is added, where the greater the score the greater the quality of life. Role Restrictive is specifically helpful instrument for evaluating the functional

effect of migraine in clinical trial including both episodic and chronic migraines (73–75).

The English version of MSQv2.1 shows good reliability and good validity. However, there is not a good validated version for many other languages such as MSQ in Chinese, even though China contributes to large number of world population and good valid MSQ in Chinese could have provided good tool for evaluation for big number of population with different culture. Thus there was a study which aimed to address a good reliable version of MSQ in Chinese, where the process of translation included both forward translation and back translation, in order to achieve semantic and content equivalencies. Then, the MSQ was administrated to 11 monolingual people with migraine for evaluation of its readability and understandability (75). Example of using the MSQ: Study that wanted to estimate the impact of their migraine on their quality of life, used different tools were including the MSQ. The study has found the longer duration of the migraines, and the more frequent the migraine attacks are the score in MSQ were higher (62).

9.3. Migraine Disability Assessment Score questionnaire

MIDAS the most common questionnaire that is being used for assessing disability associated with migraines. While its validity and reliability have been thoroughly examined, its applicability in determining treatment response is still debatable where some of the difficulties to fully assess the efficacy of migraine therapies is due to majority of it is self-reports. Since the questions used in MIDAS covering various important aspects specified by the International Classification of Functioning Disability and Health, it is frequently used to evaluate therapies for migraines in clinical trials (76,77). MIDAS Questionnaire is made of 5 questions that evaluate the time lost due to the migraine attacks in the previous 3 months. It is the only tool that has been demonstrated correlation with both physicians' evaluation of therapy needs and outcomes of the therapy.

Based on impairment caused by the migraine headaches grades ranging from I (where there is no or little disability) to IVb (where there is very severe disability).

Patients who were treated with therapies based on their MIDAS grade in a

randomized controlled study showed much better clinical results than patients who were treated with conventional care procedures. However, the association of MIDAS score on the direct medical expenses for migraine is not yet well determined, however there is hypothesis that the higher the MIDAS grade the higher the medical expenses, where study performed in united states found such correlation where examined patients with episodic migraines (77). MIDAS also helps to improve the communication between the patient and the physician about the consequences of migraine. MIDAS is being used not just by doctors but also nurses and pharmacists. The questionnaire focus on loss of time in 3 areas: work or school, house chores, and family and social actives. MIDAS is short and simple taking only a couple of minutes to accomplish (78).

10. Conclusion

Migraines can significantly affect the quality of life for those patients who suffer from it, impacting many different areas in life such as personal, family, social, and economically mainly due to their loss of productivity at work or some even ability to work at all. The chronic and debilitating nature of migraines leads to frequent disruptions in the everyday activities, contributing to a profound sense of disability and decreased life satisfaction. To estimate the impact of migraine on the life impairment different tools were developed such as MIDAS, MSQ, and MIBS-4. These tools demonstrate that migraines can often result in reduced productivity, increased absenteeism, and strained interpersonal relationships. Where MIDAS quantifies the extent of disability and its impact on work and everyday activities, by that revealing the significant economic implications due to lost productivity and healthcare costs. The MSQ quantifies especially the emotional and social effects, showing how migraines affect interactions with family and friends, leading to social withdrawal and emotional distress. MIBS-4 quantifies the continuous burden of migraines even during interictal periods, which further emphasizing the impact on overall quality of life. Collectively, these findings show the necessity for comprehensive management strategies that address not only the physical symptoms of migraines but also their psychosocial and economic effects in order to achieve effective management to improve their quality of life in all aspects.

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13. Biography

Shai Gilboa is a sixth-year medical student at the University of Zagreb, currently completing his review thesis as part of his final year of study. Born in Israel in 1995. Shai served three years in the army as a combat soldier before pursuing his medical education in Zagreb. Throughout his medical education, Shai has demonstrated a strong commitment to understanding and addressing complex medical issues. In addition to his academic pursuits, Shai is passionate about sports and intellectual activities. He is an avid tennis player and chess enthusiast. With a solid foundation in medical knowledge and a diverse range of interests, Shai aims to contribute meaningfully to the field of medicine with interest to family medicine and neurology.