RELATIONSHIP BETWEEN MIGRAINE TRIGGERS, AURAS AND TREATMENT

BERNADETTE LOUWRENS

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RELATIONSHIP BETWEEN MIGRAINE TRIGGERS, AURAS AND TREATMENT

By

BERNADETTE LOUWRENS

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Supervisor: Prof Ilse Truter

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I, Bernadette Louwrens, 183072710, hereby declare that the dissertation for my qualification of Magister Pharmaciae is my own work and that it has not previously been submitted for assessment to another University or for another qualification.

CONTENTS

TABLE OF CONTENTS

page

List of Tables

page

List of Figures

page

List of Abbreviations

5HT	5-hydroxytryptamine receptor
A.D.	"Anno Domini" (in the year of our lord)
ASD	atrial septal defect
B.C.	before Christ
BMI	body mass index
CGRP	calcitonin gene-related peptide
CM	chronic migraine
CSD	cortical spreading depression
DHE	dihydroergotamine
EHF	European Headache Federation
FHM	familial hemiplegic migraine
HM	hemiplegic migraine
ICHD	International Classification of Headache Disorders
ICHD-3	International Classification of Headache Disorders version 3
IHS	International Headache Society
NHMA	non-hemiplegic migraine aura
MRI	Magnetic Resonance Imaging
NMMU	Nelson Mandela Metropolitan University
OTC	over-the-counter
PET	positron emission tomography
SHM	sporadic hemiplegic migraine
UK	United Kingdom
US	United States
WHO	World Health Organization

ABSTRACT

Background: Migraine trigger factors are precipitating factors that can contribute to an attack by increasing the probability of a migraine occurring. For some migraineurs, the headache phase is preceded by a transient disturbance in neurological function (an aura). An aura could be visual or sensory in nature. There are medications that can be used to treat a migraine attack when it occurs (acute medication) and medication that can be used to reduce frequency and severity of migraine attacks (prophylactic medication).

Objectives: The primary aim of the study was to identify if there was a relationship between migraine trigger factors, auras and treatment.

Methods: The study was conducted in 2014 in Port Elizabeth and consisted of two self-administered questionnaire-based surveys, one for pharmacists and one for migraine patients. Migraine patient questionnaires were distributed to migraine patients who frequented pharmacies, physiotherapy practices and health shops. A total of 18 pharmacist questionnaires and 173 migraine patient questionnaires were analysed.

Results: Experiencing an aura before a migraine attack was reported by 43.9% of respondents and only “sometimes” by 22.5% of respondents. Visual auras were experienced by 92.0% of respondents who indicated that they suffered from migraine with aura and sensory auras were experienced by 71.5% of respondents, with 62.8% of respondents experiencing both visual and sensory auras. Trigger factors were experienced by 89.0% of respondents. There was no statistical relationship between aura and trigger factors, but there was a statistical relationship between trigger factors and visual aura at the 5% level (Chi-square = 7.966, d.f. = 1, p-value = 0.005). Cramér’s *V* showed a small practical significance at 0.218. About 80.0% of respondents used over-the-counter (OTC) medication and only 12.6% used migraine specific medication to abort a migraine attack. There was no statistical relationship between aura (visual or sensory) and abortive medication. There was a statistical

relationship between abortive medication and the presence of trigger factors (Chi-square = 8.775, d.f. = 3, p-value = 0.032). Cramér's *V* showed a small practical significance at 0.244. There was no statistical relationship in the presence of trigger factors between aura and abortive medication.

Conclusion: Migraine is a complex disease which affects people of all ages. There appears to be a statistical relationship between visual auras and trigger factors and between abortive medication and trigger factors. There was, however, no statistical relationship between aura and abortive medication in the presence of trigger factors. Further studies need to be conducted to substantiate these findings.

Key Words: Migraine, trigger factors, auras, abortive medication, questionnaire survey

Chapter 1

Introduction

1.1 Introduction

"And I have learned now to live with it, learned when to expect it, how to outwit it, even how to regard it, when it does come, as more friend than lodger. We have reached a certain understanding, my migraine and I".

Joan Didion
(Source: A-Z Quotes, 2016)

Migraine is a complex condition that affects people in many different ways. For patients who experience migraine for the first time, especially migraine with aura, it can be a terrifying experience as they think they could be having a stroke or that they have a brain tumour. It is only after multiple attacks that they come to realise that what they have is a recurrent benign condition.

A person who has never experienced a migraine can lose patience with those who are plagued by them. Their reaction starts with sympathetic concern, then tolerance and finally resentment and irritability. There is a "stigma" attach to migraine. The migraineur is often perceived as a person who has a "headache", a personality defect or an excuse to avoid unpleasant tasks and situations. This lack of knowledge and understanding adds to the burden of migraine. Not all patients are correctly diagnosed and this can lead to inadequate treatment. People, in general, need to be educated about migraine.

The International Classification of Headache Disorders (ICHD) defines migraine as a common disabling primary headache disorder. Pain ranges from moderate to severe, often incapacitating, lasting four to 72 hours. Pulsating or throbbing pain is often unilateral but can occur on both sides of the head or move from one side to the other during an attack. (Headache Classification Committee of the International Headache Society (IHS), 2013: 644).

Migraine is not just a “headache”. It is recurrent, intermittent, periodic attacks of debilitating throbbing, pulsating, one sided head pain, with accompanying symptoms such as nausea, vomiting and sensitivity to light, sound and/or smell (Lipton, Stewart & Scher, 2001: 6). There are a large number of people for whom certain factors act as trigger factors that can, on their own or a combination there of, trigger a migraine. What triggers one attack need not trigger another attack and what acts as a trigger for one person need not trigger an attack in others (Lipton, Pavlović, Haut, Grosberg & Buse, 2014: 1662). Migraineurs need to identify factors that act as trigger factors so that where possible they can avoid these factors and thereby reduce their incidence of migraine. For some migraineurs, the migraine headache phase is preceded by a transient disturbance in neurological function (an aura). An aura could be visual or sensory in nature. Visual auras are the most common type, taking the form of zig-zag lines, bright coloured lights that flicker and change shape and are often surrounded by an area of dimmed or absent vision. Sensory auras could be factors such as numbness of the face, arm or leg, vertigo or speech impairments. Auras usually last 20 to 30 minutes, but can last up to an hour (Schmidt & Willis, 2007: 144). There are medications that can be used to treat an acute migraine attack when it occurs (acute medication) and medication that can be used to reduce frequency and severity of migraine attacks (prophylactic medication) (Sheikh & Mathew, 2012: 19). The type of medication used depends on the intensity and frequency of migraine attacks.

Although very young children do get migraine it usually starts in puberty and diminishes after the age of fifty years. During these years, frequency and severity of migraine attacks can vary from one attack in two years to two attacks a week. Due to the frequency and incapacitating nature of migraine attacks it has a major impact on personal, social and work life (Silberstein, 2012:1-2). Migraine can evolve throughout a person’s life and can vary from attack to attack. The combination of symptoms, triggers and medication that works for one person is not necessarily the same for another person.

This study was undertaken to determine if there is a relationship between migraine trigger factors, aura and treatment. It consisted of two questionnaire-based surveys,

one for pharmacists and one for migraine patients. The pharmacist survey aimed to collect data on patients, who consult them, that suffer from migraine. The patient-questionnaire aimed to collect data on the patient and their experience of migraine.

1.2 Background to the study

The first description of possible migrainous symptoms was recorded during the Mesopotamian Era in about 3000 B.C. (Lane & Davies, 2006: 1). Aurelius Cornelius Celsus was the first person to recognise that migraine was a lifelong non-fatal disorder, with trigger factors. Paul of Aegina added “noises, cries, brilliant light, drinking of red wine and strong smells” to the list of trigger factors. Hippocrates the father of medicine was the first to describe a classical migraine with aura (Diamond & Franklin, 2005: 18, 20, 27). Historically, migraines have been treated with trial-and-error approaches, based on the prevailing medical knowledge of the time, or with primitive methods based upon superstitions, magic and religion. Some of the treatments prescribed by early physicians included: Drilling a hole in the skull to free "evil spirits"; purges and bloodletting; applying a hot iron to the site of pain; inserting a clove of garlic through an incision in the temple (Lane & Davies, 2006: 280).

Migraine is a genetic central nervous system disorder the mechanisms of which remain incompletely understood. However, new technologies have allowed formulation of current concepts that may explain parts of the migraine syndrome. Ravishankar (2010) reported that migraine pathophysiology has evolved from the vascular theory of Harold Wolff to a neurological disorder. The exact sequence of events that trigger a migraine are still not fully explained (Ravishankar, 2010: 30). Brain hyperexcitability such as abnormal neuron excitability makes a person more susceptible to migraine attacks (Aurora, 2004: 62).

1.3 Problem definition

In the Global Burden of Disease Survey 2010, migraine was ranked as the third most prevalent disorder and the seventh highest specific cause of disability worldwide

(Steiner, Stovner & Birbeck, 2013: 289). Migraine imposes a significant burden on patients, their families, healthcare systems and the economy (Blumenfeld, Varon, Wilcox, Buse, Kawata, Manack, Goadsby & Lipton, 2011: 301). The World Health Organization (WHO) estimates the worldwide prevalence of migraine to be 10% and lifetime prevalence to be 14% (World Health Organization, 2011). The adjusted prevalence of migraine is highest in North America, followed by South and Central America, Europe, Asia and Africa (Chawla, 2015: 10). The prevalence of migraine is lower in African Americans and Asian Americans than among Caucasians (Nicholson, Rooney, Vo, Laughlin, Gordon, Rooney, Vo & Louis, 2006: 754). Approximately 75% of migraineurs identify triggers that will almost always induce a migraine attack (Kelman, 2007: 401). About 30% of migraineurs experience an aura (Young, Silberstein, Nahas & Marmura, 2011: 1, 30). Regardless of the fact that migraine has a high impact on society, research on migraine prevalence, trigger factors and aura is limited in South Africa.

This study will investigate migraine, firstly as reported by community pharmacists and secondly as reported by migraineurs in the Port Elizabeth area. Data from the pharmacist survey will be analysed to determine type of medication used by migraine patients that consult them per month. Data from the patient survey will be analysed to determine if there is a relationship between trigger factors, auras and treatment.

1.4 Research objectives

The primary aim of the study is:

To gather information about migraine from migraine patients, with specific reference to migraine triggers, auras and treatment to determine if there is any link between what triggers a migraine and/or whether an aura is experienced and which treatment is being used.

This aim will be achieved through the completion of the research objectives of two questionnaire-based surveys, one for pharmacists and one for migraine patients. The pharmacist survey will gather information on migraine patients who consult with them

regarding their migraine. Information regarding migraine cocktails/kits will also be gathered. The objectives of the pharmacist questionnaire survey are to determine:

- the average number of male and female patients that consulted the pharmacy staff per month that fitted the criteria for participation in this study;
- the average age of migraine patients and what their gender distribution was;
- the percentage migraine patients with prescriptions as opposed to “walk in” migraine patients and their average age;
- the percentage and average age of migraine patients with doctors’ prescriptions as opposed to specialist prescriptions;
- how often patients were referred to confirmed diagnosis and improve treatment; and
- if the pharmacy sold a migraine cocktail/kit, ingredients of the cocktail/kit, what the demand for such a product was and what the price for the migraine cocktail/kit was at the time of completing the questionnaire.

The migraine patient survey will gather information about the migraine patient and their experience of migraine. The objectives of the migraine patient questionnaire survey are to determine:

- demographics of defined target group - gender, age and race;
- the respondents’ migraine history;
- special section for female migraine sufferers – focussing on hormonal influence and hormonal treatment;
- information on the auras, triggers, co-morbid conditions and other medical conditions that a respondent suffered from;
- the different type of medications and treatments that the participants had tried or were using. In this section information was also obtained as to whether use was being made of complementary and alternative treatments for migraine; and
- the respondent’s experience of a typical migraine attack.

1.5 Division of chapters

The division of chapters in this study are as follows:

- Chapter 1: Introduction
- Chapter 2: Overview of migraine

  In this chapter a brief history on migraine will be given. Migraine will be defined and epidemiology, pathophysiology, classification and comorbid conditions will be discussed.
- Chapter 3: Overview of trigger factors, auras and treatment

  The various trigger factors and auras will be disused as will the treatment options, acute medication, prophylactic and alternative treatments.
- Chapter 4: Methodology
- Chapter 5: Results and discussion
- Chapter 7: Conclusions and recommendations

Chapter 2

Overview of migraine

2.1 Introduction

Literature abounds with personal observations and insights, through the ages, from distinguished physicians and scientists who were fascinated with migraine. Migraine is a neurological disorder with headache being the most prominent symptom. The exact pathophysiology is still not fully explained and migraine is defined and classified entirely by its clinical history. Worldwide epidemiology of migraine gives an insight into the burden, personal, social and economic, that the migraineur experiences. There are a number of comorbid conditions associated with migraine.

2.1 Brief history of migraine

2.1.1 Migraine in ancient times (3600 B.C. to 500 A.D.)

The first description of possible migrainous symptoms were recorded during the Mesopotamian Era in about 3000 B.C. (Lane & Davies, 2006: 1). The ancient people of Mesopotamia suffered from headaches and attributed their pain to *Tiu,* the evil spirit of headaches, who supposedly attacked a victim (Diamond & Franklin, 2005: 12). The ancient Egyptians were the first to give a written description of migraine. Migraine is accurately described in the Ebers Papyrus, one of the oldest preserved medical documents which dates back to 1552 B.C. (Daniel, 2014). Historically, migraines have been treated with trial-and-error approaches, based upon the prevailing medical knowledge of the time, or with primitive methods based upon superstitions, magic and religion. Some of the treatments prescribed by early physicians included: drilling a hole in the skull to free "evil spirits"; purges and bloodletting; applying a hot iron to the site of pain; and inserting a clove of garlic through an incision in the temple (Lane & Davies, 2006: 280).

Hippocrates the “Father of Medicine”, was the first to describe classical migraine with aura in approximately 460 B.C. “*Most of the time he seemed to see something shining before him like a light, usually in part of the right eye, at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck… vomiting when it*

became possible, was able to divert the pain and render it more moderate" (Diamond & Franklin, 2005: 18).

Aurelius Cornelius Celsus (25-50 A.D.) was the first person to recognise that migraine was a lifelong non-fatal disorder, with trigger factors and the headache being localised or generalised (Daniel, 2014). Aretaeus of Cappodocia (30-90 A.D.) was the first person to distinguish migraine from other types of headache and called migraine "Heteracrania" as the pain was unilateral. He classified migraine because of its one sidedness, often associated with nausea and regular occurrence interspersed with pain free periods. Treatment proposed was blistering agents to be applied to the shaved head (Diamond & Franklin, 2005: 20).

Galen (131-201 A.D.) offered "Hemicranina" which means half of head as a descriptive and diagnostic term to describe these one sided sick headaches. "Hemicranina" was changed by later Romans to the Latin "Hemicranium", which was changed to "Hemigranea" which through translation and mistranslation to "Migranea, Mgrainea, and Migrana". The French later changed the word to the current "Migraine" (Daniel, 2014).

2.1.2 Migraine in the postclassical era (500 to 1500 A.D.)

In the seventh century, a physician from Alexandria, Paulus Aeginata listed migraine triggers: "*Noise, cries, a brilliant light, drinking of wine and strong smelling things which fill the head. Some as if the whole head where struck, and as if one half, in which case the complaint is called hemicranias*" (Daniel, 2014). Treatments for headaches in Medieval Europe were probably drug soaked poultices, composed of vinegar and opium, applied to the shaven head. The vinegar being used to open the pores in the scalp so that the opium could be absorbed (Daniel, 2014).

2.1.3 Migraine in the early modern period (1500 to 1750)

Thomas Willis (1621-1696) made accurate observations about migraine. He observed that migraine was benign, had a hereditary link, occurred with season and atmospheric

changes and was aggravated by certain diets. The vascular theory to explain the cause of migraine was introduced by Willis (Daniel, 2014). Lathan in 1872 expanded on the vascular theory, explaining that aura and subsequent headache resulted from "*Contraction of the blood vessels of the brain, so diminished supply of blood, produced by the excitation of the sympathetic; and that the exhaustion of the sympathetic following this excitement causes the dilation of the vessels and the headache*" (Lane & Davies, 2006: 20).

2.1.4 Migraine in the contemporary period (1914 to the present)

In 1868 Edward Woakes reported that ergot could stop a migraine headache. Ergotamine was synthesised by Stoll in 1916 (Koehler & Islet, 2002: 686). In 1925 ergotamine was successfully used by Rothian to terminate two migraine attacks. In 1938 Graham and Wolff experiments' demonstrated that ergotamine relieves headache by vasoconstriction of the dilated arteries during a migraine attack (Diamond, 2007: 272).

Lashley in 1941, mapped the progress of migrainous scotoma, "*through observation of his own visual auras*". He concluded that the symptomatology reflected a cortical process progressing with a speed of 3 mm/min across the primary visual cortex (Tfelt-Hansen, 2010: 780). Leão in 1944 published his discovery of a "*cortical spreading depression (*CSD*)*" – a slow moving 2-3 mm/min potassium liberating depression of activity in the cerebral cortex of laboratory animals (Daniel, 2014). He noticed its similarity to the migraine aura mapped by Lashley (Tfelt-Hansen, 2010: 780).

In 1948 Page identified the potent vasoconstrictor 5-hydroxytryptamine (5-HT) in human blood which was isolated by Rapport in 1949 (Lane & Davies, 2006: 29). While in 1965 Curran showed that serotonin levels fall during a migraine attack (Lane & Davies, 2006: 30). This lead to the development of the first 5-HT_1 receptor antagonist, sumatriptan, by Humphrey which was first synthesised by Glaxo Laboratories in 1984. and approved for uses in 1992. Triptans were introduce for use in the 1990s (Diamond, 2007: 273). To date there are seven triptans available worldwide but only five in South Africa. The triptans available in South Africa and the date first approved for use are:

sumatriptan (1992), rizatriptan (1999), naratriptan (1999), eletriptan (2001) and zolmitriptan (2003); almotriptan and fravotriptan are at present not available in South Africa.

The International Headache Society (IHS) was founded in 1981 and headed by the Danish researcher Jes Olesen (Tfelt-Hansen & Koehler, 2011: 763). This resulted in the first extensive headache classification of headache with diagnostic criteria the ICHD-1 in 1988. A revised version ICHD-2 was published in 2004, with a ICHD-3 beta version in 2013 (Ihs-headache.org, 2016).

In 1993 Joutel identified the first migraine gene. Weiller in 1995 showed brainstem activation imagery during positron emission tomography (PET) studies in migraine, thereby suggesting the brainstem as a "migraine generator" (Tfelt-Hansen & Koehler, 2011: 766). Cortical spreading depression underlying the migraine aura was illustrated by Sanchez del Rio and colleagues in 2001 using functional Magnetic Resonance Imaging (MRI), (Hadjikhani, Sanchez Del Rio, Wu, Schwartz, Bakker, Fischl, Kwong, Cutrer, Rosen, Tootell, Sorensen & Moskowitz, 2001: 4689).

Emerging treatments for migraine at present are: selective calcitonin gene-related peptide (CGRP) antagonists: olcegepant (intravenous), telcagepant (oral) and BI 44370 TA (oral), selective $5HT_{1F}$ receptor agonist lasmiditan (oral), inhibitors of nitric oxide and acid-sensing ion channel blockers (Hoffmann & Goadsby, 2014: 11). Migraine treatment will be discussed in more detail in Section 3.4.

2.2 Migraine defined

Migraine is a common, episodic neurovascular headache disorder. The headache may be preceded by visual and/or sensory disturbances (aura) Pain ranges from moderate to severe often incapacitating, lasting four to 72 hours. Pulsating or throbbing pain is often unilateral but can occur on both sides of the head or move from one side to the other during an attack. There are often accompanying symptoms such as nausea, vomiting and sensitivity to light, sound and/or noise (Schmidt & Willis, 2007: 1136). Women are three times more likely to suffer from migraine than men (Lipton, *et al.*,

2001: 6). Silberstein (2012) reported that, although very young children do get migraine it usually starts in puberty and diminishes after the age of 50 years. During these years the frequency and severity of migraine attacks can vary from one attack in two years to two attacks a week. The author reported that, due to the frequency and incapacitating nature of migraine attacks it has a major impact on personal, social and work life (Silberstein, 2012: 1-2). There are five clinical phases of migraine which have been identified (Lane & Davies, 2006: 46), namely: the prodrome phase, aura phase, headache phase, resolution phase and the recovery phase. In the following section these phases will be discussed.

2.2.1 Premonitory symptoms (prodrome phase)

The prodrome phase is the period of time before the start of a migraine and will be explained in this section. Attacks are often preceded by a sensation that a migraine is beginning hours or a day before the start of a migraine attack. These sensations may include mood changes, depression, lethargy, yawning, loss of appetite, food cravings, nausea, urinary retention or a combination of these symptoms (Lane & Davies, 2006: 46). Prodrome symptoms could be due to a dopaminergic mechanism (Rozen, 2004: 517). Imaging of the premonitory phase of migraine (before the appearance of the headache) by Maniyar and colleagues (2013) showed activation of the hypothalamic and brainstem structures. They concluded that hypothalamic involvement could explain many of the premonitory symptoms and could also explain why change in homeostasis triggers migraine (Maniyar, Sprenger, Schankin & Goadsby, 2013: 112).

Using an electronic diary, Giffin and co-authors (2003) showed that migraineurs who reported premonitory symptoms could accurately predict a full-blown headache (Giffin, Ruggiero, Lipton, Silberstein, Tvedskov, Olesen, Altman, Goadsby & Macrae, 2003: 935). A tertiary care study of migraineurs by Kelman (2004c) reported that 32.9% experienced premonitory symptoms with an average duration of 9.4 hours. The most common symptoms were tiredness, mood changes and gastrointestinal symptoms. Kelman (2004c) reported that 17% of patients with prodrome experienced all three symptoms together. Migraineurs with prodrome differed from those without in that they had: more overall triggers, a longer duration of aura, a longer time between aura and

headache, more aura without headache, longer time peak to headache, longer time to respond to triptans, longer maximum duration of headache, more headache associated with nausea and longer duration with more postdrome symptoms (Kelman, 2004c: 865).

Quintela and colleagues (2006) reported that 84% of migraineurs who consulted their general physician experienced premonitory symptoms. The most commonly reported premonitory symptoms in their study were anxiety, phonophobia, irritability, unhappiness and yawning (Quintela, Castillo, Muñoz & Pascual, 2006: 1051). A questionnaire study of 374 migraineurs by Schoonman and colleagues (2006) reported premonitory symptoms experienced as follows: 86.9% at least one, 71.1% two or more, with the average number per person being 3.2 symptoms. Women reported more premonitory symptoms (3.3) compared to men (2.5). The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%) (Schoonman, Evers, Terwindt, van Dijk & Ferrari, 2006: 1209).

A literature review by Becker (2013) reported that many different symptoms had been reported as migraine premonitory symptoms. As high as 87% and as low as 33% of migraineurs have reported premonitory symptoms (Becker, 2013: 1117). A smartphone online study (87 participants) by Houtveen and Sorbi (2013: 1) identified eight cluster prodromal features namely: sensory sensitivity, pain/stiffness, fatigue, cognitive functioning, positive affect, negative affect, effort spent and stressors encountered. The authors reported that prodromal migraine changes were found predominantly in the 12-hour window before a migraine attack, with great individual diversity. Rozen (2004: 517), for example reported that a 43-year old woman developed a red nose 24 hours before the onset of a migraine attack.

A retrospective cohort study of 1010 migraineurs by Schulte and colleagues (2015) reported that 38.9% of migraine patients experienced premonitory symptoms with an onset of two or more hours prior to the headache. The most frequent symptoms were, tense neck, phonophobia and difficulty in concentrating. A clear overlap of certain trigger factors and corresponding premonitory symptoms were found in their study: namely, flickering or bright light as a trigger was associated with higher frequency of

photophobia in the premonitory phase. This also applied to the presence of food craving and osmophobia in the premonitory phase and certain foods or odours as trigger factors. They concluded that reported migraine triggers were not so much independent precipitators of migraine pain, but most likely just misinterpreted results of enhanced attention to certain stimuli mediated by typical premonitory symptoms of migraine (Schulte, Jürgens & May, 2015: 1).

Charles (2013) in his review of premonitory evidence reported that, change in appetite, food cravings, bloating, piloerection, and change in facial expression or body perception among others were other symptoms that had been reported in the premonitory phase. Premonitory symptoms may come and go before the headache phase, while others will increase in intensity leading up to the headache, while other symptoms persist during the headache and beyond to the resolution phase (Charles, 2013: 413). Laurell and colleagues (2015) carried out a large cross-sectional study between 2002 and 2013 involving 2223 Finnish migraineurs. Of these migraineurs 77% reported that they suffered from premonitory symptoms with a mean number of three symptoms. The authors reported that yawning (34%) was the most common symptom. The results of their study showed that an increase in the number of premonitory symptoms were significantly associated with a higher frequency, duration and intensity of headache, reduced working capacity, more aura symptoms, and associated symptoms of the headache phase. These results are similar to those found in Kelman's study (2004c). Figure 2.1 from Laurell and colleagues study, shows the frequency of individual premonitory symptoms among the migraineurs in their study.

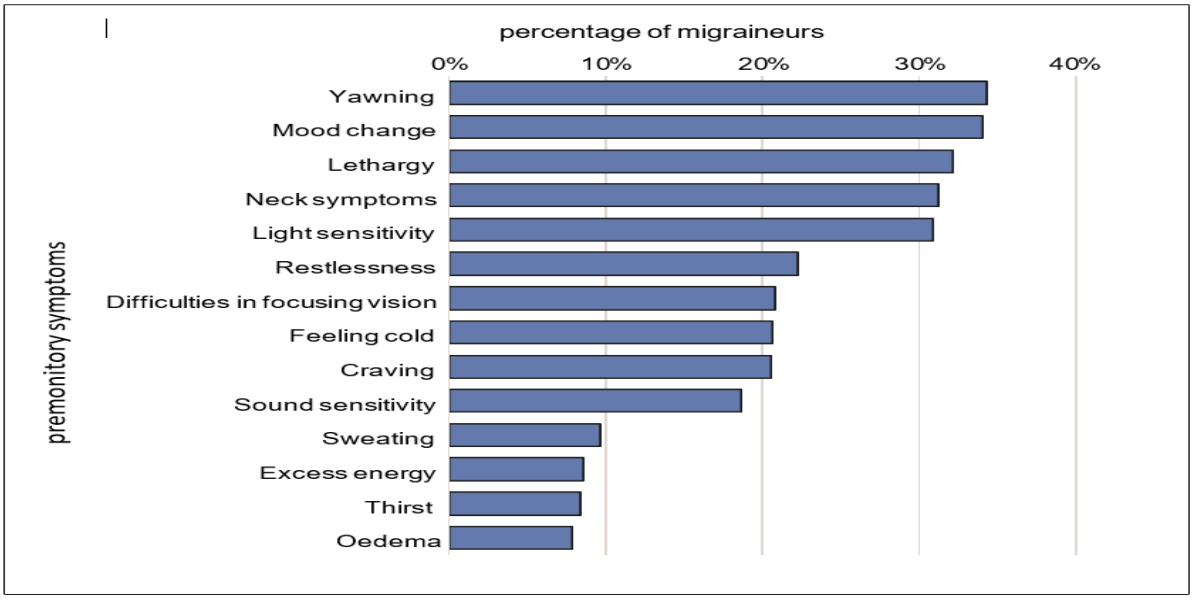


Figure 2.1 The frequency of individual premonitory symptoms among migraineurs
(Source: - Laurell, Artto, Bendtsen, Hagen, Häggström, Linde, Söderström, Tronvik, Wessman, Zwart & Kallela, 2015: 3)

2.2.2 Aura phase

The aura phase is briefly explained in this section and expanded on in Section 3.3 Migraine auras. An aura precedes an attack in about 25% of patients, consisting of focal neurological symptoms that can persist for up to one hour. Symptoms may include visual, sensory, or language disturbances (Lane & Davies, 2006: 46).

2.2.3 Headache phase

The prodrome or aura phase is usually followed by the headache phase, however, this is not always the case. Migraine headache can occur anywhere in the head, neck or face. It usually builds up over 30 minutes and can last from four to 72 hours (Lane & Davies, 2006: 46). A study by Kelman (2006) reported median headache durations as follows: minimum 12 hours, maximum 48 hours and average 24 hours. Headache intensity medians on a scale of one to 10 were as follows: minimum 4/10, maximum 10/10 and average 7/10 with greater intensity in episodic compared to chronic migraine. Kelman reported headache characteristics as follows: throbbing (73.5%), aching (73.8%), pressure (75.4%) and stabbing (42.6%), in her study of participating migraineurs. Her study showed that those with episodic migraine experienced

significantly more throbbing pain than those with probable migraine, while chronic migraineurs experienced more aching pain than those with episodic migraine (Kelman, 2006: 942).

2.2.4 Resolution phase

The resolution phase follows the headache phase and is often characterised by deep sleep although vomiting can sometimes also cause resolution of the migraine. Quintela and colleagues (2006) reported that 80% migraineurs who consulted their general physician experienced resolution symptoms. The most common resolution symptoms were asthenia, tiredness, somnolence and concentration difficulties (Quintela, *et al*., 2006: 1051).

2.2.5 Recovery (postdrome) phase

After the pain has resolved many patients experience malaise, fatigue, depression, craving for food, but there are some that experience euphoria and hyperactivity. Kelman (2006) reported that 68% of migraineurs in their study reported experiencing postdrome symptoms (female 69.1%; male 56.8%) with an average duration of 25.2 hours. The most common symptoms reported in this phase were tiredness (71.8%), head pain (33.1%), cognitive difficulties (11.7%), 'hangover' (10.7%), gastrointestinal symptoms (8.4%), mood (6.8%), and weakness (6.2%). Those migraineurs who experienced a postdrome phase were more likely to be female and suffer from full-blown migraine attacks (Kelman, 2006: 214). A study by Stanic and Sretenovic (2013: 117) obtained similar results to those from Kelman' study. One or several postdrome symptoms was experienced by 70% of females and 55% of males in their study with 88% having postdromes lasting up to 24 hours. Postdrome symptoms experienced were as follows: fatigue (72%), diffuse headache (33%), cognitive disturbances (12%), loss of appetite (7%), hunger (0.2%), depression (4%), euphoria (2%), hangover (11%) and general weakness (6%). Duration of postdrome symptoms could last as long as 48 hours (Stanic & Sretenovic, 2013: 117). According to a study by Ng-Mak and colleagues (2011) the postdrome was defined by patients as the period when they no longer experienced the migraine pain. *Postdrome* was often described as *"[being] or*

[feeling] wiped out" and "headache hangover." The most frequently reported symptoms were tiredness, difficulty concentrating, weakness, dizziness, light headedness, and decreased energy. The symptoms of the postdrome phase had a debilitating effect on those who experience it (Ng-Mak, Fitzgerald, Norquist, Banderas, Nelsen, Evans, Healy, Ho & Bigal, 2011: 105).

Figure 2.2 adapted from Pavlović and colleagues (2014), shows the proportion of premonitory symptoms experienced during 803 attacks and the proportion of postdrome symptoms experienced during 425 attacks as reported in Giffin and colleagues study of 76 patients (Pavlović, Buse, Sollars, Haut & Lipton, 2014: 1677; Giffin, *et al*., 2003: 936). Charles (2013: 413) in his review of evidence reported that several of the symptoms that occur in the premonitory phase are the same as those in the postdrome phase.

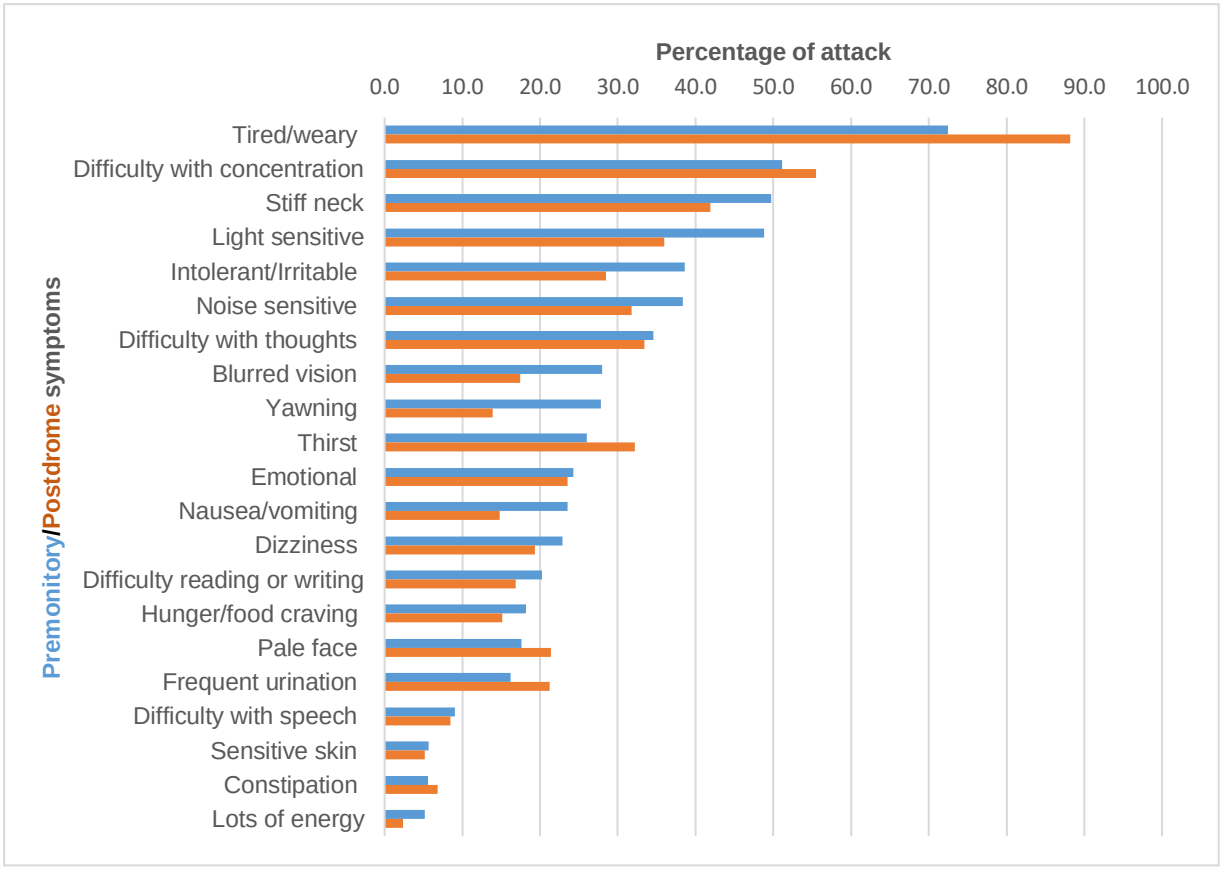


Figure 2.2 Proportion of attacks with a non-headache feature reported in the "premonitory phase" and "postdrome phase"
(Source: - Pavlović, Buse, Sollars, Haut & Lipton, 2014: 1677; Giffin, *et al.*, 2003: 936)

Not all migraine attacks will follow the above phases. Some attacks will not have all the phases, while others will have overlap of the phases. According to Quintela and colleagues (2006: 1051) migraine with aura and pain severity are risk factors for migraine premonitory and resolution symptoms. In addition, the ICHD-3 (ICHD-3, 2013: 644) and Merck Manual (Porter & Kaplan, 2011: 1886) only identify four phases (they do not identify the recovery as a phase of migraine).

2.2.6 Symptoms of migraine

A large number of symptoms are associated with migraine. In this section the following symptoms will be discussed: gastrointestinal symptoms, central nervous system symptoms and pain.

2.2.6.1 Gastrointestinal symptoms

Three different gastrointestinal symptoms will be discussed in this section, namely nausea and vomiting, gastroparesis and diarrhoea.

2.2.6.1.1 Nausea and vomiting

Nausea and vomiting are the most common gastrointestinal symptoms associated with migraine. According to the National Headache Foundation of the United States (US) nausea is a common migraine symptom in 73% of patients and 29% of patients reported vomiting as a migraine symptom (Headaches.org, 2016: 4). Maniyar and colleagues (2014) reported that using positron emission tomography scans, the rostral dorsal medulla and periaqueductal grey (which is thought to be involved in brain circuits mediating nausea) were shown to be activated in the group of patients that experienced nausea. Results from their study demonstrated that nausea could occur as a premonitory symptom in migraine, independent of pain and trigeminal activation. They concluded that nausea was a centrally driven symptom in migraine (Maniyar, Sprenger, Schankin & Goadsby, 2014: 1).

Nausea and/or vomiting as a symptom of their migraine attacks was reported by 56.9% of elderly French migraineurs (Tzourio, Gagnière, El Amrani, Bousser & Alpérovitch, 2003: 239). Golden, Evans and Hu (2009: 96), reported that nausea was experienced by 60.4% and vomiting by 57.6% of respondents in their study. Lipton and colleagues (2013) reported that among episodic migraineurs 49.5% reported nausea with high-frequency migraine headache. Females were more likely to sufferer from high-frequency nausea than males. They concluded that high-frequency nausea associated with migraine was a common marker for severe debilitating migraine (Lipton, Buse, Saiers, Fanning, Serrano & Reed, 2013: 93-94). The female to male variation in migraine symptoms was reported as follows: nausea in female patients 76.8% compared to 65.8% in male patients, and vomiting in female patients as 31.8% compared to 28.3% in male patients, by Buse and colleagues (2013). Their results showed that females were affected to a greater degree than males by migraine symptoms (Buse, Loder, Gorman, Stewart, Reed, Fanning, Serrano & Lipton, 2013: 1289).

A study by Reed and co-authors (2015) showed that nausea was a common symptom among patients who suffered from episodic migraine with 43.7% reporting nausea. Those migraineurs who reported frequent nausea that persisted over the two year study, were twice as likely to develop chronic migraine than those who suffered from no or low frequency nausea (Reed, Fanning, Serrano, Buse & Lipton, 2015: 76). A study of female migraineurs by Schürks, Buring and Kurth (2011: 865) reported that 89.1% experienced nausea and vomiting as symptoms of their migraine attacks. In a study by Hansen, Goadsby and Charles (2016: 216), nausea of mostly mild intensity was prospectively reported in only 51% of attacks. The occurrence and severity of nausea was found to decrease with advancing patient age. Migraineurs who suffer from nausea and vomiting may choose to delay taking or skip or be unable to keep down their oral medication (Silberstein, 2013: 1). This leads to a delay in relief of migraine symptoms and makes migraine attacks more difficult to treat (Headaches.org, 2016: 4).

2.2.6.1.2 Gastroparesis

Gastroparesis is a chronic stomach disorder manifested by delayed emptying of solids and liquids without evidence of mechanical obstruction. Delayed gastric emptying often occurs in migraine (Parkman, 2013: 4). Eight percent of migraineurs have slow passage of stomach contents through the gut which could affect oral medication absorption taken to treat a migraine attack (Headaches.org, 2016: 4). A study by Aurora and colleagues (2006) demonstrated that migraineurs suffer from gastric stasis both during and outside of acute migraine attacks. Experiencing gastric stasis could suggesting abnormal autonomic function in migraineurs compared to non-migrainous controls (Aurora, Kori, Barrodale, McDonald & Haseley, 2006: 57).

2.2.6.1.3 Diarrhoea

Kelman and Tanis, (2006: 549) reported that 28.2% of respondents had diarrhoea as a migraine symptom.

2.2.6.2 Central nervous system symptoms

There are a number of central nervous system symptoms associated with migraine. The following symptoms associated with a migraine attack were reported by female migraineurs: behavioural or personality changes (63.0%), sensory symptoms such as tingling and numbness (39.7%), speech or language symptoms (24.7%) and unilateral weakness in face, arms or legs 20.8% (Schürks, *et al*., 2011: 865). The following central nervous system symptoms will be discussed in this section: vision changes, vestibular symptoms, photophobia, phonophobia and osmophobia and pain.

2.2.6.2.1 Vision changes

Lipton and colleagues (2001) reported that 44% of patients had blurred vision as a symptom of migraine (Lipton, *et al*., 2001: 650). The female to male ratio for blurred vision was 45% in female migraineurs and 41.2% in male migraineurs in the study by Buse and colleagues (2013: 1289). In Schürks and colleagues' (2011: 865) study,

26.5% of female migraineurs reported double vision, and 50.9% reported other visual changes.

2.2.6.2.2 Vestibular symptoms

Vestibular symptoms such as vertigo and dizziness have been reported as symptoms of migraine attacks by migraineurs. Dizziness as a migraine symptom was reported by 72.4% of respondents in the study by Kelman and Tanis (2006: 549). Vertigo or dizziness were reported by 61.0% of female migraineurs in a study by Schürks and colleagues (2011: 865). A prevalence study by Vuković and colleagues (2007) reported that vertigo or dizziness was experienced by 51.7% of migraineurs and 31.5% in the control group. They found that the lifetime prevalence of migrainous vertigo was relatively frequent in migraineurs especially in those who experienced migraine with aura (Vuković, Plavec, Galinović, Lovrenčić-Huzjan, Budišić & Demarin, 2007: 1247). Calhoun, Ford, Pruitt and Fisher (2011: 1388) reported that the prevalence of dizziness or vertigo was twice as high in migraine with aura as opposed to migraine without aura (24.5% versus 12.1%). The duration of vertigo attacks was shown to be between one hour and one day in a study by Cha and colleagues (2009). Although benign recurrent vertigo is highly associated with migraine, a large proportion of patients with benign recurrent vertigo and migraine never have migraine symptoms during their vertigo attacks (Cha, Lee, Santell & Baloh, 2009: 550).

Vestibular symptoms such as vertigo, dizziness and motion sickness were 10 times more common in migraine patients than in those who suffered from tension type headaches. Vertigo and dizziness were four times more common in younger (18 to 34 year old) migraineurs than older (50 to 60 year old) migraineurs (Akdal, Özge & Ergör, 2015: 296). A population based study of migraineurs by Akdal and colleagues (2015) reported that vertigo was experienced by 31%, motion sickness by 15% and vertigo and motion sickness by 30% as symptoms of migraine. The group of migraineurs who experienced vestibular symptoms had more headache, aura, nausea, vomiting, osmophobia, allergy, allodynia, headache increasing with head motion, noise as trigger for headache, days needing analgesics, and higher migraine disability scores

than those who did not (Akdal, Baykan, Ertas, ZarifoĞlu, Karli, Saip & Siva, 2015: 346).

2.2.6.2.3 Photophobia, phonophobia and osmophobia

Photophobia (sensitivity to light) and phonophobia (sensitivity to sound) as migraine symptoms are often reported by migraineurs, with osmophobia (sensitivity to smell) less often. Photophobia and phonophobia as migraine symptoms were reported by 65.6% of elderly French migraineurs (Tzourio, *et al.,* 2003: 239). In Nachit-Ouinekh and colleagues' study (2004) more migraineurs reported phonophobia (94.1%) than photophobia (87.0%). These results differ from others studies in which more migraineurs experience photophobia than phonophobia (Nachit-Ouinekh, Chrysostome, Henry, Sourgen, Dartigues & El Hasnaoui, 2005: 120). The National Headache Foundation reported that 80% of patients experienced light sensitivity and 76% of patients experienced sensitivity sound as common symptoms of migraine (Headaches.org, 2016: 4). While Golden and colleagues reported photophobia (61.1%) and phonophobia (60.1%) as common migraine symptoms in their study (Golden, *et al*., 2009: 96). Kelman and Tanis (2006: 549) reported higher values for photophobia (93.9%) and phonophobia (91.4%) as migraine symptoms in their study. They also reported that osmophobia was reported by 28% of patients. A response to questions on photophobia indicated a consistency of 84.8% in those who suffered from migraine attacks. Migraineurs were significantly more likely to be sensitive to light than controls (Mulleners, Aurora, Chronicle, Stewart, Gopal & Koehler, 2001: 34). Similar values for light sensitivity (85%), and sound sensitivity (76%) were reported by Lipton and colleagues (2001: 650). The female to male ratio for photophobia was 83.2% in female patients and 76.4% in male patients and phonophobia was 78.8% in female patients and 70.7% in male patients in the study by Buse and colleagues (2013: 1289) indicating that female migraineurs experience more migraine symptoms than males. A study of female migraineurs reported that 93.0% were sensitive to light and 86.1% were sensitive to sound (Schürks, *et al.*, 2011: 865).

Baldacci and colleagues (2014) carried out a study on osmophobia in migraine and reported that 58.0% of migraineurs experienced osmophobia as a migraine symptom.

Pain intensity was higher and other migraine symptoms more likely in those migraineurs who suffer from osmophobia as opposed to those who did not (Baldacci, Lucchesi, Ulivi, Cafalli, Vedovello, Vergallo, Prete, Nuti, Bonuccelli & Gori, 2014: 45). Osmophobia is associated with a longer history of different migraine forms in a clinical sample and is related to the presence of cutaneous allodynia (Lovati, Giani, Castoldi, Mariotti D'Alessandro, DeAngeli, Capiluppi, D'Amico & Mariani, 2015: 146).

2.2.6.2.4 Pain/neck pain

A study of elderly migraineurs in France, reported moderate to severe pain (67.2%), unilateral pain (42.1%) and pulsating pain (41.7%) as the type of pain experienced during a migraine attack (Tzourio, *et al.*, 2003: 239). In Nachit-Ouinekh and colleagues study (2004), 72.2% of migraineurs experienced unilateral pain while 69.5% experienced pulsating pain as the type of migraine pain (Nachit-Ouinekh, *et al.,* 2005: 120). The frequency of headache characteristics in Kelman and Tanis', (2006: 549) study was as follows: throbbing (91.6%), aching (87.9%), pressure (89.6%) and stabbing (71%). While Schürks and colleagues (2011: 865) reported that the pain characteristics experienced by female migraineurs were: pulsating pain (30.7%), crushing pain (12.2%), sharp pain (8.4%), aching pain (17.1%) and burning pain (2.0%). Pulsating pain was reported by 85% of patients and unilateral pain by 59% of patients when describing the type of pain experienced during a migraine attack (Lipton, *et al*., 2001: 650). The female to male ratio to describe the pain intensity of a migraine attack was as follows: extremely severe pain – female 36.8% compared to male 38.3%, severe pain – female 47.6% compared to male 45.2%, moderately severe pain – female 14.6% compared to male 14.8%, and mild pain – female 1.0% compared to male 1.7%. These results indicate that males experience more pain than females with severe pain being the most common intensity for both sexes (Buse, *et al*., 2013: 1289). These studies show that the type of pain experienced comes in many forms with pulsating/throbbing pain seeming to be the most common type of pain experienced during a migraine attack.

Neck pain is highly prevalent in the general population and has the highest prevalence in those who suffer from migraine and tension type headache (89.3%). The one-year

prevalence of neck pain in pure migraine was 76.2% (Ashina, Bendtsen, Lyngberg, Lipton, Hajiyeva & Jensen, 2015: 211). Migraine attacks with neck pain as a common features was reported by 69.4% of migraineurs (Lampl, Rudolph, Deligianni & Mitsikostas, 2015: 1). A study by Florencio and colleagues (2014) showed that neck pain significantly added to the disability of both episodic and chronic migraineurs. Disability due to neck pain occurred in 69.0% of episodic migraine and 92% of chronic migraine (Florencio, Chaves, Carvalho, Gonçalves, Casimir, Dach, Bigal & Bevilaqua-Grossi, 2014: 1203). Calhoun and colleagues (2015) reported that neck pain was a more frequent migraine symptom than nausea. Neck pain prevalence correlated with cornification of migraine as it moved from episodic to chronic migraine (Calhoun, Ford, Millen, Finkel, Truong & Nie, 2010: 1273).

2.2.6.3 Other symptoms

Food cravings were reported by 28.3% of female migraineurs in the study by Schürks and colleagues (2011: 865). The symptoms experienced by migraineurs differs from person to person as well as from one migraine attack to another.

2.3 Epidemiology of migraine

2.3.1 Overview of the prevalence migraine

Epidemiological studies assess individuals and in most cases focuses on the incidence and prevalence of a disease in a defined population group (Bigal, Lipton & Stewart, 2004: 99). *Incidence* refers to the onset of new cases of a disease over a defined period in a given population group. *Prevalence* refers to the portion of a population that has a disease over a defined period which changes with the shift in population demographics (Lipton & Bigal, 2005: 4). Epidemiological data helps to describe the burden, scope and distribution of migraine whether or not the migraineur seeks medical help for their headache disorders (Bigal, *et al*., 2004: 99).

The World Health Organization in 2001 estimated the worldwide prevalence of migraine to be 10% and lifetime prevalence to be 14% (WHO, 2011). The adjusted

prevalence of migraine is highest in North America, followed by South and Central America, Europe, Asia and Africa (Chawla, 2015: 10). The prevalence of migraine is lower in African Americans and Asian Americans than among Caucasians (Nicholson, *et al*., 2006: 754). In women of all ages, migraine is estimated to account for 2.0% years of life lost due to disability. In both sexes of all ages, migraine is responsible for 1.4% of total years lost due to disability (Leonardi, Steiner, Scher & Lipton, 2005: 435).

In the Global Burden of Disease Survey 2010, migraine was ranked as the third most prevalent disorder and the seventh highest specific cause of disability worldwide (Steiner, *et al*., 2013: 290). The Global Burden of Disease Study 2013 ranks migraine as the sixth highest cause of disability worldwide (Steiner, Birbeck, Jensen, Katsarava, Stovner & Martelletti, 2015: 1).

Migraine imposes a significant burden on the individual migraineur, their families, society, health care systems and the economy (Ravishankar, 2010: 30; Blumenfeld, *et al*., 2011: 301). Manack and colleagues (2011) reported that a common disabling complication of migraine, chronic migraine had a population prevalence of about 2%. Their study estimated that 2.5% of episodic migraine progresses to chronic migraine each year. Chronic migraineurs have reduced health-related quality of life, worse socio-economic status, increased headache burden (family, social and occupational impairment), and greater psychiatric and medical comorbidities (Manack, Buse & Lipton, 2011: 70). Probable migraine is a prevalent sub-type of migraine where the patients suffers from migrainous features, buts fails to meet the International Headache Society criteria for migraine and, similar to migraine with and without aura, it produces decrements in health-related quality of life and increments in disability relative to control subjects. Similar to migraine with and without aura, probable migraine leads to a decrease in health-related quality of life and an increase in burden of life disability relative to control subjects (Bigal, *et al*., 2004: 98). The classification of migraine will be discussed in Section 2.5.

According to Lipton and colleagues (2001: 4), migraine affects 11% of the adult population in Western countries. They reported that migraine prevalence was highest during the economic productive years (25 to 35 years), increasing from age 15 years, peaking between the late 30’s to early 40’s and declining thereafter. Below the age of

12 years the prevalence of migraine was similar for girls and boys, or greater for boys. Post pubertal, the prevalence of migraine is higher (2.5 to 3 times) in females than males, with the sex ratio varying with age. This holds true even at the age of 80 years well after cyclic hormonal factors could be a contributing factor (Lipton, *et al*., 2001: 4-6). Bigal and Lipton (2006) carried out a study of migraine at all ages and reported the following, they reported that the prevalence of both migraine and probable migraine decreased with age past 40 years, which suggested remission in a fraction of migraineurs. In intermediate years there was a greater number of migraineurs than probable migraineurs. The opposite was true for the extremes of ages assessed in their study. They also suggested that migraine flourishes between the ages of 30 and 49 years and is less typical in extremes of ages. In young individuals, migraine attacks tend to be more typical than those in the elderly. The profile of migraine changes over the patient's lifespan. For a subgroup of migraineurs, migraine remits, for others migraine becomes less typical and more like probable migraine than full migraine, while for others migraine is progressive (Bigal & Lipton, 2006: 213).

A prospective study by Riederer and co-authors (2011) of headache in 25 consecutive patients with atrial septal defect (ASD) reported that the prevalence of migraine without aura (28%) and migraine with aura (16%) was higher than in the general population. Three patients that had reported migraine with aura before the intervention, noted no migraine with aura attacks at follow-up, two of them reported ongoing tension-type headache and one migraine without aura. Their study confirmed the high prevalence of headache, particularly migraine, in ASD patients and suggests a possible small beneficial effect of ASD closure (Riederer, Baumgartner, Sándor, Wessely & Wöber, 2011: 1297). A study on ASD and migraine prevalence was carried out by Kato and colleagues (2013). They reported that the prevalence of migraine in the ASD patients was 24.2% compared to 9.4% in the Japanese general population. All patients with migraine aura were female and significantly younger than patients who did not suffer from migraine. They concluded that their findings suggested that the susceptibility to develop migraine with aura differed according to age and sex of patients with cardiac shunt (Kato, Hayashi, Kobayashi & Tanahashi, 2013: 2).

Pavlović and colleagues (2015) reported that nearly 60% of female migraineurs reported an association between migraine and menses. These women reported

greater headache impact and migraine-related burden on functioning than those whose migraines were not related to menstruation. Women with migraine attacks that only or predominantly occur at the time of menses suffered more impaired migraine attacks. Women with attacks commonly associated with menses, but that also occur at other times of the month had overall highest burden, which was likely due to experiencing migraines on additional days (Pavlović, Stewart, Bruce, Gorman, Sun, Buse & Lipton, 2015: 1).

Bond and co-authors (2011) reported, that research suggested, that migraine and obesity were directly related. Obesity exacerbated migraine in the form of greater headache severity and frequency and/or increasing the risk of having a migraine attack. The relationship between migraine and obesity could be explained through a variety of physiological, psychological and behavioural mechanisms, many of which are affected by weight loss (Bond, Roth, Nash & Wing, 2011: 362). With regards to migraine and obesity, similar results to those found in the literature were reported by Vo and colleagues (2011) in their study of female migraineurs. Relative to normal weight women, obese women had a 1.48-fold increased odds of migraine, severely obese had a 2.07-fold increased odds of migraine and morbidly obese had a 2.75-fold increased odds of migraine (Vo, Ainalem, Qiu, Peterlin, Aurora & Williams, 2011: 559).

Bigal and co-authors reported that migraine prevalence was not associated with body mass index (BMI), but attack frequency, severity, and clinical features of migraine increased with BMI (Bigal, Liberman & Lipton, 2006: 545). A study of female migraineurs aged 40 to 70 years in Sweden by Mattsson (2007), reported that the distribution of frequency, intensity, duration or severity of migraine attacks did not differ between obese and non-obese women with migraine. In his study there were no significant associations between migraine or migraine characteristics on the one hand and obesity on the other (Mattsson, 2007: 877). Winter and associates (2009) reported that women with a BMI of ≥35 kg/m² had an increased risk for low and high migraine frequency, with women who reported daily migraine having the highest estimate. Women who suffered with a migraine frequency of < 6 times/year and a BMI between 27.0 and 29.9 kg/m² had the lowest associated risk. A BMI ≥35 kg/m² among the women with active migraine was associated with an increased risk of phonophobia and photophobia and decreased risk of a unilateral pain characteristic and migraine

aura. Their data confirmed previous findings that the association between BMI with migraine was limited to migraine frequency and specific migraine features (Winter, Berger, Buring & Kurth, 2009: 269). A survey in China by Yu and colleagues (2012) reported that the one-year prevalence for migraine was 9.3%. No association was identified between patients with a BMI <30 kg/m² and migraine. Morbid obesity (BMI ≥30 kg/m²) was associated with a two-fold odds of migraine in Chinese men and women in this survey. No association was found between migraine severity, frequency, or disability and obesity, which differed from Winter and associates study (Yu, Liu, Yang, Zhao, Qiao, Feng, Fang, Cao, He & Steiner, 2012: 531).

Santos and co-authors (2014) in their large sample cohort study in Brazil, found an association between daily migraine and obesity, but not abdominal obesity, in individuals aged 35 years and older. Abdominal obesity influenced the association between BMI and daily migraine in migraineurs aged 35 to 49 years (Santos, Goulart, Passos, del Carmen Molina, Lotufo & Bensenor, 2014: 426). According to Jahromi and colleagues in Iran (2013), lower fat free mass increased the risk of migraine in overweight and obese individuals. Therefore exercise could reduce the risk of migraine as it is associated with an increases in fat free mass (Jahromi, Abolhasani, Meysamie & Togha, 2013: 23).

The prevalence of migraine on the different continents varied according to the type and number of articles written. First world countries such as those in Western Europe and North America produced more research than developing countries in Africa and Asia (Stovner, Hagen, Jensen, Katsarava, Lipton, Scher, Steiner & Zwart, 2007: 193). The following sections sum up prevalence on the different continents in different countries.

2.3.2 Prevalence of migraine in Europe

2.3.2.1 Western Europe

Bloudek and colleagues (2012) reported that migraine affected 14.7% of Europeans in their study, looking at the cost of healthcare for migraineurs in five European

countries (United Kingdom (UK), France, Germany, Italy and Spain). Per patient, annual costs were highest in UK and Spain and lower in France and Germany. Chronic migraine was associated with higher total cost and medical resource use, compared to episodic migraine (Bloudek, Stokes, Buse, Wilcox, Lipton, Goadsby, Varon, Blumenfeld, Katsarava, Pascual, Lanteri-Minet, Cortelli & Martelletti, 2012: 361). Steiner and colleagues (2003) reported that in England the one-year prevalence of migraine with or without aura for patients aged 16 to 65 years was, 7.6% for males and 18.3% for females. Their study showed that migraine prevalence varied with age increasing through early adult life and decreasing in the late 40's and early 50's. Caucasians had a higher prevalence than other races. The authors reported that in most migraineurs migraine attack rates were greater than one per month. More than 50% of migraine attacks experienced by patients had an influence on daily activities, with an average estimate of 5.7 working days lost per year. Projected to the entire UK population they estimated that 5.85 million people aged 16 to 65 years experienced 190 000 migraine attacks every day and lost 25 million days from school/work each year as a result of these migraine attacks (Steiner, Scher, Stewart, Kolodner, Liberman & Lipton, 2003: 519).

The overall prevalence for migraine in a nationwide survey in France by Michel and colleagues (1991) was 8.1%, with 4% classified as "borderline" migraine which they considered definite migraine. Migraine frequency, duration of attacks and length of disease did not differ with gender, but expressed intensity of attacks was greater in female patients (Henry, Michel, Brochet, Dartigues, Tison & Salamon, 1992: 229). A French nationwide population based survey by Lucas and associates (2006) reported that 21.3% of the patients interviewed were identified as migraineurs. Only 60% of migraine patients were aware that they suffered from migraine (Lucas, Géraud, Valade, Chautard & Lantéri-Minet, 2006: 715).

Lampl and co-authors (2003) carried out a study of one-year prevalence of migraine in the Austrian adult population. They identified 10.2% patients who suffer from migraine, of which 5.6% suffered from migraine without aura, 2.3% from migraine with aura and 2.3% from borderline migraine. Another 8.5% had probable migraine. Doctor attendance rates were very low and the most used acute medications were OTC drugs. Working people with migraine took 14 sick leave days per year (Lampl, Buzath,

Baumhackl & Klingler, 2003: 280). A study in Austria of eight headache centres reported the prevalence rates of migraine to be 48.5% as opposed to other types of headaches (Zebenholzer, Andree, Lechner, Broessner, Lampl, Luthringshausen, Wuschitz, Obmann, Berek & Wöber, 2015: 1).

Prevalence of headache in Germany was studied by Radtke and Neuhauser (2009). The one-year prevalence for migraine was 10.6%. Approximately 60% of headache sufferers reported severe headaches, of which 30% were migrainous headaches. Compared to non-migrainous severe headache patients, migraineurs were more likely to reported frequent headaches, disability, use of analgesics, and medical consultations. Despite the disability associated with their disease, only 42% of migraineurs had consulted a physician and the majority relied exclusively on OTC medication. Although migraine accounts for a great part of the healthcare impact of headache in Germany, the majority of migraineurs do not seek medical care and may not be optimally treated (Radtke & Neuhauser, 2009: 79). The prevalence of chronic migraine was reported to be 1.1% by Schramm and colleagues (2013) in their population based German Headache Consortium Study. Those participants with chronic migraine were more likely to be female, to smoke, to be obese and to report frequent use of acute pain medication (Schramm, Obermann, Katsarava, Diener, Moebus & Yoon, 2013: 1). The one-year prevalence rates of headache syndromes in an epidemiologic cohort study of young adults ages 29 to 30 in Zurich, Switzerland by Merikangas and co-authors (1994), were 3.3% for migraine with aura and 21.3% of migraine without aura. Patients with migraine reported pervasive impairment in nearly every life role including occupation, leisure, and social relationships. Despite these impairments an extremely low proportion of patients had received professional treatment for their headaches (Merikangas, Whitaker, Isler & Angst, 1994: 145).

A survey in Italy over a period of three months of patients attending 10 headache centres was carried out by Cevoli and co-authors (2009). Of the 2675 patients who attended headache centres for the first time during the study period, 71% received a diagnosis of migraine. Only 26.8% of migraine patients had a previous diagnosis of migraine; 62.4% of them visited their general practitioner in the previous year, 38.2% saw a specialist for headache, 23% attended an Emergency Department and 4.5% were admitted to hospital for migraine. Non-specific migraine drugs were used by

82.8% of patients for migraine attacks, whereas 17.2% used triptans and only 4.8% used a preventive migraine medicine. Of those patients with a previous diagnosis of migraine, 46.4% used triptans. Over-the-counter medications were used by about 80% of migraine patients (Cevoli, D'Amico, Martelletti, Valguarnera, Del Bene, De Simone, Sarchielli, Narbone, Testa, Genco, Bussone & Cortelli, 2009: 1285). In Leonardi and colleagues' study (2010) of migraineurs attending an Italian specialty headache clinic, disability scores were worse and health related quality of life scores were lower than those of the general population. These scores worsened consistently with increased migraine severity. This study provided information on migraine's burden, where economic impact was minimal. However, these scores had an important effect on patients' daily lives in terms of interpersonal relationships, perceived quality of life and emotional status (Leonardi, Raggi, Bussone & D'Amico, 2010: 1576). Ferrante and associates in their study of adults in Parma reported that the one-year adjusted prevalence of definite migraine (migraine with and without aura and chronic migraine), was 24.7% of which 13.0% were men and 32.9% were female. One-year prevalence of probable migraine was 5.1% of which 5.2% were men and 5.0% female. These results were higher than for those in the literature (Ferrante, Manzoni, Russo, Taga, Camarda, Veronesi, Pasquarella, Sansebastiano & Torelli, 2014: 358).

Fernández-de-las-Peñas and colleagues (2010) reported a one-year prevalence of migraine in Spanish adults to be 11.0%. Females (15.9%) showed a significantly higher prevalence than males (5.9%) with the highest values in the 31 to 50 year age group (Fernández-de-las-Peñas, Hernández-Barrera, Carrasco-Garrido, Alonso-Blanco, Palacios-Ceña, Jiménez-Sánchez & Jiménez-García, 2010: 97). The one-year prevalence of migraine in Spain in Matías-Guiu and co-authors study (2011) was 12.6% (17.2% females, 8.0% males). The prevalence of migraine with and without aura was 8.4% and probable migraine was 4.2%. The prevalence rates showed significant geographic variations, from 7.6% in Navarra to 18% in the Canary Islands. One-half of the patients had migraine with aura while one-third of the patients were never diagnosed with migraine (Matías-Guiu, Porta-Etessam, Mateos, Díaz-Insa, Lopez-Gil & Fernández, 2011: 643). The prevalence of migraine in the Romany population (29.4%) was significantly higher than in the general Spanish population. Romanies with migraines reported worse self-perceived health status and higher incidence of depression than those without (Jiménez-Sánchez, Fernández-de-las-

Peñas, Jiménez-García, Hernández-Barrera, Alonso-Blanco, Palacios-Ceña, & Carrasco-Garrido, 2013: 6). A study was carried out by Fernández-de-las-Peñas and colleagues (2014) as to whether migraine in a Spanish population had changed from 2003 to 2012. The study found that the prevalence of migraine increased from 6.54% in 2003 to 9.69% in 2012 with significant time trends. As age increased the trend was a decrease in migraine prevalence. Migraine was associated with being female, mid-age, low educational level, not being an immigrant, worse self-rated health status and presence of comorbid conditions (Fernández-de-las-Peñas, Palacios-Ceña, Salom-Moreno, López-de-Andres, Hernández-Barrera, Jiménez-Trujillo, Jiménez-García, Gallardo-Pino, García-Gómez-de-las-Heras & Carrasco-Garrido, 2014: 1).

Lyngberg and colleagues (2005) looked at the change in the prevalence of migraine over a 12-year period in the Danish population. They reported that the prevalence of migraine did not change significantly (11% to 15%). There was an increase from 12% to 38% for the portion of migraineurs with migraine on 14 days or more per year. The increase in migraine frequency suggested a higher individual and social impact now as opposed to 12 years previously (Lyngberg, Rasmussen, Jørgensen & Jensen, 2005: 243). The one-year prevalence of migraine in Sweden was found to be 13.2 ±1.9% (16.7% female: 9.5% male) in the study by Dahlöf and Linde (2001). The prevalence of migraine in their study did not differ between the northern, middle and southern part of Sweden, or between urban and rural areas. Physicians only diagnosed about half (49%) of the migraineurs (Dahlöf & Linde, 2001: 664). The lifetime prevalence of migraine in Norway was reported to be 26.5% (34.1% female: 18.1% male). In men and women over the age of 45 years the prevalence of migraine decreased slightly (Russell, Kristiansen, Šaltyté-Benth & Kværner, 2008: 339).

2.3.2.2 Eastern Europe

The prevalence of migraine in Croatia was studied by Zivadinov and co-authors (2001). They reported that the lifetime prevalence of migraine was 19% (22.9% female: 14.8% male) with the highest lifetime prevalence of migraine being in women in the age group 40 to 49 years (38.1%). The prevalence for active migraineurs was 55.8% for migraine without aura, 35.2% for migraine with aura, and 6.9% migraine

both with and without aura (Zivadinov, Willheim, Jurjevic, Sepic-Grahovac, Bucuk & Zorzon, 2001: 805). In Hungary, the one-year prevalence for migraine without aura was 7.6% (female: male ratio 3:1) and migraine with aura 2% (female: male ratio 2:1). Most patients who suffered from migraine without aura were between the ages of 20 and 40 years, while those with aura were over 40 years of age. Although patients experienced migraine attacks, one to four times per month lasting 24 hours, only 43% consulted a physician (Bánk & Márton, 2000: 164).

A study of females in Kayseri Turkey by Köseoglu and co-authors (2003) reported the one-year prevalence of migraine to be 12.5%, comprising 7.3% of patients with migraine with aura and 5.2% of patients with migraine without aura. Migraine prevalence was found to be statistically higher in 35 to 44 year age group, lower above 65 years of age and higher for those living in urban areas (Köseoglu, Naçar, Talaslioglu & Çetinkaya, 2003: 382). A nationwide study in Turkey by Ertas and colleagues (2012) reported a one-year prevalence rate of migraine to be 16.4% (24.5% for female: 8.5% for male) and probable migraine 12.4%. The rate of migraine with aura among migraineurs was 21.5%. The prevalence of migraine was highest among females in the 35 to 40 year age group with no real differences in age groups among men. Their study reported that more than two thirds of migraineurs had consulted a physician. This was higher than what had been reported in other studies (Ertas, Baykan, Kocasoy Orhan, Zarifoglu, Karli, Saip, Onal & Siva, 2012: 150).

2.3.3 Prevalence of migraine in Asia

A study by Wang and colleagues (2008) of migraine in eight Asian countries reported that 66.6% of patients seen by neurologists were diagnosed with migraine, ranging from 50.9% to 85.8% across different countries. Prior to this consultation, 41.4% of those patients diagnosed with migraine had not been previously diagnosed as migraineurs. On average, patients with migraine had 4.9 severe headaches per month with 65% of patients missing school, work, or household chores. Medications for acute treatment was used by most (87.5%) patients with migraine. Only 29.2% of migraine patients were on prophylactic medications for migraine. According to Wang's study migraine was reported to be the most common headache diagnosis in neurological

services in Asia (Wang, Chung, Chankrachang, Ravishankar, Merican, Salazar, Siow, Cheung, Phanthumchinda & Sakai, 2008: 1356).

A study of the epidemiology of headache disorders in the Asia-Pacific region by Peng and Wang (2014), reported the one-year prevalence for migraine to be 9.1%. The extremes in the one-year prevalence of migraine in earlier studies from Hong Kong (1.5%) and South Korea (22.3%) were not repeated in later surveys (Hong Kong: 12.5%; South Korea: 6%). They reported that over the last two decades the prevalence of headache disorders had remained stable in this region, where the diversity of geography, race, and development is wide (Peng & Wang, 2014: 610). A study of patients from 28 regions in China by Dong and co-authors (2012) reported that migraine accounted for 39.1% of primary headaches. Sex differences and age distribution for onset of migraine were reported with the first decade for males and the second decade for females (Dong, Di, Dai, Liang, Pan, Zhang, Zhou, Li, Liu & Yu, 2012: 1). In Taipei, Taiwan the prevalence for migraine was 9.1% (female 14.4%: male 4.5%). In the Taipai study a physician was consulted by 54% of migraineurs in the last year, but only 18% of the respondents reported that their migraine had been diagnosed by a physician (Wang, Fuh, Young, Lu & Shia, 2000: 566).

The first nationwide survey of migraine prevalence in Japan was carried out by Sakai and Igarashi (1997). One-year migraine prevalence was reported to be 8.4%, of which 5.8% was for migraine without aura and 2.6% for migraine with aura. Their study reported a low attendance rate for doctors with 64.4% having never consulted a physician for headache. Only 11.6% of patients were aware that their headaches where migraine with 56.9% using OTC drugs (Sakai & Igarashi, 1997: 15). One-year prevalence of migraine in the Daisen study in Japan by Takeshima and co-authors (2004) was 6.0%. The prevalence of migraine in men was 2.3% (migraine with aura, 0.4% and without aura, 1.9%) and in women 9.1% (migraine with aura, 1.0% and migraine without aura, 8.1%). Females observed a 5.9 times higher risk of migraine than men. Only 7.3% of those with migraine with aura and 5.3% of those with migraine without aura had consulted a physician, and of those with migraine, 61.0% with aura and 71.8% without aura had never consulted a medical doctor for their headache (Takeshima, Ishizaki, Fukuhara, Ijiri, Kusumi, Wakutani, Mori, Kawashima, Kowa, Adachi, Urakami & Nakashima, 2004: 8).

Episodic migraine, whether definite or probable was, reported to be 20.3% in a study in Russia (Ayzenberg, Katsarava, Sborowski, Obermann, Chernysh, Osipova, Tabeeva & Steiner, 2015: 1). A study in Korea reported the one-year prevalence of strict migraine to be 6.0% and probable migraine to be 11.5%. Some strict migraine and probable migraine patients experience decreased activity and missed activity due to headache (Kim, Chung, Kim, Lee & Chu, 2013: 1106). A study in India by Menon and Kinnera (2013), at a medical colleague, reported that 68% of the medical students suffered from headaches. The prevalence of migraine in the whole cohort was 28%; however, migraine constituted 42% of the headache group. Weekly or daily attacks were experienced by 25% of the students with 31% of students reporting an increase in their headache intensity and frequency. In this study of medical students, self-medication with the use of analgesics was reported by 27% of students. Only 6% realised that they had migraine, though 25% of the students had migraine associated disability (Menon & Kinnera, 2013: 221). The one-year prevalence of migraine was reported as 25.2% (10.6% definite migraine: 14.6% probable migraine) in a study in Karnataka state in India by Kulkarni and associates (2014). Prevalence of migraine was greater in females and in rural areas and peaked between the ages of 35 to 40 years in both genders. In 40% of patients headache intensity was severe (Kulkarni, Rao, Gururaj, Subbakrishna, Steiner & Stovner, 2014: 1).

2.3.4 Prevalence of migraine in the Middle East

Murtaza and colleagues (2009) reported that migraine was the most common headache disorder for patients who sought medical advice for their headache in Pakistan. Patients were usually in the most productive years of their lives with migraine onset being earlier in those patients with first-degree family history of migraine. Their study reported that those women who suffered from menstrual related migraine endured migraines with headache episodes of longer duration than other patients (Murtaza, Kisat, Daniel & Sonawalla, 2009: 1). The prevalence of migraine amongst students from seven educational institutes in Pakistan was reported to be 30.0% (38.3% migraine with aura: 61.7% migraine without aura). The frequency of female migraineurs (31.4%) was higher than male migraineurs (27.9%). Their study showed a higher frequency for migraine (65.0%) existed in the age group above 30 years. A

family history of migraine was reported by migraineurs. Most migraineurs (40.2%) self-medicated and did not consult a physician (Zahid, Sthanadar, Kaleem, Latif, Sthanadar, Ali, Sthanadar, Ismail, Imtiaz & Shah, 2014: 508).

A study in district 8, (which could be considered as a representative region of a Tehran urban area with a middle class socio- economic and health status), by Shahbeigi and colleagues (2013) reported the prevalence of migraine to be 18.2%. The prevalence of migraine increased considerably from 8.8% in persons younger than 15 years to a maximum of 22.8% amongst middle aged adults in the 35 to 44 year age group. The prevalence rate of migraine was reported as 6.7% in persons over 65 years of age (Shahbeigi, Fereshtehnejad, Mohammadi, Golmakani, Tadayyon, Jalilzadeh & Pakdaman, 2013: 1160). Deleu and co-authors (2002) reported that the prevalence for migraine was 12.2% (female 15.5%: male 13.9%) in medical students in Oman. Only 23.3% of students, sought medical assistance during headache episodes. In this study 80.3% of students took medication, of which 24.6% took prescription medication, 72.9% took non-prescription medication, and only 2.5% took traditional remedies (Deleu, Khan, Humaidan, Al Mantheri & Al Hashami, 2001: 798). Alzoubi and associates (2009) reported on headaches amongst adults in Jordan. In their study of those who complained of headache, 7.7% were diagnosed with migraine. Positive family history of headache was found in most of their participants. Only 17.3% of participants sought medical care for their headaches of which 49.7% suffered from migraines (Alzoubi, Mhaidat, Azzam, Khader, Salem, Issaifan & Haddadin, 2009: 267). Migraine prevalence amongst medical students in a Kuwait University was 27.9% (31.1% female: 21.4% male). Their migraine prevalence was higher than other international studies (Al-Hashel, Ahmed, Alroughani & Goadsby, 2014: 3).

2.3.5 Prevalence of migraine in the Americas

A survey of migraine by Stang and Osterhaus (1993) in the US reported that migraine was most prevalent in patients aged 25 to 44 years and 2.5 times more common in females and increased with the level of education. Migraine was most common in Caucasians (85%). At some point of their disease 85% of female migraineurs and 77% of male migraineurs visited a physician for their migraine (Stang & Osterhaus, 1993:

29). Lipton and colleagues (2001) in their study reported that the prevalence of migraine was 18.2% in females and 6.5% in males. Prevalence of migraine increased from 12 years of age to about 40 years of age and then decreased thereafter for both genders. Results from their study showed that Caucasians had a higher migraine prevalence than Blacks. Severe headache caused substantial impairment in activities or required bedrest in 53% of respondents (Lipton, Stewart, Diamond, Diamond & Reed, 2001: 646).

Two studies in the US, conducted 10 years apart, showed that the prevalence and distribution of migraine had remained stable over the decade (1989 to 1999) (Lipton, *et al*., 2001: 646). Hazard and co-authors (2009) reported that migraine affected millions of US citizens in the most productive years of their lives. Migraine imposed a substantial burden on patients, families, society and employers. According to emerging evidence, migraine is a chronic and progressive disease (Hazard, Munakata, Bigal, Rupnow & Lipton, 2009: 55). Of the 54% of identified migraine participants that completed a follow up survey in 2006, 4.6% developed transformed migraine. Those identified migraineurs that developed transformed migraine had significantly more primary care visits, neurologist or headache specialist visits, pain clinic visits, and emergency room visits compared with participants whose migraine remained episodic. Compared to other forms of migraine, transformed migraine exacts a significantly higher economic toll on patients and health care systems (Munakata, Hazard, Serrano, Klingman, Rupnow, Tierce, Reed & Lipton, 2009: 498).

A study using a large US population sample by Buse and co-authors (2013) reported an 11.8% (17.3% females: 5.7% males) prevalence for migraine and 4.6% of patients met the criteria for probable migraine (5.3% females: and 3.9% males). In their study migraine and probable migraine were more common among women and held true across age and most other sociodemographic variables with the exception of race. African American males had a slightly higher prevalence for probable migraine than migraine (Buse, *et al*., 2013: 1278). A review of nine studies by Loder and Colleagues (2015) reported that the prevalence of migraine was highest amongst Native American, then Caucasians, followed closely by Hispanic and Blacks. Across all included studies, migraine prevalence was higher in females of all races and ethnic groups compared to males. One study reported that chronic migraine was highest in

Hispanic females, whereas Caucasian males had the lowest prevalence (Loder, Sheikh & Loder 2015: 214).

The analysis of data from respondents with migraine in the US and Canada reported that in the US approximately 26.2% of chronic migraine patients versus 13.9% of episodic migraine patients reported visiting a primary care physician in the preceding three months in Canada, 48.2% of chronic migraine patients visited primary care physician, compared with 12.3% of episodic migraine patients. Chronic migraine was associated with higher medical resource use and total costs compared to episodic migraine (Stokes, Becker, Lipton, Sullivan, Wilcox, Wells, Manack, Proskorovsky, Gladstone, Buse, Varon, Goadsby & Blumenfeld, 2011: 1058).

A population-based survey of the prevalence of migraine was carried out by O'Brien, Goeree and Streiner (1994) in Canada. They reported the prevalence of migraine to be 7.8% for males and 24.9% for females. For female migraineurs, prevalence appeared to increase with age peaking at 40 to 44 years and declining thereafter. Only 46% of 500 migraineurs reported migraine diagnosis by a physician (O'Brien, Goeree & Streiner, 1994: 1020). Cooke and Becker (2010) calculated in their study (the last study was in 1994) of Canadian women that the prevalence of migraine was 26%. Female migraineurs relied on OTC medication and only 51% had consulted a physician for their headaches. They reported that the prevalence of migraine in Canadian women appeared static (Cooke & Becker, 2010: 580). Ramage-Morin and Gilmour (2014) reported that in 2010/2011 an estimated 8.3% of Canadians reported being diagnosed with migraine. Females (11.8%) were more likely than males (4.7%) to report migraine with prevalence highest among people in their 30s and 40s (17.0% female: 6.5% male). Compared with the national figure, the prevalence of migraine was lower in Quebec (6.8%) and higher in Manitoba (9.5%), Nova Scotia (9.1%) and Ontario (8.8%). Among respondents who reported a migraine diagnosis, 42% took prescription medication for their condition, and 56% incurred medication-related out-of-pocket expenses (Ramage-Morin & Gilmour, 2014: 10).

The one-year prevalence of migraine in 12 Latin American urban communities was reported by Morillo and colleagues (2005) to be: - Argentina: female 6.1%: male 3.8%, Brazil: female 17.4%: 7.8% male, Colombia: female 13.8%: 4.8% male, Ecuador:

female13.5%: male 2.9%, Mexico: female 12.1%: male 3.9%, and Venezuela: female 12.2%: male 4.7% for each country. Migraine prevalence was highest in females aged 30 to 50 years. In the year prior to the study, a health professional was consulted by 42% of individuals identified with migraine. The most frequently consulted professional was a general practitioner (14%). No previous diagnosis of migraine was reported by 65% of individuals with headache (Morillo, Alarcon, Aranaga, Aulet, Chapman, Conterno, Estevez, Garcia-Pedroza, Garrido & Macias-Islas, 2005: 106). A survey in Santiago Chile reported that 63% of respondents consulted a health professional with regards to their headache. Migraineurs were more likely to be female (Lavados & Tenhamm, 2001: 733). A community survey about migraine in Brazil, reported the one-year prevalence to be 20.4% for migraine and 8.4% for chronic migraine. Prevalence of migraine was greater in women and among employed people (Lucchetti & Peres, 2011: 971).

2.3.6 Prevalence of migraine in Australia

According to Headache Australia, no major studies on migraine prevalence have been undertaken (Headache Australia, 2016). Heywood, Colgan and Coffey (1998) in their study in Melbourne Australia reported prevalence of typical migraine to be 17% of participants (22% female: 10% male). Of those that reported migraine headache in the last year, the most commonly used medications were simple analgesics (55%), combination analgesics (34%), anti-inflammatory drugs other than aspirin (4%), and ergotamine (3%). Less than 1% of respondents had used sumatriptan, dihydroergotamine or narcotic analgesics. Preventative medication was used by 2% of migraineurs. Migraineurs sought advice for their migraines as follows: - from general practitioners (23%), pharmacists (11%), dentists (7%), chiropractors (4%), medical specialists, physiotherapists, eye practitioners, and masseurs (each 2%). Migraineurs did not regularly seek advice with regards to treatment (Heywood, Colgan & Coffey, 1998: 485). A study by Mitchell and colleagues (1998) on prevalence in older Australians reported a lifetime past history of typical migraine as 17% of patients (22% female: 10% male). A marked trend for declining lifetime migraine frequency with increasing age was found for both sexes (Mitchell, Wang, Currie, Cumming & Smith, 1998: 627).

Stark, Valenti and Miller (2007) reported that in general practice, migraine was diagnosed in 11.5% of patients in their study. Prevalence was 14.9% for females and 6.1% for males. Frequency of migraine attacks was one or fever per month (77.1%), two per month (10.5%), and three of more per month (12.3%). Prophylactic medication was only being used by 8.3% of patients (Stark, Valenti & Miller, 2007: 142). A survey on migraine in Australia in 2011 reported that 94% of migraine sufferers said that migraine had prevented them from going to work, with 83% having to miss going to work more than a few times a year. Three out of four migraine sufferers had been unable to attend an important family event (such as a wedding, baptism, birthday party) due to migraine. Twenty one per cent said that migraine has prevented them from taking on a full time job (Anon, 2011).

2.3.7 Prevalence of migraine in Africa

A report on community-based studies in Africa by Haimanot (2003) put the prevalence rates of migraine at 3% to 6.9%. The clinical features of migraine in the African population are similar to those described among Caucasians although classical migraine appears to be rare in Africans. Few African migraineurs use specific medications with the majority opting for traditional and herbal therapies (Haimanot, 2003: 47). Woldeamanuel and colleagues (2014) carried out a 43-year systemic review on migraine in Africa. Twenty-one community-based studies were included and pooled results from these studies reported that migraine prevalence was 5.6% among the general population. Prevalence of migraine was higher among the urban population compared to rural settings. Migraine burden is progressively increasing in Africa and the study by Woldemanuel and colleagues demonstrated that migraine burden was projected to increase by more than 10% (Woldeamanuel, Andreou & Cowan, 2014: 1).

The one-year prevalence of migraine in textile workers in Akaki in Ethiopia was 6.2% (10.1% female: 3.7% male). Migraine resulted in a great burden due to lost workdays especially in females (Takele, Haimanot & Martelletti, 2008: 119). Of the Ethiopians who took part in the study of sub-Saharan migraineurs, 14% met the criteria for

migraine. As in western countries, migraine prevalence is high amongst Ethiopians and is associated with poor sleep quality and lower quality of life (physical, psychological and social) (Morgan, Eguia, Gelaye, Peterlin, Tadesse, Lemma, Berhane & Williams, 2015: 12). A door-to-door survey in a rural area in South Tanzania by Dent and colleagues (2004) reported the overall prevalence of migraine to be 5.0% (7.0% female: 2.6% male). Prevalence of migraine without aura was 1.4% (1.8% female: 0.9% male) and migraine with aura was 3.6% (5.2% female: 1.6% male). For females (11.1%) the peak prevalence was in the fourth decade of life and for males (3.8%) in the third decade of life (Dent, Spiss, Helbok, Matuja, Scheunemann & Schmutzhard, 2004: 960). Winkler and co-authors (2010) reported that in Norther-Tanzania the overall one-year prevalence of migraine headache was found to be 4.3%. Of these individuals, not all fulfilled all criteria for migraine headache, hence, these patients had to be classified as migrainous disorders with a crude prevalence rate of 1.8%. Those that met all criteria for migraine resulting in a one-year prevalence of 2.5%. This survey showed that migraine headache was not uncommon in northern Tanzania. The recorded prevalence of migraine headache was located within the median of previous African prevalence surveys, which confirmed the trend of lower migraine frequencies in rural Africa compared with western countries (Winkler, Dent, Stelzhammer, Kerschbaumsteiner, Meindl, Kaaya, Matuja & Schmutzhard, 2010: 582). The one-year prevalence of migraine in Zambia was reported to be 22.9% (Mbewe, Zairemthiama, Yeh, Paul, Birbeck & Steiner, 2015: 30). Reported mean intensity of migraine attacks was 2.7, representing severe pain. People with migraine spent approximately 10.0% of their time suffering from migraine. The three months average lost productive time for migraine was 4.1 days from work (Mbewe, Zairemthiama, Paul, Birbeck & Steiner, 2015: 36).

Lifetime prevalence for migraine amongst university students in Cotonou (Benin) was reported by Adoukonou and co-authors (2009) to be 11.3% (18.3% female: 6.8% male). The mean age at onset of the disease was 15.0 ± 2.5 years. Migraine without aura (57.9%) was more frequent than migraine with aura. The mean attack frequency per month was 3.8 migraine attacks and the peak migraine attack duration was between four and six hours (Adoukonou, Houinato, Kankouan, Makoutode, Paraiso, Tehindrazanarivelo, Viader & Preux, 2009: 887). A study in the rural area of Abomey (Benin) by Houinato and associates (2009) reported the lifetime prevalence to be 3.3%

(4.0% female: 2.2% male). The peak prevalence of migraine was found in persons in the second decade of life. Higher levels of education were associated with migraine. Migraine without aura (67.5%) was the more frequently reported form of migraine. The low prevalence rate of migraine in Benin confirmed the results of the few available African studies. Migraine occurs in young adults and could lead to a high socio-economic burden (Houinato, Adoukonou, Ntsiba, Adjien, Avode & Preux, 2010: 62).

2.3.8 Conclusion

Table 2.1 Ten Lessons on the Epidemiology of Migraine from Lipton and Bigal (2007) gives an overview of what migraine is and what needs to be achieved to improve the burden of the disease.

Table 2.1 Ten lessons on the epidemiology of migraine

Lesson	Epidemiological Facts
Lesson 1:	Migraine is common, disabling, and costly.
Lesson 2:	Migraine is comorbid with a number of other disorders.
Lesson 3:	Most people with migraine do not seek medical care for their headaches and nearly half never receive a diagnosis.
Lesson 4:	Migraine is sub-optimally treated.
Lesson 5:	Primary care providers, not neurologists and headache specialists, provide the majority of migraine care.
Lesson 6:	Strategies are needed to improve diagnosis, treatment, and patient outcomes
Lesson 7:	Screening may improve diagnosis.
Lesson 8:	Recognition of migraine disability is a crucial step towards improving treatment.
Lesson 9:	Migraine is sometimes a clinically progressive disorder.
Lesson 10:	Preventing migraine progression is an important clinical goal.

(Source: - Lipton & Bigal, 2007: 2-9).

Descriptive epidemiology of migraine has reached its maturity with prevalence rates and sociodemographic rates being stable for over 50 years (Leonardi, 2015: 1). Approximately 50% of those with frequent and/or severe migraine do not receive professional treatment, despite increasing efforts to increase awareness of migraine (Merikangas, 2013: 230). A common effort is needed worldwide that will have an impact on health care organisations so that migraine can benefit from research on new

and potentially preventive drugs and have clear public health actions that will reduce the burden. Migraine needs to be diagnosed correctly with proper care and preventative measures put in place to reduce the burden and improve the quality of life of millions of migraineurs (Leonardi, 2015: 3).

2.4 Pathophysiology

2.4.1 Introduction

The mechanisms of migraine remain incompletely understood as the pathophysiology is complicated. It is not completely clear what produces migraine aura, pain and concurrent neurological symptoms. The exact sequence of events that trigger a migraine are still not fully explained (Ravishankar, 2010: 30). However, new technologies have allowed for the formulation of concepts that may explain parts of the migraine syndrome. Migraine pathophysiology has evolved from the vascular theory of Harold Wolff to a neurological disorder (Silberstein, 2004: 2). Migraine is a genetic central nervous system disorder. Brain hyper-excitability such as abnormal neuron excitability makes a person more susceptible to migraine attacks (Aurora, 2004: 62). It has been demonstrated with functional magnetic resonance imaging (MRI) that a migraineur who is not having a migraine attack has a state of neuronal hyper-excitability in the cerebral cortex especially in the optical cortex. This explains how migraineurs have brains more susceptible to headache (Chawla, 2015: 4). Migraine is a complex headache condition occurring in a sequence of phases namely: premonitory phase, possible aura, headache, and postdrome followed by the resolution of headache. The pathophysiological mechanisms involved in each phase are probably mediated by different neuro-anatomical structures (Ashina, Bendtsen & Ashina, 2013: 15). Encompassing the wide neurological effects migraine has on the body, is the key to fully explaining its pathogenesis. What the earliest changes are during the evolution of an attack are still unknown, however CSD and abnormal brain stem activity clearly are involved. Likely there are other pathways involved that modulate the process (Benoit, 2009: 8).

The varies theories, pathways and aspects put forth to try and explain and get a clearer understanding of the pathophysiology of migraine will be discussed in the following section.

2.4.2 Vascular theory of migraine

The vascular theory of migraine was pioneered by Harold Wolff (Silberstein, 2004: 2). According to this theory abnormality in cerebral blood flow accounted for the neurological symptoms. Cerebral vasodilation caused the aura, while vasoconstriction caused the migraine headache (Ravishankar, 2010: 30). This vascular theory was based on the following three observations: "*Extracranial vessels become distended and pulsatile during a migraine attack. Stimulation of intracranial vessels in an awake person induced headache. Vasoconstrictors (ergots) improve the headache, whereas vasodilators (nitroglycerin) provoke an attack"* (Chawla, 2015). The prodrome and accompanying features were not explained by the vascular theory. Researchers found with the new imaging technologies that intracranial blood flow patterns were inconsistent with the vascular theory. Due to these anomalous findings the vascular theory was supplanted by the neurovascular theory (Goadsby, 2007: 39) where activation and sensitisation of primary afferent neurons that innervate the dural vasculature can promote the headache phase (Dussor, Yan, Xie, Ossipov, Dodick & Porreca, 2014: 1086).

A study carried out by Asghar and colleagues (2011), however, reported that migraine without aura was associated with dilatation of extra- and intracerebral arteries and that the headache location was associated with the location of the vasodilatation. Furthermore, improvement of the headache was associated with contraction of extracerebral, and not intracerebral, arteries. They concluded that their data suggested that vasodilatation and perivascular release of vasoactive substances was an integral mechanism of migraine pathophysiology (Asghar, Hansen, Amin, Van Der Geest, Koning, Larsson, Olesen & Ashina, 2011: 635). Their study proved that the vascular theory in part holds true as vasodilation does play a part in the throbbing head pain characteristic of migraine.

2.4.3 Neurovascular theory of migraine

According to the neurovascular theory, migraine is primarily a neurogenic process with secondary changes in cerebral perfusion associated with a sterile neurogenic inflammation (Chawla, 2015: 4). Although there are observable vascular phenomena in migraine, vascular changes are neither necessary nor sufficient for the generation of migraine attacks. The vessels do not simply constrict and dilate spontaneously. These vascular changes must be triggered by neuronal and/or glial signalling (Cutrer & Charles, 2008: 1413).

2.4.4 Cortical spreading depression

The idea behind CSD was first hypothesised by Lashley (1941) when experiencing his own visual auras which numbered more than 100. Over a period of one year he observed and mapped a large number of scotomas which were uncomplicated by other migraine symptoms. He mapped the figures he observed in time and space and concluded that cortical velocity spread at a rate of three millimetres per minute (Tfelt-Hansen & Koehler, 2011: 756). He suspected that there may be some event originating in the visual cortex that propagates further to involve the entire cortex at a rate of 3 mm/min (Benoit, 2009: 7). In 1944 Leão put forth the concept of CSD to explain the mechanism of migraine aura (Leo, 1944). Cortical spreading depression is a well-defined wave of neuron excitation in the cortical grey matter that spreads form its site of origin across the cortex at a rate of 3mm/min. During the CSD there is a reduction in electrical activity and a decrease in blood flow (Silberstein, 2004: 2). The threshold for initiation of CSD is presumably lower in migraineurs than in the normal population and possibly is linked to overall cerebral hyper-excitability. It is plausible to hypothesise that migraineurs have enhanced cerebral excitability (Eikermann-Haerter & Ayata, 2010: 167, 168). Cortical spreading depression could be triggered by endogenous factors, such as hormones and drugs, and might also be influenced by environmental factors such as weather, stress and food (Costa, Tozzi, Rainero, Cupini, Calabresi, Ayata & Sarchielli, 2013: 2).

Spreading depression is a slowly propagating wave of neuronal and glial depolarisation lasting a few minutes that can develop within the cerebral cortex or other brain areas after stimulation of an electrical, mechanical or chemical depolarising nature. Cortical spreading depression is considered the neurophysiological correlate of migraine aura characterised by massive increases in both extracellular potassium (K+) and glutamate, as well as rises in intracellular sodium (Na+) and calcium (Ca2+). These ionic shifts produce slow direct current potential shifts that can be recorded extracellularly. Changes in cortical parenchymal blood flow is associated with CSD. Biochemical changes of CSD may trigger the activations of meningeal trigeminal endings and trigeminal vascular system, causing the headache phase. The headache phase can occur through matrix metalloproteases activation that increases vascular permeability and through the release of nociceptive molecules from mast cells, including pro-inflammatory cytokines. The pain phase is due to peripheral and central sensitisation of the trigeminal system, as well as to the release of CGRP, both peripherally and centrally. Calcitonin gene-related peptide is also released from cortical slices during CSD and this calcium-dependent release can mediate the dilatation of cortical arterioles. Functional and structural periacqueduttal gray matter abnormalities occurring in migraineurs, contribute to the hyper-excitability of trigeminal nociceptive pathways. Dysfunction in brainstem pain-inhibiting circuitry may explain many facets of the headache phases, even in migraine with aura (Costa, *et al*., 2013: 1, 11).

2.4.5 Activation of the trigeminal vascular system

During a migraine attack, activation of the trigeminal vascular system occurs, with the release of neuropeptides and inflammatory mediators, leading to neurogenic inflammation with vasodilation of the meningeal vessels and plasma extravasation which can activate the trigeminal nociceptors and cause pain (Bohár, Fejes-Szabó, Tar, Varga, Tajti, Párdutz & Vécsei, 2013: 1597). Several vasoactive neuropeptides including: substance P, CGRP, neurokinin A, nitric oxide and pituitary adenylate cyclase-activating peptide are stored in the trigeminal sensory nerves. Released of these neuropeptides lead to vasodilation and increase blood flow leading to oedema in the meningeal vasculature as well as an inflammatory response around vascular

structures in the meninges which is believed to be responsible for head pain (Gasparini, Sutherland & Griffiths, 2013: 301). It has been suggested that migraine headache originates in the nociceptive sensory fibres conveying pain signals from intracranial and extracranial blood vessels (Olesen, Burstein, Ashina & Tfelt-Hansen, 2009: 679). The development of throbbing in the initial phase of migraine is mediated by sensitisation of peripheral trigeminovascular neurons (first-order trigeminovascular neurons) that innervate the meninges. The throbbing pain is aggravated during routine physical activities such as coughing, sneezing, bending over, rapid head shake, holding one's breath, climbing up the stairs, or walking. Stimulation of the dura also leads to activates and sensitises second-order trigeminovascular neurons located in the medullary dorsal horn. Development of cephalic allodynia is propelled by this sensitisation of second-order trigeminovascular neurons in the spinal trigeminal nucleus which receive converging sensory input from the meninges as well as from the scalp and facial skin. Sensitisation of third-order trigeminovascular neurons in the posterior thalamic nuclei which receive converging sensory input from the meninges, facial and body skin leads to the development of extracephalic allodynia (Bernstein & Burstein, 2012: 89-91).

2.4.6 Calcitonin gene-related peptide and its role in migraine pathophysiology

Migraine is associated with an increase in plasma CGRP levels. Calcitonin gene-related peptide is a neuropeptide released from activated trigeminal sensory nerves which dilates intracranial blood vessels and transmits vascular nociception. Therefore, it is proposed that CGRP may have an important role in the pathophysiology of migraine, as inhibition of trigeminal CGRP release or CGRP-induced cranial vasodilatation could abort a migraine attack. Triptans abort migraine headache primarily by constricting the dilated cranial blood vessels and by inhibiting the trigeminal CGRP release (Arulmani, MaassenVanDenBrink, Villalón & Saxena, 2004: 315). Calcitonin gene-related peptide is thought to be released from peripheral endings of perivascular meningeal nociceptors and to promote vasodilation during migraine. A current hypothesis suggests that peripheral CGRP and it's related meningeal vasodilation results in activation and sensitisation, leading to the generation of migraine headache. Both human and animal studies are consistent in supporting a

critical role for CGRP in the pathophysiology of migraine, most likely through a central action on second-order neurons in the medullary dorsal horn that process nociceptive input from the meninges (Levy, Burstein & Strassman, 2005: 698, 705). Raddant and Russo (2011) proposed that CGRP could enhance neurotransmission in migraine by both peripheral and central mechanisms. It is thought that local release of CGRP from the nerve endings of meningeal nociceptors following their initial activation by CSD is critical for the initiation of vasodilation, plasma protein extravasation, neurogenic inflammation and the consequential sensitisation of meningeal nociceptors. Within the brain, the wide distribution of CGRP and CGRP receptors provides numerous possible targets for CGRP to act as a neuromodulator (Raddant & Russo, 2011).

The model of calcitonin gene-related peptide-induced hypersensitivity is shown in Figure 2.3. Figure 2.3 (a) shows relatively low CGRP levels, leading to normal neurotransmission and proper filtering of sensory input and (b) shows elevated CGRP levels (initiated by migraine triggers) increase synaptic transmission in the hypersensitive migraine brain. This increased perception of sensory inputs is registered in the cortex as painful stimuli.

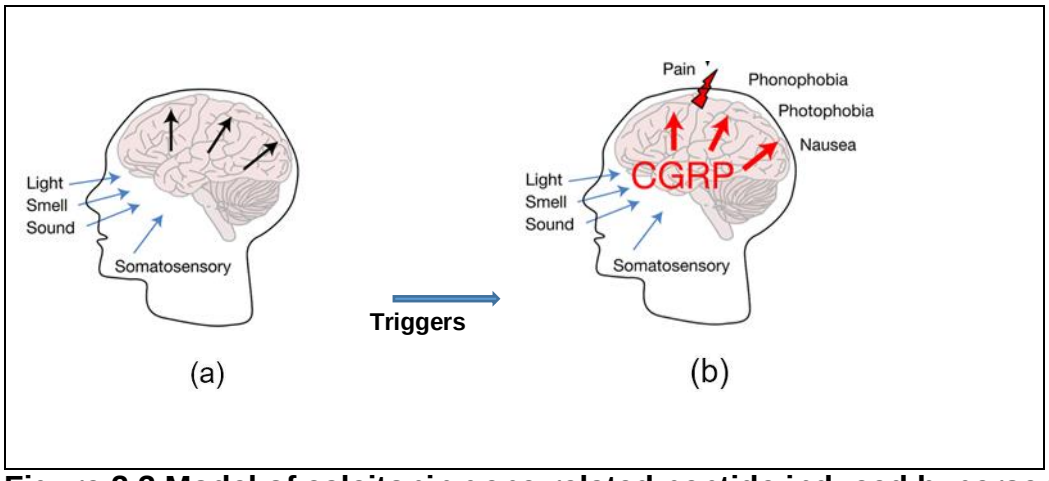


Figure 2.3 Model of calcitonin gene-related peptide induced hypersensitivity
(Figure adapted from source: - Raddant & Russo, 2011: 21).

2.4.7 Serotonin component of migraine pathophysiology

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter which is impicated in the pathogenesis of migraine. Activation of 'trigeminovascular system', causes the release

of vasodilators and a decrease in the levels of neurotransmitter like serotonin in trigeminal nerve and cranial vessels. Serotonin vasoconstricts the nerve endings and blood vessels and in this way affects nociceptive pain. Migraineurs often report that the headaches stop after they have vomited. Vomiting stimulates intestinal motility and raises blood serotonin (Aggarwal, Puri & Puri, 2012: 90, 92). There is hypersensitivity of central 5-HT receptors in migraine without aura (Cassidy, Tomkins, Dinan, Hardiman & O'Keane, 2003: 32).

According to (Schwedt, 2007: 1301), the following trends have been noted in migraine and serotonin studies: -

1. *Serotonin levels in the plasma are altered in subjects with migraine. Interictally, 5-HT levels are lower, whereas 5-hydroxyindolacetic acid (5-HIAA) levels are higher than in non-migraine controls. During migraine attacks, 5-HT levels increase, whereas 5-HIAA levels decrease.*
2. *There is a reduction in platelet serotonin concentration during migraine without aura attacks. Platelets are the main repository of serotonin in the blood. A similar reduction has not been demonstrated during migraine with aura.*
3. *There is an increase in 5-HIAA concentrations in the urine during migraine attacks.*
4. *There is increased brain serotonin synthesis in patients with migraine. 5-HIAA concentrations are elevated in the cerebrospinal fluid of migraine patients, suggesting increased breakdown of serotonin in the central nervous system.*

A study by Schuh-Hofer and colleagues (2007) demonstrated for the first time that there was a significant increase of brainstem serotonin transport protein availability in migraineurs, suggesting a dysregulation of the brainstem serotonergic system (Schuh-Hofer, Richter, Geworski, Villringer, Israel, Wenzel, Munz & Arnold, 2007: 789). The serum dissolved serotonin concentration increases during a migraine attack. This was evidence of the pumping of granule serotonin from thrombocytes into the plasma, and rapid extraction of serotonin from the blood into the urinary excretory system. This gives rise to the pathophysiological mechanism and clinical cascade of the migraine attack. Serotonin deficiency in the post-attack phase of migraine results from excess serotonin excreted in urine. The low content of granule serotonin in thrombocytes and the increase in the serum serotonin concentration provided evidence of impairment in

the storage of endogenous serotonin in thrombocytes during migraine attacks and release of thrombocyte associated serotonin into the plasma (Izzati-Zade, 2008: 504). The documented changes in 5-HT metabolism and the processing of central 5-HT-mediated responses during and in between migraine attacks have led to the suggestion that migraine is a consequence of a central neurochemical imbalance that involves a low serotonergic disposition. Evidence suggests that a low 5-HT state facilitates activation of the trigeminovascular nociceptive pathway, as induced by CSD (Hamel, 2007: 1295).

2.4.8 The role of the brainstem in migraine

Positron emmission tomagraphy has shown that the brainstem is involved in the pathophysiology of migraine. Increased blood flow was found in the cerebral hemispheres in cingulate, auditory and visual association cortices and the brainstem during a migraine attack. After injection of sumitriptan which induced complete relief from headache, phono- and photophobia, brain stem activation persisted. These findings support the idea that the pathogenesis of migraine is related to an imbalance in activity between brainstem nuclei regulating antinociception and vascular control (Weiller, May, Limmroth, Jüptner, Kaube, Schayck, Coenen & Diener, 1995: 658). Brainstem nociceptor sensitisation may occur prior to or simultaneously with the development of neurogenic inflammation. Brainstem nuclei nociceptors that are involved in the central control of pain may be dysfunctional in migraineurs, and may have an increased tolerance for trigeminal neuronal hyperexcitability (Silberstein, 2004: 4).

2.4.9 The basal ganglia and migraine attacks

It has been suggested that the basal ganglia through its role in pain processing plays a signigicant role in the pathophsiology of episodic migraine. The basal ganglia are a major site for adaptive manipulability in the brain and is involved through direct connections from sensory inputs including pain. Basal ganglia may be involved in most aspects of pain processing including sensory discriminative, emotional/affective, cognitive dimension of pain, and pain modulation. Brain imaging studies of migraineurs

have shown decreased response to pain stimuli in the basal ganglia of migraineurs versus controls as well as increased activation (blood flow) in the basal ganglia during the ictal state and lesions in the basal ganglia of migraineurs (Maleki, Becerra, Nutile, Pendse, Brawn, Bigal, Burstein & Borsook, 2011: 1). Yuan and colleagues' (2013) study revealed the presence of reduced volume in the nucleus accumbens and caudation of the basal ganglia and interictal dysfunctional dynamics within basal ganglia networks in migraine witout aura. The abnormal structure and function within the pain-related pathways of the basal ganglia were possibly associated with impaired pain processing and modulatory processes in migraine without aura (Yuan, Zhao, Cheng, Yu, Zhao, Dong, Xing, Bi, Yang, Von Deneen, Liang, Gong, Qin & Tian, 2013: 836).

2.4.10 Genetic/gender component of migraine

Genetic studies have shown that migraine with aura has a much stronger genetic predilection than migraine without aura (Benoit, 2009: 7). A large list of genes implicated in migraine have been produced by genetic studies, but how they actually participate in migraine processes is still poorly understood (Gasparini, *et al.,* 2013: 309). Three familial hemiplegic migraine (FHM) causative genes have been identified, all encoding ion channels or transporters. Migraineurs with FMH are subdivided dependent on which gene causative mutation has occurred. *Familial hemiplegic migraine type 1* – causative mutation on the CACNA1A gene has been demonstrated. *Familial hemiplegic migraine type 2*– causative mutation on the ATP1A2 gene has been demonstrated. *Familial hemiplegic migraine type 3*– causative mutation on the SCN1AATP1A2 gene has been demonstrated (ICHD-3, 2013: 248-249). Studies in monogenic migraine syndromes have identified mutations in six genes for migraine. Clinical and genetic studies have shown that migraine is a multifactorial disorder with complex interaction between multiple predisposing genetic and modulating nongenetic factors (Gupta, Mehrotra, Villalón, Perusquía, Saxena & MaassenVanDenBrink, 2007: 76). Genomic regions that increase individual risk to migraine have been identified in neurological, vascular and hormonal pathways (Gasparini, *et al*., 2013: 300).

Compared with male migraineurs and healthy controls of both sexes, female migraineurs had thicker posterior insula and precuneus cortices. Evaluation of functional responses to heat within the migraine groups, indicated concurrent functional differences in male and female migraineurs and a sex-specific pattern of functional connectivity of these two regions with the rest of the brain. These results support the notion of a 'sex phenotype' in migraine and indicate that male and female brains are differentially affected by migraine. Futhermore, emotional circuitry compared with sensory processing appears involved to a greater degree in female than male migraineurs supporting the notion that sex differences involve both brain structure as well as functional circuits (Maleki, Linnman, Brawn, Burstein, Becerra & Borsook, 2012: 2546).

Basic and clinical studies suggest an intricate relationship between female sex steroids and the occurrence of migraine, thereby contributing to the high prevalence of migraine in women, as well as changes in the frequency or severity of migraine attacks that are in tandem with various reproductive milestones in women's life (Gupta, *et al*., 2007: 321).

Gupta and colleagues (2007) reported that female sex steroids have been shown to enhance:

- *Neuronal excitability by elevating calcium (Ca^{2+}) and decreasing magnesium (Mg^{2+}) concentrations, an action that may occur with other mechanisms triggering migraine;*
- *The synthesis and release of nitric oxide and neuropeptides, such as CGRP, a mechanism that reinforces vasodilatation and activates trigeminal sensory afferents with a subsequentstimulation of pain centres;*
- *The function of receptors mediating vasodilatation, while the responses of receptors inducing vasoconstrictionare attenuated; and*
- *The serotonergic, adrenergic and γ-aminobutyric acid (GABA)-ergic systems are also modulated by sex steroids, albeit to a varying degree and with potentially contrasting effects on migraine outcome*.

Female sex steroids modulate several mediators and/or receptor systems via both genomic and non-genomic mechanisms. These actions may be perpetuated at the central nervous system, as well as at the peripheral (neuro)vascular level (Gupta, *et al*., 2007: 321).

2.4.11 Histamine and migraine

Histamine is another key component of the neuroinflammatory process, with trigeminovascular activation and plasma protein extravasation, mast cells degranulate and release histamine. In the nervous system, histamine acts mainly on H_1 and H_3 receptors. Histamine H_1 receptors mediate inflammation, whereas histamine H_3 receptors are much more sensitive to histamine and serve as negative feedback to inhibit further excessive release of histamine by C-fibers. Histamine triggers both immediate and delayed headaches, more frequently and intensely in migraineurs. (Gupta, Nahas & Peterlin, 2011: 14). The period when there is reduced susceptibility for migraine attacks corresponds with less central histaminergic firing (Alstadhaug, 2014: 246).

2.4.12 Magnesium and migraine

Magnesium is an important intracellular element that is involved in numerous cellular functions. Magnesium deficiencies may play an important role in the pathogenesis of migraine headaches by promoting CSD, alteration of neurotransmitter release, platelet aggregation and vasoconstriction. Magnesium deficiency also results in the generation and release of substance P, which is believed to act on sensory fibers and produce headache pain. It has been speculated that, during headaches, migraine sufferers excrete excessive amounts of magnesium as a result of stress, resulting in transient serum hypomagnesemia. However, there was actually a trend towards increased magnesium concentrations in patients with migraine without aura (Sun-Edelstein & Mauskop, 2009: 370-371). A study by Samaie, Asghari, Ghorbani and Arda (2012: 1) reported that the serum magnesium level was on average significantly lower in patients with migraine compared to the healthy group. However, the serum total

magnesium levels in migraineurs remained constant within and between migraine headache attacks. No significant difference was found in magnesium levels between migraine with aura and migraine without aura (Sadeghi, Nasiri, Bayatiyani, Rasad, Pahlavani, Maghsoudi & Askari, 2015: 15). The main findings of Lodi and colleagues (2001) study was a reduced interictal cytosolic free magnesium concentration in the occipital lobes of patients with different types of migraine. This was matched by a decreased amount of energy released by the reaction of adenosine triphosphate hydrolysis. Both these variables were found to be more abnormal in migraine patients with more severe clinical phenotypes. Total and ionised magnesium has been found to be reduced in serum and erythrocytes of patients with different forms of migraine (Lodi, Iotti, Cortelli, Pierangeli, Cevoli, Clementi, Soriani, Montagna & Barbiroli, 2001: 439).

2.4.13 Dopamine/platelets and migraine

Dopamine has been considered to play a role in the pathogenesis of migraine. Akerman and Goadsby (2007) stated that the literature indicates that migraineurs have brains that are hypersensitive to dopamine agonists. There are a number of polymorphisms of dopaminergic genes related to migraine. Dopamine agonists cause the premonitory symptoms of migraine such as nausea and yawning, drowsiness, mood changes, irritability and hyperactivity in the days and hours preceding an attack. Dopamine migraine pathogenesis mechanism can be explained by the fact that dopamine can induce premonitory symptoms, by an action at dopaminergic proteins that are in some way hypersensitive to dopamine, and this is carried forward into the migraine pain generated in the trigeminovascular systems, mediated predominantly by dopamine D_2 receptors. Although dopamine antagonists are effective in migraine treatment it is still not clear whether their action is via dopamine receptors or some other mechanism (Akerman & Goadsby, 2007: 1308, 1311).

According to Shukla, Khanna, Vinod, Sankhwar and Yadav (2009: 532) platelets are a useful model to understand brain dopaminergic mechanisms. Platelet levels of dopamine were higher in both types of migraine when compared with controls, but the with the difference only being significant in migraine without aura (D'Andrea, Granella,

Perini, Farruggio, Leone & Bussone, 2006: 585). Inflammation represents another plausible link between platelet biology and migraine. Increased release of several pro-inflammatory cytokines, especially interleukins one, six and eight and tumour necrosis factor-alpha, may occur after formation of platelet-leukocyte aggregates. These cytokines can further contribute to increase sterile inflammation in the brain and facilitate pain signalling and ultimately promote development or worsening of migraine pain. Platelet activation may be involved in triggering migraine attacks through 5-HT metabolism (Danese, Montagnana & Lippi, 2014: 17-21).

2.4.14 Migraine and the hypothalamus

Alstadhaug (2009) reorted that positron emission scanning during spontaneous migraine attacks had shown activation of the hypothalamus. Up to several hours before the migraine aura and the migraine headache, many patients experience vague symptoms like hunger, thirst, lassitude, tiredness, yawning and, on some occasions, a sense of oppression, desire to urinate and various other symptoms. Given the central role of the hypothalamus in maintaining homeostasis, one may claim that premonitory symptoms may reflect temporary hypothalamic dysfunction that precedes a migraine attack (Alstadhaug, 2009: 811).

Migraine pathways in the brain are shown in Figure 2.4. During a migraine attack dysfunction of brain-stem pathways that normally modulate sensory input occur. The trigeminovascular input from the meningeal vessels are the key pathways for the pain associated with migraine. The “migraine centre” which is supposed to be located in the brain stem is activated by impulses from the cortex, thalamus and hypothalamus and this is responsible for generation of a migraine attack.

A summary of the supposed pathophysiology of a migraine attack and the therapeutic targets of acutely acting antimigraine drugs is shown in Figure 2.5.

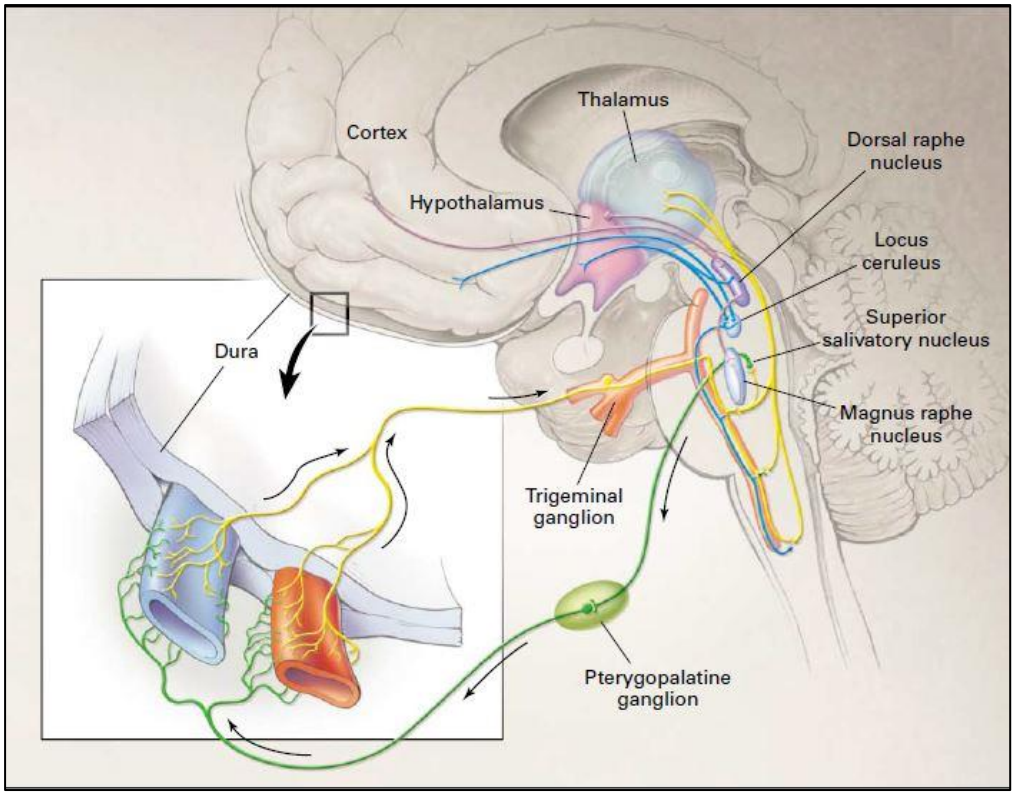


Figure 2.4 Migraine pathways in the brain
(Source: - Goadsby, Lipton & Ferrari, 2002: 259)

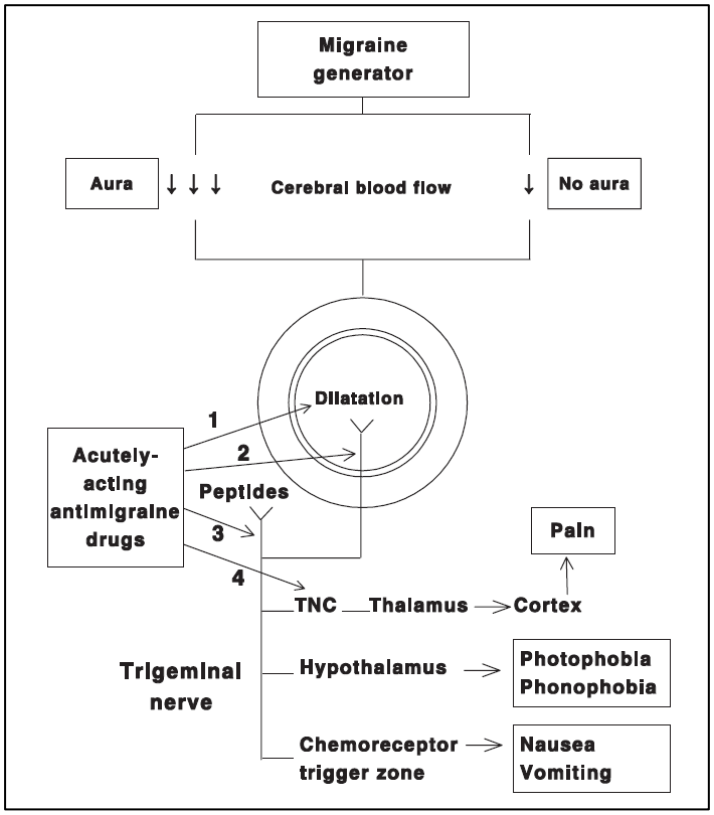


Figure 2.5 Summary of migraine pathophysiology and the therapeutic targets of acutely acting antimigraine drugs
(Source: - Villalón, Centurión, Valdivia, De Vries & Saxena, 2002: 200)

2.5 Migraine classification

The Headache Classification Committee of the International Headache Society (IHS) has compiled a classification document for headaches, The International Classification of Headache Disorders (3rd edition (beta version)) (ICHD-3) (2013). Certain diagnostic criteria need to be met for the classification of migraine in the different sub-types. Migraine is sub-divided into two main categories, migraine without aura and migraine with aura. These two types of migraine will be discussed in this section.

2.5.1 Migraine without aura

Migraine without aura, according to the ICHD-3, is described as a recurrent headache disorder manifesting in attacks lasting four to 72 hours, treated or untreated. This is the most common type of migraine. Typical characteristics are that the headache is unilateral of moderate or severe intensity with a pulsating quality, aggravated by routine physical activity and associated with nausea and/or photophobia and phonophobia. For a headache to be classified as a migraine without aura, certain diagnostic criteria have to be meet in accordance with the ICHD-3. Table 2.2 depicts the criteria required by the ICHD-3 for a headache to be classified as migraine without aura.

Table 2.2 ICHD-3 criteria for the classification of a migraine without aura

Criteria	Characteristics/symptoms
A.	At least five attacks fulfilling criteria B–D
B.	Headache attacks lasting four to 72 hours (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 (e.g. 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

(Source: - ICHD-3, 2013: 645)

2.5.2 Migraine with aura

Migraine with aura is a migraine which has an aura phase. The aura is a recurrent disorder manifesting in attacks of reversible focal neurological symptoms with a mix of positive and negative features. Aura usually evolves over a period of five to 20 minutes, lasting up to an hour and is usually followed by a headache but aura can also accompany the headache. For a headache to be classified as a migraine with aura, certain diagnostic criteria must be meet in accordance with the ICHD-3. Table 2.3 depicts the criteria required by the ICHD-3 for a headache to be classified as migraine with aura.

Table 2.3 ICHD-3 criteria for the classification of migraine with aura

Criteria	Characteristics/symptoms
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 two of the following four characteristics: 1. at least one aura symptom spreads gradually over five minutes, and/or two or more symptoms occur in succession 2. each individual aura symptom lasts five to 60 minutes 3. at least one aura symptom is unilateral 4. the aura is accompanied, or followed within 60 minutes, by headache
D.	Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

(Source: - ICHD-3, 2013: 646)

There are migraineurs who suffer from both migraines with and without aura. Migraine with aura is further sub-divided into: -

- *Migraine with typical aura* which is migraine with aura in which aura consists of visual and/or sensory and/or speech/language symptoms, but no motor weakness, brainstem or retinal symptoms and is characterised by gradual development, duration of each symptom no longer than one hour, a mix of positive and negative features and complete reversibility. The aura is accompanied or followed within one hour by headache.
- *Typical aura with headache* which is migraine with typical aura in which aura is accompanied or followed within 60 minutes by headache with or without migraine characteristics.
- *Typical aura without headache* which is migraine with typical aura in which aura is neither accompanied nor followed by headache of any sort (ICHD-3, 2013: 746).

2.5.3 Migraine with brainstem aura (previously basilar migraine)

The ICHD-3 classifies migraine with brainstem aura as migraine with an aura that originates from the brainstem, but has no motor weakness. Aura consists of fully reversible visual, sensory and or speech /language symptoms but no motor or retinal symptoms. Brainstem symptoms could be any two or more of the following, dysarthria (difficult or unclear articulation of speech that is otherwise linguistically normal), vertigo, tinnitus, hypacusis (partial loss of hearing), diplopia (double vision), ataxia (the loss of full control of bodily movements), or decreased level of consciousness. During most attacks, typical aura symptoms as well as brainstem symptoms occur. Aura is accompanied or followed by headache (ICHD-3, 2013: 648). This subgroup of migraine patients was first described by Bickerstaff and colleagues in 1961. Kaniecki (2009) in his article on basilar-type migraine reported that Bickerstaff described a rare sub group of migraine with aura that mainly affected women, with 26 of the 34 case reports being adolescent girls. These patients reported aura that included ataxia, vertigo, dysarthria, tinnitus, or bilateral visual or sensory symptoms that lasted for two to 45 minutes, followed by a severe throbbing headache that was often occipital in location (Kaniecki, 2009: 217).

A study by Ying and colleagues (2014) found that of 1526 headache patients studied, 348 patients suffered from migraine and 23 patients (1.5%) were diagnosed with

basilar type headache. The mean age at onset was 20.3 ± to 11.7 years (range 4 to 49 years). They concluded that basilar type migraine is an episodic disorder suffered by 1.5% of headache patients with age of onset in the second and third decade of life (Ying, Fan, Li, Wang, Li & Tan, 2014: 1230).

2.5.4 Hemiplegic migraine

Hemiplegic migraine (HM) is migraine with aura that includes motor weakness. Motor weakness may last for weeks in some patients. The ICHD-3 classification reports that hemiplegic migraine is sub-divided into familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM). Familial hemiplegic migraine is migraine with aura including motor weakness, and at least one first- or second-degree relative having migraine aura including motor weakness. Migraineurs with FMH can be further subdivided dependent on which gene causative mutation has occurred.

- *Familial hemiplegic migraine type 1* – causative mutation on the CACNA1A gene has been demonstrated.
- *Familial hemiplegic migraine type 2*– causative mutation on the ATP1A2 gene has been demonstrated.
- *Familial hemiplegic migraine type 3*– causative mutation on the SCN1AATP1A2 gene has been demonstrated.
- *Sporadic hemiplegic migraine* is migraine with aura including motor weakness, and no first- or second-degree relative has migraine aura including motor weakness (ICHD-3, 2013: 248-249).

Hemiplegic migraine is a rare sub-type of migraine with aura with attacks typically starting in the first or second decade of life (Russell & Ducros, 2011: 457). An epidemiological survey by Thomsen and colleagues found the prevalence of HM at the end of 1999 to be 0.01% in Denmark. Equal frequency of familial and sporadic hemiplegic migraine were found (Thomsen, Eriksen, Romer, Andersen, Ostergaard, Keidin, Olesen & Russell, 2002: 361). Cha and colleagues (2007) did a study on identical male twins with late onset HM. The similar symptoms exhibited by genetically identical twins supports the underlying genetic factor of HM (Cha, Millett, Kane, Jen & Baloh, 2007: 1169). A positive family history may point to FHM. Genetic and

environmental factors may lower the CSD threshold, thereby increasing migraine susceptibility. Diagnosis can be confirmed, but not ruled out by genetic testing as some HM patients could have as yet unidentified genes which are involved (Pelzer, Stam, Haan, Ferrari & Terwindt, 2013: 13-17).

2.5.5 Retinal migraine

Grosberg and colleagues (2005) reported that the term "*Retinal Migraine"* was introduced in 1970 by Carroll to describe patients with transient and permanent monocular visual loss in the absence of migraine headache. Subsequently retinal migraine has been used for those cases of monocular visual impairment temporally associated with migraine attacks (Grosberg, Solomon & Lipton, 2005: 268). Patients who suffer from retinal migraine have repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache (ICHD-3, 2013: 650).

Retinal migraine manifests itself as recurrent attacks of unilateral visual disturbances or blindness lasting from a few minutes to one hour. A gradual visual disturbance in a mosaic pattern of scotomata which gradually enlarges producing total unilateral visual loss is experienced by patients with retinal migraine (Srinivasa & Kumar, 2010:15). Documented visual effects may last for days, weeks or even become permanent. This disease usually occurs in young adults who suffer from migraine with or without aura. The most likely mechanism for retinal migraine is spasm of the ophthalmic artery, the central retinal artery, or the branches of the retinal artery (Solomon, 2001: 166). Retinal migraine is less benign than migraine with conventional visual aura due the fact that there are a high number of patients with transient monocular visual loss who eventually develop permanent monocular vision loss (Evans & Grosberg, 2008: 144).

2.5.6 Chronic migraine

Chronic migraine (CM) describes a subset of migraineurs who were previously diagnosed with episodic migraine and have progressed over time to having a headache for more than 15 days of a month for at least three consecutive months,

with headache having clinical features of migraine with aura for at least eight days of the 15 days of headache (ICHD-3, 2013: 650). Twenty percent of episodic migraine progresses to CM suggesting that for a sub group of migraineurs, migraine is a progressive neurological disease. Retrospective studies suggest that it takes on average 10.8 years for episodic migraine to progress to chronic migraine. Over use of acute medications often complicates CM (Cady, Schreiber & Farmer, 2004: 426,432).

According to Bigal and Lipton (2008: 14), migraine should be seen as a chronic recurrent disease that is progressive in patients with high biological predisposition or susceptibility to risk factors. Migraines progress clinically, physiologically and anatomically. Progression could be as a result of the underlying mechanisms that generate migraine attacks (CSD) or may be a function of the activations generated by attacks (lesions of the periaqueductal grey area). This hypothesis is supported by the increase in number of lesions with increase in frequency of attacks. Common genetic and environmental factors could also explain progression of migraine attacks (Bigal & Lipton, 2008: 14). A study by Manack and colleagues (2011) concluded that the prevalence of CM was 2% of the population. Approximately 2.5% of episodic migraineurs develop new onset chronic migraine each year (Manack, Buse & Lipton, 2011: 70).

Population based studies have shown that CM has a higher individual and social burden due to the fact that CM has a high association of disability (Katsarava, Buse, Manack & Lipton, 2012: 86). Schramm and colleagues (2013) found in their studies that patients who suffered from CM where more likely to be female, to smoke, to be obese and to report frequent intake of acute pain drugs (Schramm, *et al.,* 2013). Research suggests that CM is associated with brain abnormalities that are progressive and could be persistent or permanent (Silberstein, Lipton & Dodick, 2014: 1258).

2.5.7 Complications of migraine

The ICHD-3 in their classification of migraine list a number of complications associated with migraine. These complications are namely: -

- *Status migrainosus*: - A debilitating migraine attack lasting for more than 72 hours.

- *Persistent aura without infarction*: - Aura symptoms persisting for one week or more without evidence of infarction on neuroimaging.
- *Migrainous infarction*: - One or more migraine aura symptoms associated with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging.
- *Migraine aura-triggered seizure*: - A seizure triggered by an attack of migraine with aura (ICHD-3, 2013: 653).

2.5.8 Probable migraine

The term used previously for probable migraine was “migrainous disorder”. Migraine-like attacks missing one of the features required to fulfil all criteria for a subtype of migraine coded above, and not fulfilling criteria for another headache disorder. Probable migraine is subdivided into: -

- *Probable migraine without aura*: - This is a migraine like attack without aura fulfilling all but one criteria for a migraine without aura.
- *Probable migraine with aura*: - This is a migraine like attack with an aura fulfilling all but one criteria for a migraine with an aura.

All the characteristics necessary for a migraine attack diagnosis are not always present in mild migraine attacks or those attacks that are treated early. These attacks should be counted as migraine if they respond to migraine specific treatments (ICHD-3, 2013: 653).

2.5.9 Episodic syndromes that may be associated with migraine

The terms previously used were: - “childhood periodic syndromes”; “periodic syndromes of childhood”. In this section the recurrent gastrointestinal disturbances, cyclic vomiting syndrome and abdominal migraine will be discussed.

Cyclic vomiting syndrome and abdominal migraine occur mainly in childhood. *Cyclic vomiting syndrome* is described as recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes. Attacks may be associated with pallor and lethargy. There is complete resolution of symptoms between attacks (ICHD-3, 2013: 653). A study by Stickler (2005) showed

that patients with cyclic vomiting syndrome had a higher prevalence of migraine compared to the control population (22% vs. 5%). Almost twice as many cyclic vomiting syndrome patients had mothers and grandmothers with migraines compared to controls. According to Stickler (2005: 507) these associations supported the opinion that migraine is a genetically inherited diseases that occurs more frequently in relatives affected with cyclic vomiting syndrome. Although cyclic vomiting syndrome is considered to be mainly a childhood disease, it was seen in up to 14% of adults at a gastrointestinal motility clinic. Approximately 39% to 87% of children who suffer from cyclic vomiting syndrome go on to develop migraine later in adulthood and 24% to 70% of adults with cyclic vomiting syndrome have migraine as a comorbid disease (Evans & Whyte, 2013: 987).

Abdominal migraine is described as an idiopathic disorder seen mainly in children as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting two to 72 hours and with normality between episodes. Headache does not occur during these episodes (ICHD-3, 2013: 653). According to Russell and colleagues (2002) abdominal migraine is predominately a childhood disease but although rare, is not unknown in adults. Abdominal migraine can be the precursor of adult migraine (Russell, Abu-Arafeh & Symon, 2002: 5). It was found by Marugán and colleagues (2008) that one third of patients who suffered from recurrent abdominal pain as children were likely to suffer from migraine in adolescence and young adulthood (Marugán, Fernández-Castaño, Del Carmen Torres & Del Carmen De Fuentes, 2008: 571).

Roberts and deShazo (2012) did a cohort study on suspected abdominal migraine in adults. They concluded that abdominal migraine is often undiagnosed and missed diagnosis in adult migraineurs (Roberts & deShazo, 2012: 1135). Case reports by Cervellin and Lippi (2015: 864) and Woodruff and colleagues (2013) concluded that abdominal migraine as a diagnosis should be considered when patients report recurrent abdominal pain for which no alternative diagnosis after complete gastrointestinal workup has be made (Woodruff, Cieri, Abeles & Seyse, 2013: 27).

2.5.10 Recurrent painful ophthalmoplegic neuropathy

The term previously used to describe these symptoms was "*ophthalmoplegic migraine".* The symptoms are repeated attacks of paresis of one or more ocular cranial nerves with ipsilateral headache. *Ophthalmoplegic migraine* was rejected because this syndrome was not migrainous but rather a recurrent painful neuropathy (ICHD-3, 2013: 781). Levin and Ward (2004) reported that the concept of "*ophthalmoplegic migraine"* was first described by Gubler in 1860 and labelled "ophthalmoplegic migraine" in a paper published by Charcot in 1890. Although "*ophthalmoplegic migraine"* generally occurs in children under 10 years of age, a number of adult cases have been reported (Levin & Ward, 2004: 306). Ophthalmoplegic migraine is a very rare condition with an incidence of about 1.7 per million people. Almost all patients with "*ophthalmoplegic migraine"* have a current or previous history of migraine without ophthalomoplegia as seen in the case study of two patients by Lane and Davies (Lane & Davies, 2010: 660). Characteristics of "*ophthalmoplegic migraine"* are a migraine-like headache accompanied or followed within four days of its onset by paresis of one or more of the III, IV and/or VI cranial nerves. Prognosis is good because symptoms almost always resolve (four to 84 days), although after recurrent episodes, some deficits may persist. Ambrosetto and colleagues in their study on "*ophthalmoplegic migraine"* concluded that it was the same disease in children and adults and that it should be classified as a migraine (Ambrosetto, Nicolini, Zoli, Cirillo, Feraco & Bacci, 2014: 914).

2.5.11 Menstrual migraine

Menstrual migraine can be divided into pure menstrual migraine and menstrual-related migraine, which is mostly migraine without aura. Pure menstrual migraine is migraine that occurs only on certain days, specifically two days before the start to three days after the start of menstruation and at no other time of the cycle. This must occur for at least two out of three menstrual cycles. For menstrual-related migraine, migraine can also occur at other times during the cycle (ICHD-3, 2013: 792).

The prevalence of migraine in women increases at the onset of puberty and considerably exceeds that of men so that at its peak (35 to 45 years) women have a three times higher prevalence than men (Gupta, *et al*., 2007: 321). According to Martin and Lipton (2008), 50% of female migraineurs reported that migraine is more likely during perimenstrual time periods. Menstrual migraine may have a greater impact than migraine that occurs at other times of the menstrual cycle (Martin & Lipton, 2008: 124, 130). Migraine associated with menses may be more frequent, more severe, more difficult to treated and more likely to relapse than non-menstrual migraines (MacGregor, Victor, Hu, Xiang, Puenpatom, Chen & Campbell, 2010: 537). Pinkerman and Holroyd's (2010: 1187) study suggests that menstrual related migraines do not respond in the same way to treatment and so treatment has to be approached differently. Patients with menstrual migraine may have more affected relatives than patients with non-menstrual migraine (Russell, 2010: 385). A population based study of the prevalence of menstrual migraine by Vetvik and colleagues (2013) found that that one in five female migraineurs (30 to 34 years) have migraine in about 50% of their menstruations. The ICHD-3 beta appendix criteria for menstrual migraine is not complete as Vetviks' study found that one in eight women had migraine with aura although the majority had migraine without aura (Vetvik, MacGregor, Lundqvist & Russell, 2013: 1).

2.5.12 Vestibular migraine

Vestibular migraine is a combination of vertigo, dizziness and balance disturbance with migraine and can occur at any age. Vestibular symptoms which can be moderate to severe can last from five minutes to 72 hours. Transient auditory symptoms, nausea, vomiting, prostration and susceptibility to motion sickness may be associated with vestibular migraine (ICHD-3, 2013: 794). According to Cha and Baloh (2007) a hereditary predisposition to migraine with vertigo is supported by family studies (Cha & Baloh, 2007: 121). Epidemiology of vestibular migraine is 1% of the general population, about 10% of patients in dizziness clinics and 9% in migraine clinics (Lempert & Neuhauser, 2009: 333). A study of vestibular migraine by Hsu and colleagues (2011) showed a strong female predominance (five to one ratio) and vestibular migraine beginning several years after typical migraine. The one-year

prevalence for vestibular migraine was 5% in women aged 40 to 54 years (Hsu, Wang & Fuh, 2011: 79). Vestibular migraine has become recognised as a distinct disease that accounts for a high proportion of patients with vestibular symptoms (Furman, Marcus & Balaban, 2013: 707). For most patients, vestibular migraine is an episodic disorder with duration of attacks ranging from a few seconds (10%), to a few minutes (30%), to a few hours (30%) or even a few days (30%). Patients without aura are more likely to have attacks of vestibular migraine than patients with aura. Headache accompanied by dizziness and vertigo occurs in less than one quarter of patients. Thirty percent of vestibular migraine are not accompanied by a headache and some patients never have a headache at the same time as the vertigo. Dizziness and vertigo can occur before, during or after the migraine attack (Stolte, Holle, Naegel, Diener & Obermann, 2015: 264). There are a few sub-groups of vestibular migraine namely:

- *Benign paroxysmal vertigo* is a disorder characterised by recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children.
- *Benign paroxysmal torticollisis* is a recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously. The condition occurs in infants and small children, with onset in the first year (ICHD-3, 2013: 654).

2.5.13 Refractory migraine

Until recently refractory migraine has been largely overlooked (Schulman & Brahin, 2008: 776). The ICHD-3 does not include a definition for refractory migraine despite there being are a group of patients with refractory (intractable, treatment resistant) headache. These patients fail to respond to or tolerate current evidence based treatments. Goadsby and colleagues (2006) were the first to propose criteria for intractable headache (Goadsby, Schoenen, Ferrari, Silberstein & Dodick, 2006: 1169).

Irimia and colleagues (2011) did a study on refractory migraine in a headache clinic population. Refractory migraine was found in 5.1% of patients with a Migraine Disability Assessment Score of 96. The mean age for patients with refractory migraine was 43 years and 58% were female. They concluded that refractory migraine was a

relatively common and very disabling condition (Irimia, Palma, Fernandez-Torron & Martinez-Vila, 2011: 1).

Recommendations for defining intractable headache were laid out by the Refractory Headache Special Interest Section. Table 2.4 lays out the proposed criteria for refractory migraine as recommended by the Refractory Headache Special Interest Section of the American Headache Society.

Table 2.4 Proposed criteria for definition of refractory migraine and refractory chronic migraine

Criteria	Characteristics/symptoms
Primary diagnosis	A. ICHD-2 migraine or chronic migraine
Refractory	B. Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy 1. Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: a Beta-blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers 2. Failed adequate trials of abortive medicines from the following classes, unless contra-indicated: a. Both a triptan and DHE intranasal or injectable formulation b. Either nonsteroidal anti-inflammatory drugs or combination analgesics
Adequate trial	Period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum tolerated dose, unless terminated early due to adverse effects
Modifiers	With or without medication overuse, as defined by ICHD-2 With significant disability, as defined by MIDAS ≥11
DHE = dihydroergotamine; ICHD = International Classification of Headache Disorders; MIDAS = Migraine Disability Assessment.	

(Source: - Schulman, Lake, Goadsby, Peterlin, Siegel, Markley & Lipton, 2008: 780; Martelletti, Katsarava, Lampl, Magis, Bendtsen, Negro, Russell, Mitsikostas & Jensen, 2014: 3; Robbins, 2015: 50).

The European Headache Federation felt the need to develop new consensus criteria to define refractory chronic migraine. In Table 2.5 the proposed criteria for refractory migraine as define by the European Headache Federation is laid out.

Table 2.5 European Headache Federation proposed criteria for refractory chronic migraine

Criteria	Characteristics/symptoms	
A.	ICHD-3 beta chronic migraine. No medication overuse	
B.	Prophylactic migraine medications in adequate dosages used for at least 3 months each.	
C.	Contra-indications or No effect of the following preventive medication with at least 3 drugs from the following classes:	
	•Beta-blockers	Propranolol up to 240 mg/d Metoprolol up to 200 mg Atenolol up to100 mg Bisoprolol up to 10 mg
	•Anticonvulsants	Valproate acid up to 1.5 g/d Topiramate up to 200 mg/d • Tricyclics Amitriptyline up to 150 mg/d
	•Others	Flunarizine up to 10 mg/d Cardesartan 16 mg/d
	•OnabotulinumtoxinA	155 - 195 U according to the PREEMPT protocol
D.	Adequate treatment of psychiatric or other comorbidities by multidisciplinary team, if available.	
	Notes:	- Secondary Headache must be excluded - MRI provides no underlying cause - Laboratory and CSF analyses within normal range, including
	CSF pressure	- Meaning of efficacy: reduction on HA days >50% - Detoxification procedure (in/out hospital setting): intravenous, oral and advice only are all accepted.
U = units; PREEMPT = REsearch Evaluating Migraine Prophylaxis Therapy; CSF = cerebrospinal fluid; HA = headache.		

(Source: - Martelletti, *et al.,* 2014: 4)

Refractory migraine is particularly difficult to treat. In the opinion of Martelletti and colleagues (2014: 4), exclusively headache experts should conduct the management of refractory migraineurs. Despite the fact that there are no formal criteria that characterises refractory migraine, headache specialist recognises this sub-group of migraineurs who remain refractory to treatment. To foster communication and enhance compliance, a trusting physician–patient relationship is very important. The treating physician should be open minded about continuing care as patients often lapse from the management plan. Close physician-patient interaction and cooperation for management of the problem is required as refractory migraine is a long-term disease (Schulman & McGeeney, 2013: 40).

An article by Jones (2014) highlights the hypothesis that a poor outcome to treatment always implies patient noncompliance. All disease states have a spectrum of severity, with the most severe end representing treatment failures, despite patient compliance and patients receiving excellent care. Some refractory headache patients fall into this group of compliant patients, who have excellent care but bad disease (Jones, 2015: 183). Robbins (2015) refers to the fact that patients are often blamed for the poor outcome of treatment and treated dismissively. This leads to the patient feeling hopeless and helpless as they are compliant. The patient in turn starts to doubt the competence of the person treating them and thus become discouraged and lose hope. The usual treatments only help 50% of patients long term with treatment options for refractory patients remaining limited and inadequate (Robbins, 2015: 575).

The degree of refractory migraine can change over time either by improving or worsening. There is no set of rules for migraine treatment. The choices of medication and therapy varies for each patient, depending on age, headache severity comorbidities, tendency towards addiction, sleep and medical conditions. A follow up study by Robbins (2015) categorised refractory chronic migraine patients according to a unique refractory rating scale. Patients were evaluated and then re-evaluated 10 years later. Sixty percent of patients in the study had at least a 30% improvement in quality of life, while 73% also experienced a 30% (or more) improvement in pain levels. While severe patients also improved over 10 years, they still had significantly lower quality of life, and higher pain scores than the mild or moderate patients. In this

refractory group, opioids and frequent triptans were the most commonly used medications (Robbins, 2015: 50, 52, 107).

2.6 Migraine and comorbid conditions

2.6.1 Introduction

The Oxford Dictionary defines comorbidity as “existing simultaneously with and usually independently of another medical condition” (Oxforddictionaries.com, 2016). The term comorbidity is widely used to refer to the greater than coincidental association of more than one separate condition in the same individual (Scher, Bigal & Lipton, 2005: 305). Lal and Singla (2010) reported that coexisting disorders are more likely to be found in migraineurs than non-migraineurs. Comorbid disorders are more likely to cause distress, poor response to treatment leading to unnecessary investigations and referrals (Lal & Singla, 2010: 18). Due to the high degree of symptom overlap between migraine and comorbid conditions, diagnosis can become complicated. The challenge is to recognise that there may be more than one disease present when diseases coexist (Lipton & Silberstein, 1994: S4). Migraineurs are more likely to have psychiatric, neurological, vascular disorders and other medical disorders (Lal & Singla, 2010: 18). Significant comorbidities associated with chronic migraine was found in Asian patients in Chen and colleagues’ study (2012). Chronic migraineurs had a higher risk of hyperlipidaemia, asthma, depression, bipolar disorder and anxiety disorders compared to other types of migraine. Migraineurs had a 1.6-to 3.9-fold increase risk of cardiovascular disease, sinusitis, asthma, gastrointestinal ulcers, vertigo and psychiatric disorders than non-migraineurs (Chen, Tang, Ng & Wang, 2012: 311).

In the next section, the most common psychiatric, neurological and other medical comorbid conditions with migraine will be discussed.

2.6.2 Psychiatric disorders

Migraine is strongly associated with the psychological factors: depression, anxiety and other mood disorders (Yavuz, *et al*., 2013: 1). Data from a study by Peroutka and

associates (1998) indicated that migraine with aura, anxiety disorders and major depression were comorbidities associated with the *NcoI* polymorphism within the dopamine D_2 receptor. Therefore these conditions may not be comorbid but a manifestation of a single underlying genetic variation (Peroutka, Price, Wilhoit & Jones, 1998: 19). A study in Turkey among students of Cumhuriyey University found that 43.2% of the students in the study who were migraineurs had a lifetime diagnosis of comorbid psychiatric disorders (Semiz, Şentürk, Balaban, Yağız & Kavakçı, 2013: 1).

Masruha and colleagues (2009) demonstrated in their study the inverse relationship between 6-Sulphatoxymelatonin levels in migraineurs and the comorbid conditions of depression anxiety and fatigue. Lower levels of melatonin were reported in patients with comorbid conditions as opposed to those with a single disease state or controls (Masruha, Lin, De Souza Vieira, Minett, Cipolla-Neto, Zukerman, Vilanova & Peres, 2010: 413). Migraineurs have lower plasma blood levels of melatonin than control subjects (Vogler, Rapoport, Tepper, Sheftell & Bigal, 2006: 1).

In this section the psychiatric comorbid conditions: depression, anxiety, panic disorder and bipolar disorder will be discussed.

2.6.2.1 Depression

Wacogne and colleagues (2003) reported that in their study the depression scores were significantly different for female migraineurs as opposed to controls, but the scores were still under the level of clinical significance. They concluded that when migraine and depression coexist it could more likely be a consequence than a cause, which is not the universally held opinion (Wacogne, Lacoste, Guillibert, Hugues & Le Jeunne, 2003: 453). Chai, Rosenberg and Lee Peterlin (2012) found that studies showed a consistently increased prevalence of major depression in migraineurs. As opposed to those without migraine, migraineurs had an approximately 2-5 fold greater odds ratio of major depressive disorder. It has been suggested that there is a bidirectional relationship between migraine and major depression disorder as patients

with depression have an increased ratio of developing migraine compared with non-depressed (Chai, Rosenberg & Lee Peterlin, 2012: 8).

2.6.2.2 Anxiety

Clinical and population studies support that migraine is associated with generalised anxiety disorders (Chai, *et al.*, 2012: 8). Stress and anxiety disorders were higher among migraineurs than controls and above the clinical level in Wacognes' study (Wacogne, *et al*., 2003: 453). Emerging evidence suggests that anxiety disorders have a greater impact on migraineurs than depression as panic disorders are nearly twice as common among migraineurs than depression (Smitherman, Kolivas & Bailey, 2013: 38). A study by Senaratne and colleagues (2010) showed that anxiety disorder patients with migraine presented with a significantly greater number of comorbid psychiatric disorders than patients without migraine. The severity of anxiety disorder symptoms were significantly higher in migraineurs compared to patients without migraine (Senaratne, Van Ameringen, Mancini, Patterson & Bennett, 2010: 76).

2.6.2.3 Panic disorder

Smitherman and colleagues (2013) reported that migraineurs have a 3.7 times higher odds of comorbid panic disorders than non-migraineurs. Panic disorder is more prevalent among chronic migraineurs and migraineurs with aura (Smitherman, *et al*., 2013: 38). A high migraine comorbidity rate (61.1%) was observed in outpatients with panic disorders in a study done in Tokyo (Yamada, Moriwaki, Oiso & Ishigooka, 2011: 145).

2.6.2.4 Bipolar disorder

Migraine is a common comorbidity in bipolar patients. Twenty-six percent of bipolar patients in a study in Turkey were diagnosed with migraine (Ibiloglu & Caykoylu, 2011). Ortiz and colleagues (2009) reported that 24.5% of bipolar patients in their study had comorbid migraine. Those patients with bipolar type II had a higher prevalence (34.8%) than those with bipolar type I (19.1%) (Ortiz, Cervantes, Zlotnik, van de Velde,

Slaney, Garnham, Turecki, O'Donovan & Alda, 2010: 397). Data from a genetic study of migraine and bipolar disorder by Oedegaard and colleagues (2010) suggested that genetic variants in the KIAA0564 gene region could predispose a sub-groups of patients to migraine and bipolar disorder (Oedegaard, Greenwood, Johansson, Jacobsen, Halmoy, Fasmer, Akiskal, Haavik & Kelsoe, 2010: 673).

2.6.3 Neurological comorbid conditions with migraine

There are a number of neurological comorbid conditions associated with the migraine. The following conditions will be discussed in this section: epilepsy, Tourette's syndrome and fibromyalgia.

2.6.3.1 Epilepsy

Effectively prophylactic migraine treatment, with antiepileptic drugs, suggest that migraine and epilepsy may share a similar pathophysiology. The median prevalence of epilepsy in migraineurs is 6% compared with 0.5% in the general population. While 12% of the general population suffer from migraine, 8% to 23% of epileptics have migraine headaches (Lal & Singla, 2010: 18). The findings of a study conducted by Winawer and Connors (2013: 288) support the hypothesis of a shared genetic susceptibility to migraine with aura and epilepsy. Migraine and rolandic epilepsy (benign, autosomal dominant form of epilepsy occurring in children) are strongly comorbid according to a study by Clarke and colleagues (2009). Results suggest shared susceptibility to migraine and rolandic epilepsy that is not directly mediated by epileptic seizures (Clarke, Baskurt, Strug & Pal, 2009: 2428). Comorbid migraine in rolandic epilepsy appears genetically influenced (Addis, Chiang, Clarke, Hardison, Kugler, Mandelbaum, Novotny, Wolf, Strug & Pal, 2014: 333).

2.6.3.2 Tourette's syndrome

A study by Kwak, Vuong and Jankovic (2003: 1595) reported, that the frequency of migraine headache in a clinic sample of Tourette's syndrome subjects was nearly four times greater than the frequency of migraines reported in the general population.

2.6.3.3 Fibromyalgia

Fibromyalgia syndrome is frequently associated with migraine (Marcus & Bhowmick, 2013: 1553). Fibromyalgia is defined by widespread body pain, tenderness to palpation of tender point areas, and constitutional symptoms. A study by Marcus and colleagues (2005) of fibromyalgia patients reported that migraine was diagnosed in 63% of patients in their study. The onset of migraine predated fibromyalgia in 67% of patients, occurred during the same year as fibromyalgia in 11% of patients, and occurred at least one year after onset of fibromyalgia in 22% of patients (Marcus, Bernstein & Rudy, 2005: 600). A study by Küçükşen and colleagues (2013) diagnosed fibromyalgia in 31.4% of migraine patients. Fibromyalgia comorbidity was equally distributed across patients with and without aura. Migraineurs with comorbid fibromyalgia reported more severe headaches than those without fibromyalgia (Küçükşen, Genç, Yılmaz, Sallı, Gezer, Karahan, Salbaş, Cingöz, Nas & Uğurlu, 2013: 986). In a study conducted in Pittsburg in the US, 24.3 % of migraineurs reported comorbid fibromyalgia (Marcus, & Bhowmick, 2013: 1554). Ifergane and colleagues (2006) reported that 22.2% of the female migraineurs met criteria for fibromyalgia, while none of the male migraineurs did. Migraine severity was similar in female migraineurs with and without fibromyalgia (Ifergane, Buskila, Simiseshvely, Zeev & Cohen, 2006: 455). A systematic review by de Tommaso (2012) of eight studies concluded that fibromyalgia affects about one in three individuals who suffer from migraines. Migraine without aura had the highest probability of sharing fibromyalgia comorbidity, while migraine with aura is rarely associated with fibromyalgia (de Tommaso, 2012: 293).

2.6.4 Vascular comorbid conditions with migraine

In this section the vascular comorbid conditions, stroke hypertension and patent foramen ovale will be discussed.

2.6.4.1 Stroke

Women who suffer from migraine with aura have a higher risk factor for ischaemic stroke (Hering-Hanit, Friedman, Schlesinger & Ellis, 2001: 137). Guidetti and colleagues (2014) reported that it has been demonstrated that there is an increased frequency of ischaemic lesions in the white matter of migraineurs, especially silent infarcts in the posterior circulation territory in patients with at least 10 migraine attacks per month. They reported that migraineurs have about a two-fold higher risk of ischaemic stroke. The increased risk has been well-defined for migraine with aura, but does not apply to migraine without aura. The risk is further increased by female gender, being younger than 45 years, smoking, and/or being on oral contraceptives (Guidetti, Rota, Morelli & Immovilli, 2014: 8).

2.6.4.2 Hypertension

A migraine attack can be associated with transient hypertension. Hypertension can increase the frequency and severity of migraine and can lead to the transformation of episodic migraine into chronic migraine (Mathew, 1999: 17). A study in Italy by Mancia and colleagues (2011) reported that the prevalence of migraine and hypertension comorbidity was substantial and that patients with comorbidity had a higher probability of history of cerebrovascular events, compared to hypertensive-only patients. Their study reported an onset of comorbid migraine and hypertension occurring at about 45 years of age. Migraine started significantly later in life than in the migraine-only group, and hypertension significantly earlier in life than in the hypertension-only group (Mancia, Rosei, Ambrosioni, Avino, Carolei, Daccò, Di Giacomo, Ferri, Grazioli, Melzi, Nappi, Pinessi, Sandrini, Trimarco & Zanchin, 2011: 309).

2.6.4.3 Patent foramen ovale

Schwedt, Demaerschalk and Dodick (2008) in their quantitative systematic review reported that an association between patent foramen ovale and migraine had been identified in multiple studies. The prevalence of patent foramen ovale in migraineurs ranged from 39.8% to 72.0%. The prevalence of patent foramen ovale in migraineurs

with aura ranged from 40.9% to 72.0% and in migraineurs without aura from 16.2% to 33.7%. In migraineurs with and without aura, resolution of headaches occurred in 10.4% to 80.0%. Although patent foramen ovale closure seemed to affect migraine patterns favourably, the very low grade of available evidence to support this association precludes definitive conclusions (Schwedt, Demaerschalk & Dodick, 2008: 531-533). Ailani (2014) stated that observational studies report patent foramen ovale to be more prevalent in patients who suffered from migraine with aura, and that patients who suffered from migraine with aura had a higher incidence of patent foramen ovale. However, the only population-based study did not support this association. It was possible that an association existed between large-sized patent foramen ovale and migraine. Numerous studies have reported improved migraine after patent foramen ovale closure, but the only prospective placebo-controlled trial aimed at closure of patent foramen ovale in patients with migraine with aura did not support this (Ailani, 2014: 1).

2.6.5 Other medical disorders

There are other medical disorders which are also comorbid with migraine. In this section allergic rhinitis, asthma, diabetes, gastrointestinal disorders and allodynia will be discussed.

2.6.5.1 Allergic rhinitis

A study by Martin and colleagues (2011) suggested that the association of migraine with allergy depended upon age, degree of allergic sensitisation and the administration of immunotherapy. The “degree of atopy” depended on the frequency of migraine attacks. A lower “degree of atopy” was associated with less frequent and disabling migraine headaches in younger patients while higher “degrees of atopy” were associated with more frequent migraines. Decreased prevalence, frequency, and disability of migraine headache in younger subjects was associated with the administration of immunotherapy (Martin, Taylor, Gebhardt, Tomaszewski, Ellison, Martin, Levin, Al-Shaikh, Nicolas & Bernstein, 2011: 8). A study in Turkey by Ozturk and colleagues (2013) reported that 50% of the patients with allergic rhinitis had

comorbid migraine of which 95% were migraine without aura, and 5% were migraine with aura. Migraine frequency in the control group was 18.75% all of whom suffered from migraine without aura. Patients with allergic rhinitis were four times more likely to suffer from migraine, compared with the control group (Ozturk, Degirmenci, Tokmak & Tokmak, 2013: 528). It was reported by Saberi and colleagues (2012) in Iran that there was an 8.2-fold chance of migraine and allergic rhinitis comorbidity. They found that the correlation of allergic rhinitis and migraine, especially migraine with aura was greater with increase in age (Saberi, Nemati, Shakib, Kazemnejad & Maleki, 2012: 508). Migraine frequency and disability are higher in persons with rhinitis, particularly those with mixed rhinitis (Martin, Fanning, Serrano, Buse, Reed, Bernstein & Lipton, 2014: 336).

2.6.5.2 Asthma

A large case-control study in the UK by Davey and colleagues (2002) provided evidence for an association between migraine and asthma. In their study the relative risk of asthma in patients with migraine was 1.59 (Davey, Sedgwick, Maier, Visick, Strachan & Anderson, 2002: 723)**.** Aamodt and colleagues (2007) carried out a large population based study and reported that those with current asthma and asthma-related symptoms were approximately 1.5 times more likely to suffer from migraine and non-migrainous headaches. The association increased with increased headache frequency (Aamodt, Stovner, Langhammer, Hagen & Zwart, 2007: 204).

2.6.5.3 Diabetes

A study in Turkey (2009), demonstrate that migraine prevalence in metabolic syndrome was higher than in the general population (Guldiken, Guldiken, Taskiran, Koc, Turgut, Kabayel & Tugrul, 2009: 55). Insulin resistance, which represents the main causal factor of diseases involved in metabolic syndrome, is more common in patients with migraine (Casucci, Villani, Cologno & D'Onofrio, 2012: 81). A prospective study by Burch and colleagues did not support migraine and diabetes comorbidity (Burch, Rist, Winter, Buring, Pradhan, Loder & Kurth, 2012: 991).

2.6.5.4 Gastrointestinal disorders

According to a literature review by van Hemert and colleagues (2014) several studies had demonstrated significant associations between migraine and celiac disease, inflammatory bowel disease, and irritable bowel syndrome. Increased gut permeability and inflammation could possibly be the underlying mechanisms of migraine and gastrointestinal diseases. Patients who experience regular gastrointestinal symptoms had a higher prevalence of headaches, while children with a mother with a history of migraine were more likely to have suffered from infantile colic (van Hemert, Breedveld, Rovers, Vermeiden, Witteman, Smits & de Roos, 2014: 1).

Approximately 10% to 20% of the general population (usually young adults) are affected by migraine and irritable bowel syndrome with prevalence greater in women (Mulak & Paradowski, 2004: 55 polish). Irritable bowel syndrome patients in a cohort study by Cole, Rothman, Cabral, Zhang and Farraye (2006: 1) had a 40% to 80% higher prevalence odds of migraine. A study in Taiwan by Lau and co-authors (2014) reported that the incidence of irritable bowel syndrome was 1.9 fold higher in the migraine cohort than the control group particularly in the young population. The incidence of irritable bowel syndrome in migraine sufferers tended to increase with the frequency of migraine diagnoses (Lau, Lin, Chen, Wang & Kao, 2014: 1198). Irritable bowel syndrome and migraine, are both distinct chronic pain disorders that share many similarities (Chang & Lu, 2013: 301). What appears to link migraine and irritable bowel syndrome is a disease model of a genetically sensitive nervous system transformed into one that is hypervigilant, and that over time can often develop into a disabling and pervasive disease (Cady, Farmer, Dexter & Hall, 2012: 278)**.**

2.6.5.5 Allodynia

Allodynia is a condition in which ordinarily non-painful stimuli evoke pain. Burstein, Cutrer and Yarnitsky (2000: 1703) showed that most migraneurs exhibited cutaneous allodynia inside and outside their pain-referred areas when examined during a fully developed migraine attack. A study by Matthew and colleagues (2004) showed that there was a correlation between the duration of migraine disorder and the

development of allodynia. The longer the length of time a patient had suffered from migraine, the more allodynic symptoms they exhibited. Migraineurs who had migraine for up to five years were 32.2% likely to exhibit allodynia symptoms, while those who had migraine for 21 to 35 years had a 75% chance of exhibiting allodynia symptoms. Patients with allodynia were on average eight years older than those without allodynia (Mathew, Kailasam & Seifert, 2004: 852). Tietjen and colleagues (2009) reported that 60% of their migraine study population reported at least one migraine-related allodynic symptom and 10% reported four symptoms. Symptoms of cutaneous allodynia were associated with female gender, body mass index, current smoking, presence of aura, chronic headaches, transformed headaches, severe headache-related disability, and duration of migraine illness from onset (Tietjen, Brandes, Peterlin, Eloff, Dafer, Stein, Drexler, Martin, Hutchinson, Aurora, Recober, Herial, Utley, White & Khuder, 2009: 1333). The presence of allodynia in the course of migraine attack greatly increases the disability of the patient (Aguggia, 2012: 12).

2.6.5.6 Conclusion

Comorbidity could be based on genetic factors and or common environmental factors. There are cases were the temporal relationship is unclear and one disease can cause another disease (Diener, Küper & Kurth, 2008: 1290).

2.7 Summary of chapter 2

The history of migraine is rich with observations, theories and treatments. The complexities of migraine pathophysiology and classification are still being debated by researchers. Migraine is a prevalent disorder which starts mainly in the second decade of life and decreases in the fifth decade of life. It is a recurrent, intermittent neurological disorder, characterised by pulsating, throbbing pain companied by nausea and vomiting with sensitivity to light and sound. Migraine is classified into two main types of migraine namely, migraine with aura and migraine without aura with aa number of sub-types of migraine. The correct diagnosis needs to be made by using ICHD-3 classification criteria and taking into account any comorbid conditions that could be present.

Chapter 3

Overview of migraine auras, triggers and treatment

3.1 Introduction

In this chapter migraine trigger factors, auras and medication used in the treatment of migraines will be discussed. An overview of migraine trigger factors will be given, followed by the different types of trigger factors which will be divided into sub-categories. A general explanation of aura will be followed by a more detailed explanation of the various aura types associated with a migraine. Finally, the different types of medication, both pharmaceutical, complementary and alternative, and practices relating to treatment will be discussed. Treatment will be divided into acute migraine treatment and prophylactic treatment of a migraine.

3.2 Migraine trigger factors

Trigger factors do not cause the migraine disorder in individuals. Migraine triggers are precipitating factors that can contribute to an attack by increasing the probability of a migraine occurring (Lipton, *et al.*, 2014: 1662). Research indicates that migraineurs have a lower threshold for light-induced discomfort, noise tolerance and olfactory sensitivity compared to the population in general (Friedman & De ver Dye, 2009: 941). Various extrinsic and intrinsic factors can trigger a migraine attack. The interval between exposure to a trigger and onset of a migraine attack can vary from a few hours to days (Daniel, 2014). At least 60 different migraine triggers have been identified (Becker, 2011: 387). In a study by Kelman (2007: 402) of 1750 migraine patients, it was found that patients reported on average seven migraine trigger factors.

Studies show that stress is the most common trigger, with a migraine after stress being more common than during stress. Females are more likely to suffer from stress as trigger factors (Mollaoğlu, 2013: 992). Stress is followed in reducing order of frequency by hormonal changes, fasting, weather, odours, neck pain, alcohol, sleep disturbances, light, smoke, heat, sleeping late, food and physical activity (Kelman, 2007: 396). The occurrence of one trigger factor may increase the likelihood of exposure to other trigger factors, thereby showing that trigger factors may not act independently. For some migraineurs, more than one trigger factor needs to be present to precipitate a migraine attack (Martin, 2010: 223). Table 3.1 gives an overview of categories with sub-categories for trigger factors.

Table 3.1 Categories with sub-categories for trigger factors

Trigger factor	Sub-category of trigger factor
Stress	Emotional stress Work-based stress Financial stress Environmental stress
Weather	Temperature changes (heat, cold) Lighting Wind Barometric pressure (thunderstorms) Dust
Excessive stimuli	Visual patterns (flashing lights, glare, high contrast stripes) Strong odours Exercise
Food	Water deprivation Artificial sweeteners Chocolate Caffeine Alcohol (red wine) Fasting/skipping meals Processed foods Cheese Fruit (nuts, citrus fruit) Vegetables (tomatoes) Monosodium glutamate (Chinese food) Yeast
Sleep	Insufficient sleep Excessive sleep
Hormonal factors	
Smoking/smoke	
Neck pain	

(Source: - Porter & Kaplan, 2011: 1186; Gilman, 2010: 201)

Migraineurs find that trigger factors differ between individual attacks. What might trigger a migraine for one attack will not necessary be the same for other migraine attacks (Kelman, 2007: 397-399). Most of the research on triggers is based on retrospective self-reporting studies. However, the possibility of selective memory and causal explanation challenges the validity of the data collected (Wöber, Brannath, Schmidt, Kapitan, Rudel, Wessely, Wöber & Wöber-Bingöl, 2007: 305). Approximately 75% of migraineurs identify triggers that will almost always induce a migraine attack (Kelman, 2007: 401). Differences in trigger factors are seen between men and women, migraine with and without aura, episodic and chronic migraine, and migraine or probable migraine (Kelman, 2007: 401). According to Hauge, Kirchmann and Olesen

(2010: 249), if all trigger factors are included, women are affected by more trigger factors than men. They reported that if hormonal triggers are excluded, there is no significant difference in the number of triggers factors for men and women.

A clinic-based survey in China by Wang and colleagues (2013), reported trigger factors in 89.2% of the of 394 migraine patients. They reported that the most common trigger was sleep disturbance (40.1%), followed by negative affect (34.2%) and sunlight (32.7%). Weather was ranked fourth with 31.1%. More than one trigger was reported by 64.2% of migraineurs in their study (Wang, Huang, Li, Tan, Chen & Zhou, 2013: 689, 691).

A study in India by Yadav Kalita and Misra (2010), at a tertiary teaching hospital of 182 patients (of which 131 patients were female), showed that migraine triggers were present in 87.9% of patients. Results of trigger factors reported in their study were as follows, emotional stress (70%), physical exhaustion or travel (52.5%), fasting (46.3%), sleep deprivation (44.4%), menstruation (12.3%) and weather changes (10.1%). Trigger factors in Indian migraine patients were similar to that found in the Western literature with the exception of dietary factors. Fasting as a common trigger among Indian migraineurs may in part be due to religious practice as opposed to occupation or lack of food (Yadav, *et al.*, 2010: 44, 46).

A Turkish study by Kutlu and colleagues (2010) of 190 migraine patients (of which 156 patients were female), was carried out at a headache outpatients' unit. The most common trigger factor for migraine was stress (58.7%). Other trigger factors were reported by migraineurs in decreasing order as follows, noise (19.8%), sleep disturbances (16.1%), fatigue (15.6%), hunger (10.9%), physical effort (8.9%), light (6.8%), sun (5.8%), cold compress (5.2%), factors affecting scalp (4.1%), travelling by motor vehicle (3.1%), eye strain (3.1%), crowds (2.1%), odour (2.1%), crying (2.1%), weather (1%), high blood pressure (0.5%), cigarette smoke (0.5%) and menstruation (0.5%), respectively (Kutlu, Yaluğ, Mülayim, Temel Obuz & Selekler, 2010: 59).

Medical students in Brazil did an interview study to determine migraine trigger factors in 200 patients diagnosed with migraine of which 162 were female (Fukui, Gonçalves, Strabelli, Lucchino, Matos, dos Santos, Zukerman, Zukerman-Guendler, Mercante,

Masruha, Vieira & Peres, 2008: 498). Trigger factors had not previously been studied in a large sample of Brazilian migraineurs. They observed that all the patients had at least one trigger factor and about 95.5% had two trigger factors. The most common trigger factor reported by patients in their study were dietary factors of which fasting (84.5%) was the most common, followed by alcohol intake, chocolate and caffeine consumption. Other trigger factors were reported by migraineurs in decreasing order as follows, sleep (75.5%) of which lack of sleep was the most common, environmental (68.5%), stress (65%) with tension being the most common source of stress, hormonal factors (43.5%) with pre-menstruation and menstruation being report most often, and exertional activities (15.5%). An international cross-cultural questionnaire study of 292 patients (of which 80% were female) recruited from three Neurology Outpatient clinics, two in Spain and one in Brazil was carried out in 2009. The most commonly identified trigger factors in Brazilian and Spanish patients were as follows, stress (73.1% *vs*. 46.4%), menstrual period (55.6% *vs.* 38.1%), sleep (56.7% *vs.* 28.5%), odours (52.5% *vs.* 9.3%) and food (30.5% *vs.* 12.6%) (Carod-Artal, Ezpeleta, Martín-Barriga & Guerrero, 2011: 25).

The first epidemiological study of migraineurs in Croatia, in which IHS criteria was used to investigate trigger factors, was carried out by Zivadinov and colleagues. A face-to-face, door-to-door structured interview was done and 720-lifetime migraineurs identified. In total 555 migraineurs had at least one trigger factor. The results of trigger factors were as follows, stress (57.8%), travelling (54.6%), menstrual cycle (49.4%), changes in weather conditions and temperature (49.0%), and sleep disturbance (40.1%) (Zivadinov, Willheim, Sepic-Grahovac, Jurjevic, Bucuk, Brnabic-Razmilic, Relja & Zorzon, 2003: 339).

In a clinic-based population (Alabama US) analysis of migraine triggers by Andress-Rothrock and colleagues, 200 new patients were evaluated and 182 patients reported at least one trigger factor and 165 reported multiple trigger factors. The most commonly reported trigger factors were emotional stress (59%), followed by too much or too little sleep (53.5%), odours (46.5%) and missing meals (39%). Of the 85 actively cycling female patients, 53 reported menses as a trigger factor (Andress-Rothrock, King & Rothrock, 2010: 1366). A headache trigger factor questionnaire study of US Army soldiers and military dependents at two US Army Medical Centres found that

(77%) had migraine with (74%) reporting trigger factors. The common trigger factors were as follows, environmental factors (74%), stress (67%), consumption-related factors (60%), and fatigue-related factors (57%). Active-duty service members had similar headache trigger factors to those seen in civilians. Stress-related trigger factors were significantly more common in soldiers (Theeler, Kenney, Prokhorenko, Fideli, Campbell & Erickson, 2010: 790).

In the following section specific trigger factors will be discussed, namely: - weather changes, stress, excessive stimuli, dietary factors, sleep as a migraine trigger factor, hormonal trigger factors and smoking as a migraine trigger factor.

3.2.1 Weather changes

Similar environmental trigger factors are reported by migraineurs worldwide (Friedman & De Ver Dye, 2009: 941). Weather is one environmental trigger factor and studies have shown that seven percent to 61% of migraineurs report weather as a trigger factor (Bolay & Rapoport, 2011: 1426). Weather patterns reflect a complex interaction involving multiple meteorological factors (Yang, Fuh, Huang, Shia, Peng & Wang, 2011: 1). A survey by the National Headache Foundation found the following specific weather triggers:- temperature changes, high humidity, high winds (51 to 62 km/h), sun glare and barometric pressure changes (Chillemi, 2013: 12).

3.2.1.1 Temperature and humidity

Yilmaz and colleagues (2015) did a retrospective study of migraine patients admitted to the emergency department of a hospital over a period of one year in Turkey. They determined that there was an increase in the incident patients on days with high temperature and low humidity (Yilmaz, Gruger, Atescelik, Yildiz & Gurbuz, 2015: 409). A study in Vienna of 238 migraine patients by Zebenholzer and colleagues (2010: 391) showed that the influence of weather factors on migraineurs to be small and questionable. They did, however, find that a ridge of high pressure increased the risk of a headache, so did a lower mean wind speed as did a day-to-day change of daily sunshine duration. An increase in day-to-day minimum air temperature only caused a

minimal decrease in the risk of migraine persistence (Zebenholzer, Rudel, Frantal, Brannath, Schmidt, Wöber-Bingöl & Wöber, 2010: 391). Hoffman and colleagues, in 2011 did a one-year headache diary-based study on 12 migraine patients in Berlin, Germany. Their results showed that onset of an attack and high headache intensity were associated with lower temperatures and higher humidity. High sensitivity to changes in certain weather components was only experienced by a subgroup of the migraineurs in their study (Hoffmann, Lo, Neeb, Martus & Reuter, 2011: 596). In another study by Hoffman and colleagues in 2014 involving 100 migraineurs, only 13 indicated that weather triggered their migraines. The results of their study suggested that meteorological changes, regardless of which direction it moved, could be associated with migraine (Hoffmann, Schirra, Lo, Neeb, Reuter & Martus, 2014: 27).

In a study of 77 migraineurs, by Prince and colleagues in 2004, 39 were found to be sensitive to weather changes, although 48 believed they were sensitive to weather. Their study found that some patients were sensitive to high temperatures and high humidity, while others were sensitive to low temperatures and low humidity, with several patients being sensitive to more than one weather trigger factor. A combination of temperature and humidity had the most significant impact on a headache (Prince, Rapoport, Sheftell, Tepper & Bigal, 2004: 601). Scheidt and colleagues (2013) did a pilot study using smartphone apps and a web form to collect about 4700 migraine messages in Germany (June 2011 and January 2012) to determine the influence of temperature changes on migraine occurrence. They found that a 5°C temperature increase resulted in an increase of 19±7% in the number of migraine messages, while a 5°C temperature decrease resulted in an increase of 24±8 % in the number of migraine messages (Scheidt, Koppe, Rill, Reinel, Wogenstein & Drescher, 2013: 649).

3.2.1.2 Lighting

An observational cohort study was done by Martin and colleagues in 2012, to determine if lightning influenced the frequency of a headache in migraineurs. There was a total of 90 patients, mainly female, 23 from Ohio and 67 from Missouri, who recorded daily headache activity over a period of three to six months. Quantitative lightning data was used to determine the precise location and timing of lightning

strikes. This was the first study to report that lightning and its associated meteorological changes represented a significant trigger factor for a headache in migraineurs. Lightning days were associated with a 28% increase in the frequency of migraine and a 23% onset of new migraine attacks (Martin, Houle, Nicholson, Peterlin & Martin, 2013: 375, 380). It is unclear what the mechanisms are that generate a headache during lightning and accompanying atmospheric conditions. However, lightning channels are significant sources of nitric oxide, which plays a pivotal role in migraine pathogenesis as seen by its use in experiments to induce a migraine. Therefore inhalation of nitric oxide on days of atmospheric conditions producing lightning could cause an inflammatory cascade leading to head pain (Bolay, 2013: 363). Lightning channels radiate low frequency, low-intensity electromagnetic pulses called sferics. Walach and colleagues (2001) tested the hypothesis that sferics are part of the supposed sensitivity to weather changes reported by headache sufferers. They found that a random sample of headache patients could be sensitive to the low-intensity electromagnetic radiation of sferics pulses (Walach, Betz & Schweickhardt, 2001: 685).

3.2.1.3 Wind

In 1999, Cooke and colleagues did a study to determine the effect of chinook winds on migraine patients. Data were collected from 75 patient diaries from the University of Calgary Headache Research Clinic. It was determined that the probability of a migraine attack increased on both pre-chinook days and chinook wind days, compared to non-chinook days. Analysis of wind velocity on chinook days revealed that the risk of migraine onset was increased only on high-wind chinook days (velocity > 38km/h). A subset of 17 migraineurs was found to be sensitive to pre-chinook days with another subset 15 migraineurs sensitive to chinook days and a small subset of migraineurs (two) were found to be sensitive to both pre-chinook and chinook wind days. Thirty-nine migraineurs were found not to be influenced by chinook weather (Cooke, Rose & Becker, 2000: 302). In Prince and colleagues' study, 88% of migraineurs reported that chinook weather influenced their migraines, but was demonstrated this to be true from the dairy analysis for only 20% of these patients (Prince, *et al.*, 2004: 601). In Zebenholzer and colleagues' (2010) study in Vienna, patients perceived the presence

of a lower daily mean wind speed on 29.9% of headache days as opposed to 22.2% of a headache free days (Zebenholzer, *et al.*, 2010: 397).

3.2.1.4 Barometric pressure

Kimoto and colleagues (2011) did a study to determine the influence of barometric pressure on migraineurs. They evaluated the correlation between headache frequency from the headache diaries of 28 migraine patients over a period of one year, and the changes in barometric pressure two days before and two days after a headache. It was found that 18 patients showed a migraine headache associated with weather changes. Fourteen patients reported low barometric pressure as a cause of a headache. They thus concluded that barometric pressure changes could be a trigger factor for migraine headaches (Kimoto, Aiba, Takashima, Suzuki, Takekawa, Watanabe, Tatsumoto & Hirata, 2011: 1923).

3.2.1.5 Dust

The first study to test the hypothesis that Saharan dust in the atmospheric air could trigger a migraine was carried out by Doganay and colleagues in 2009 (Doganay, Akcali, Goktaş, Çaglar, Erbas, Saydam & Bolay, 2009: 1059). They found the first evidence that an unidentified factor existing in the atmosphere could activate the trigeminovascular system, thereby triggering a migraine headache, due to the neurogenic inflammation in the dura. When the Saharan dust was sterilised, it did not activate the trigeminovascular system making it less likely to be the sole trigger. A significant number of microorganisms were found in the Saharan dust. It was therefore suggested that triggering of the trigeminovascular system was due, not to the dust itself, but to the microorganisms or by-products of the microorganisms.

3.2.1.6 Conclusion

A study carried out by Hoffman and colleagues (2011) demonstrated that the change of specific weather components was associated with the onset of migraine attacks in a significant subset of migraineurs. Their findings suggested that affected migraineurs

had an increased susceptibility to those weather conditions (Hoffmann, *et al*., 2011: 601). Changes in weather conditions such as an increase or decrease or both in temperature, humidity and barometric pressure could affect migraineurs and trigger a migraine attack. Similarly, lighting, high winds and micro-organisms and by-products of micro-organisms found in the Saharan dust could act as precipitating factors and trigger a migraine attack. Therefore, meteorological changes, regardless of which direction they moved in, could be trigger factors.

3.2.2 Stress

Stress is a specific adaptive and defensive physiological reaction to a great variety of physical or psychological stimuli (Wacogne, *et al.,* 2003: 451). Stress involves the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis and is generally associated with the person's subjective feeling of threats and demands both internally and externally (Hedborg, Anderberg & Muhr, 2011: 187). It has been suggested that migraineurs have more life stressors than healthy controls (Sauro & Becker, 2009: 1381). Literature shows that stress is one of the most common trigger factors for migraine attacks. Individuals perceive and react differently to stress depending on duration, frequency and severity of the stress factor and their general health. In a study of 1750 migraineurs, by Kelman (2007) in the US, 75.9% reported trigger factors, of which 79.7% reported stress as their most common trigger factor (Kelman, 2007: 394).

A study of 24 German migraineurs to determine the altered processing of emotional stimuli in migraineurs was carried out by Andreatta and colleagues (2012). This was the first study investigating the processing of emotional facial stimuli in migraineurs. They demonstrated that response to facial stimuli was controlled by the level of social anxiety. Migraineurs may have an altered cortical activity linked to the processing of emotional information. Individuals with high cortical excitability may preferentially process high arousing and threatening events (Andreatta, Puschmann, Sommer, Weyers, Pauli & Muhlberger, 2012: 1101). Wacogne and colleagues (2003) in their study showed that migraineurs had a greater emotional stress response than non-migraineurs (Wacogne, *et al*., 2003: 455).

Schoonman and colleagues (2007) did a prospective ambulatory study of 17 migraineurs to determine if stress was a trigger factor for migraine. They assessed changes in perceived stress and objective biological measures for stress. They concluded that stress sensitive patients perceived more stress in days before an impending migraine attack in contrast to those that were not stress sensitive. However, they failed to detect any objective evidence for a biological stress response before or during a migraine attack (Schoonman, Evers, Ballieux, de Geus, de Kloet, Terwindt, van Dijk & Ferrari, 2007: 532).

Hedborg and colleagues' (2011) study of 150 migraineurs (106 female) in the Netherlands, confirmed previous research that showed the importance of stress as a trigger factor in migraine. High-stress susceptibility was the most deviant personality trait for the entire group of migraineurs studied. Their study indicated that high-stress susceptibility was characteristic of migraineurs and that stress correlated with the individual's level of stress (Hedborg, *et al.*, 2011: 196).

Mäki and colleagues (2007) did a prospective cohort study in London of 19 469 female individuals to examine the relationship between work stress and new onset migraine. The results obtained led them to conclude that there was no correlation between job stress and the onset of a migraine. They did, however, find that perception of a high effort–reward imbalance by the employees increased the risk of a migraine. For those female employees who reported high effort-reward imbalance, the excess risk of migraine onset was 25% and this factor was calculated to account for 6.25% of new onset migraines in their study (Mäki, Vahtera, Virtanen, Elovainio, Keltikangas-Järvinen & Kivimäki, 2008: 18). A structured, validated questionnaire study in Brazil, was done by Santos and colleagues (2014) to determine the association between job stress and civil servants. Their results conflicted with the results from the study conducted by Mäki and colleagues (2008), in that they observe a consistent association between high strain jobs and migraine. Job control was a stronger migraine related factor for women, while low social support was associated with migraine in both sexes (Santos, Griep, Alves, Goulart, Lotufo, Barreto, Chor & Benseñor, 2014: 1290).

Migraine attacks themselves can act as a stressor, thereby leading to a vicious circle of increasing migraine frequency. This fear of having a headache is called cephalalgiaphobia (Peres, Mercante, Guendler, Corchs, Bernik, Zukerman & Silberstein, 2007: 56). Giannini and colleagues (2013) did a pilot study to determine if cephalalgiaphobia increased the frequency of migraine. The results of their study showed that migraineurs with higher migraine attack frequency suffered more frequently from cephalalgiaphobia (Giannini, Zanigni, Grimaldi, Melotti, Pierangeli, Cortelli & Cevoli, 2013: 1).

The individual's response to stressors rather than the stressors themselves are the important factor in the stress-migraine interaction. By acquiring effective stress management skills, the impact of stressors on migraineurs can be reduced (Sauro & Becker, 2009: 2378).

3.2.3 Excessive stimuli

Yang and colleagues (2014) did a study to determine the effect of negative emotions evoked by light, sound and taste on the trigeminal thermal sensitivity in healthy human participants. Conditional stimuli (light, sound and taste) had very little effect, with multifunctional having a stronger effect on trigeminal thermal sensitivity. They concluded that migraineurs experience headache attacks triggered by exogenous stimuli, such as visual, auditory or gustatory, due to an impaired somatosensory function (Yang, Baad-Hansen, Wang, Xie & Svensson, 2014: 1). A study in Germany to determine whether photophobia, osmophobia and phonophobia were trigger factors of migraine or part of migraine symptoms was carried out by Schulte and colleagues (2015). They concluded that these reported trigger factors of migraine were not independent trigger factors of acute migraine pain, but were misunderstood symptoms of the premonitory phase of a migraine attack (Schulte, *et al.*, 2015: 1).

Certain visual patterns, such as high contrast stripes and flickering lights, can trigger a migraine due to abnormal cortical processing in certain migraine sufferers. A study by Sheperd and colleagues (2013) on visual pattern sensitivity revealed that migraineurs were more likely to see illusions and distortions in the pattern sensitivity

test when viewing high contrast black and white stripes than the control group. The illusion of motion was more commonly report by migraineurs than illusions of shape and colour. Their study confirmed that visual environmental features such as glare, flicker, and repetitive patterns provoked migraine (Shepherd, Hine & Beaumont, 2013: 1087, 1101).

Intolerance to smell is often reported by migraineurs as a migraine trigger. Osmophobia, or an aversion to smell, is also reported to occur between attacks and during attacks. A study of 60 women migraineurs by Sjőstrand and colleagues (2010) found a high frequency of patients reported odours as a migraine trigger and hypersensitivity to odours during and between migraine attacks. In their study patients reported an avoidance of odours due to general hypersensitivity to odours and risk of triggering an attack (Sjöstrand, Savic, Laudon-Meyer, Hillert, Lodin & Waldenlind, 2010: 249). Silva-Néto and colleagues did a study to investigate which odours triggered migraine and investigated the lag time between exposures to the odour and onset of a headache. Of the 200 migraineurs in their study, 70% reported odours as a trigger factor with pain occurring 25.5±1.9 minutes after exposure to the odour. Odour trigger factors for migraine were in the following order of frequency, perfume (75.7%), paints (42.1%), gasoline (28.6%) and bleach (27.1%). They concluded that odourants, isolated or in association could trigger a migraine within minutes of exposure (Silva-Néto, Peres & Valença, 2014: 14).

A study of 74 migraineurs and 30 controls was carried out by Demarquay and colleagues (2006) to evaluate olfactory hypersensitivity between migraine attacks in migraineurs. They identified a subgroup of migraineurs who complained of evaluated olfactory hypersensitivity between migraine attacks. These migraineurs demonstrated a significantly altered hedonic judgement in the linear scale rating of the 12 odours evaluated and also suffered from more frequent odour triggered migraines than other migraineurs (Demarquay, Royet, Giraud, Chazot, Valade & Ryvlin, 2006: 1123, 1129). Kelmans' study of osmophobia and taste abnormality in migraineurs found that during an acute migraine attack one-quarter of migraineurs had osmophobia and taste abnormality. Perfume or odour as a migraine trigger factor was found in almost 50% of patients, with females being more susceptible than males (Kelman, 2004a: 1109).

Sport and exercise migraines are difficult to distinguish from exertion headaches as headaches can be directly caused by exertion itself (Nadelson, 2006: 29). Sport and exertional activities have been reported as migraine trigger factors by various authors, for example - Yadav and others in India (42.5% physical exertion), Kutlu and others in Turkey (8.9% physical effort) and Fukui and others (15.5% exertional activity) (Yadav, *et al.*, 2010: 44; Kutlu *et al.,* 2010: 59; Fukui, *et al*., 2008: 496). A case history of a 20-year old male athlete was done over a three-year period by Evans and colleagues (2002). Migraines were triggered by the following activities, playing tennis on a hot day, swimming for two hours, running inside, and/or weight lifting. Twenty minutes after trigger factor activity was completed the visual aura started followed by throbbing headache 20 minutes later lasting six to eight hours and occurring every two to three months. Identical physical activities could be performed without triggering a migraine (Evans, Finkel & Mokri, 2002: 690). A Dutch study of migraineurs from an outpatient headache clinic by Kloppen and Veldhoven found that lifetime prevalence of exercise triggered migraines was high. Migraineurs with exercise triggered migraines frequently quit high-intensity exercise (Koppen & van Veldhoven, 2013: 4).

There are a sub-group of migraineurs who are more susceptible visual, auditory and olfactory stimuli than the general population. Light, sound and smells can be trigger factors for these individuals. There are those for whom exercise could be a trigger factor. Excessive stimuli can there be a trigger factor for some migraineurs.

3.2.4 Dietary factors

Research suggests that diet plays a role in trigger factors for migraineurs. Rockett and colleagues (2012) did a literature review of 45 studies to evaluate the published evidence of dietary triggers. They found that the results were dependent on the type of study, type of questions asked and the area in which the study took place. Studies in rural areas had the lowest frequency of trigger factors which could be due to rural populations not being exposed to the asked dietary factors. A general overview of their findings was that fasting and skipping meals was the most frequent dietary trigger for migraineurs. Other dietary trigger factors were alcoholic beverages (mainly red wine), chocolate, caffeine, citrus fruit and vegetables, lipids, fluid deprivation or low intake of

fluids, ice cream and ice water, milk, cheese and other dairy products, meat and eggs and other dietary factors such as processed meats, monosodium gluconate (MSG), aspartame, nuts and sugary foods (Rockett, de Oliveira, Castro, Chaves, Perla & Perry, 2012: 337-351).

Finocchi and Sivori (2012) evaluated dietary triggers in 100 subjects in Italy. Food was reported by twenty migraineurs to occasionally be a precipitating factor, triggering a migraine within 24 hours of ingestion. The foods reported by these subjects were chocolate (45%), cheese (30%), wine (20%), tomatoes (20%), carbohydrates (20%), leavened products (15%) and nuts (10%). Multiple dietary triggers were reported by 55% of subjects (Finocchi & Sivori, 2012: 80). A group of 123 outpatient migraineurs was studied by Rockett and colleagues (2012) to determine the frequency of 36 possible migraine trigger factors. Among the dietary trigger factors, fasting and skipping meals was found to be almost as frequent as stress as a migraine trigger factor. Consumption of alcohol (distilled) was the second most common trigger followed by caffeine withdrawal, fried or fatty foods and beer. The dietary factors, consumption of chocolate, caffeine, ice cream, cheese, tea, cola-based soft drinks, milk and Chinese food occasionally triggered a migraine rather than consistently (Rockett, Castro, Oliveira, Perla, Chaves & Perry, 2012: 485).

3.2.4.1 Water

Two groups of migraineurs in London were asked by Blau (2005) if water deprivation could trigger their migraines. Group one consisted of 50 migraineurs of which 40% were confident that inadequate water intake triggered their migraine, while 14% were unsure. Group two consisted of 45 members of the Migraine Action Association of which 31% responded to inadequate water intake as a migraine trigger (Blau, 2005: 757). A case report by Martins and Gouveia (2007) of a migraineur in Lisbon found that his number of migraine attacks experienced per month decreased with increase water consumption. Attack frequency decreased on average from 10.5 to 5.4 migraine attacks per month (Martins & Gouveia, 2007: 372).

3.2.4.2 Artificial sweeteners

Artificial sweeteners are reported by migraineurs as possible migraine trigger factors. A review article by Rockett and colleagues reported that aspartame triggered a migraine in around 9% of migraineurs (Rockett, *et al*., 2012: 351). A double-blind cross-over trial by Schiffman and colleagues found that aspartame was no less likely to case a headache as a placebo in the population tested (Schiffman, Buckley, Sampson, Massey, Baraniuk, Follett & Warwick, 1987: 1181). A controlled 13-week, double-blind, randomised cross-over study by Koehler and colleagues compared the effect of aspartame to that of a matched placebo on the frequency and intensity of a migraine headache. The results of this study indicated that aspartame caused a significant increase in headache frequency for some migraineurs (Koehler & Glaros, 1988: 1181). A questionnaire survey of 171 patients at the Montefiore Medical Centre Headache undertaken by Lipton and colleagues, found that 8.2% reported aspartame as a trigger factor for their headache (Lipton, Newman, Cohen & Solomon, 1989: 90). A case study by Patel and colleagues (2006) reported on a 47-year old Caucasian male physician migraineur controlled with prophylactic amitriptyline therapy. The physician reported that after drinking a diet soda containing the artificial sweetener sucralose for the first time he developed a migraine attack a few hours later. It was ascertained that sucralose-containing drinks triggered his migraine (Patel, Sarma & Grimsley, 2006: 1303). Similarly, Bigal and colleagues (2006) reported on a case study of a 30-year old woman who reported an increase in frequency and severity of her migraine attacks. Analysis of her daily trigger diary revealed that 90% of her attacks were on days that she had an artificial sweetener-containing sucralose 30 minutes to three hours before her headache occurred. When asked she realised that she had changed from an aspartame-based sweetener to a sucralose-based sweetener (Bigal & Krymchantowski, 2006: 515).

3.2.4.3 Chocolate

Lippi and colleagues (2014) did a short review on the ambiguous association of chocolate as a migraine trigger. Analysis of 10 epidemiological surveys from 1984 to 2010 found the frequency of migraine episodes attributed to chocolate ranged from

0% to 20%. Three double-blind studies demonstrated that the likelihood of developing a migraine from ingesting chocolate to be the same as a placebo (Lippi, Mattiuzzi & Cervellin, 2014: 216).

3.2.4.4 Caffeine

Caffeine is the most widely consumed psychostimulant drug (Shapiro, 2008: 311). Caffeine consumption or caffeine withdrawal have been identified as migraine trigger factors. In Rockett and associates' (2012) literature review, the frequency of coffee as a trigger factor varied from 6.4% to 14.5% among migraineurs (Rockett, *et al*., 2012: 350).

3.2.4.5 Alcohol

Alcohol has traditionally been considered a migraine trigger. Red wine has been reported since antiquity as a migraine trigger. Celsus (25 B.C.-50 A.D.) described pain attributed to drinking red wine as did Paul of Aegina (625-690 A.D.) six centuries later (Daniel, 2014). Alcohol as a trigger factor was reported by 37.8% of patients in Kelman's (2007: 400) study and 32% of migraineurs in Garcia-Martin and colleagues' (2009) study (García-Martín, Martínez, Serrador, Alonso-Navarro, Navacerrada, Agúndez & Jiménez-Jiménez, 2010: 87). Finocchi and Sivori (2012: s78) reported that wine was a trigger factor in 20% of their patients. Garcia-Martin and colleagues (2010) found that consumption of alcohol during stress periods increased the frequency of migraine attacks. The type of alcohol consumed was also a factor. In decreasing order, the type of alcohols was spirits and sparkling wine, followed by red wine, white wine and beer (García-Martín, *et al*., 2010: 89).

Krymchantowski and da Cunha Jevoux (2014: 972) did a study which comparing different types of red wine from France and South America and their potential to trigger a migraine. The French red wines were reported to trigger migraine attacks more often than the South American red wines, suggesting that components other than just alcohol in the red wine trigger migraine. Panconesi and colleagues (2012) reported that in a large number of retrospective studies in America and Europe of migraineurs

with and without aura, that alcohol as a trigger factor was about 31%. In studies in India, Japan and Turkey, however, the percentage was much lower which could be attributed to a lower rate of alcohol consumption and different beverage strength (Panconesi, Bartolozzi, Mugnai & Guidi, 2012: S203).

A study of Medline articles from 1988 to 2007 by Panconesi showed that when it came to alcohol as a trigger factor for migraine the type of alcohol differed in certain countries. The most commonly reported alcoholic beverage was red wine in the UK, white wine in France and Italy and champagne in France. This could be in part due to the fact that people in different countries consume different types of alcoholic beverages of different compositions (Panconesi, 2008: 19). A study by Panconesi and colleagues of retrospective studies found that one-third of migraineurs retrospectively reported alcohol as a migraine trigger. They believe that reports overestimate alcohol as a trigger in migraineurs (Panconesi, Bartolozzi & Guidi, 2011: 177). The International Classification of Headache (2013) defines an alcohol-induced headache as “If the headache occurs within three hours of alcohol ingestion and resolves within 72 hours after ingestion of alcohol ingestion has ceased, the headache is classified as an immediate alcohol-induced headache. If it has developed within five to 12 hours after ingestion of alcohol and has resolved within 72 hours of onset, it is known as delayed alcohol-induced headache” (ICHD-3, 2013: 728).

3.2.4.6 Fasting/skipping meals

Fasting or skipping meals has been documented as a migraine trigger. The International Classification of Headache (2013) classifies a fasting-induced headache as, a diffuse non-pulsating headache, usually mild to moderate, occurring during and caused by fasting for at least eight hours and relieved by eating (ICHD-3, 2013: 755). The likelihood of a fasting-induced headache is increased with the duration of fasting. Migraineurs are more likely to suffer from a headache during fasting. The lifetime prevalence is four percent for a fasting-induced headache. During the fasting periods of Yom Kippur (Jews) and Ramadan (Muslims) the number of reported migraines increases (Dalkara & Kiliç, 2013: 1). A cohort cross-over study was carried out by Adu-Salameh and colleagues of 32 Bedouin Muslim migraineurs in Turkey, during the

fasting month of Ramadan. Two migraineurs failed to fast due to the severity of their migraines, with increases of the average migraine days per month from 3.7 to 9.4 for the other migraineurs in the study (Abu-Salameh, Plakht & Ifergane, 2010: 513). Latsko and colleagues did a study on frovatriptan as a preemptive treatment for a fasting-induced migraine. Twenty-five percent of patients at the Thomas Jefferson University/Jefferson Headache Clinic experienced fasting or a hunger-induced migraine. Of the 74 subjects in the study, 36.4% receiving frovatriptan developed a headache of any sort with 52.9% on the placebo developed headache after fasting for 20 hours (Latsko, Silberstein & Rosen, 2011: 369)

3.2.5 Sleep as a migraine trigger

Sleep is paradoxical as it can abort or trigger a migraine attack. Migraine is known to occur during nocturnal and daily sleep with deprivation and excessive sleep being trigger factors. In headache clinics, two-thirds of migraineurs suffer from insomnia. Excessive daytime sleepiness may also be noted in migraineurs. A large study of 1698 migraineurs having 3582 migraine attacks over a period of three years found that the chances of waking up with a migraine attack twice as high between four and nine in the morning compared to other hours. This relates to the later part of rapid eye movement sleep (Singh & Sahota, 2013: 705-706). There is a complex relationship between sleep and migraine. Many patients who suffer from migraine have sleep disorders and vice versa. Sleep disorders and migraine are often comorbid (Freedom & Evans, 2013: 1358). Engstøm and colleagues (2013) carried out a study to investigate sleep quality, arousal and pain threshold in migraineurs. Results indicated that more insomnia and sleep-related symptoms were reported by migraineurs than control subjects. They hypothesised that migraineurs on average suffered from relative sleep deprivation and needed more sleep than healthy controls. Lack of adequate sleep could trigger a migraine attack (Engstrøm, Hagen, Bjørk & Sand, 2013: 1).

3.2.6 Hormonal trigger factors

Menstrual cycle as a migraine trigger has been reported in a number of studies. Migraine is three to four times more common in females than males, suggesting that

female hormones play a role in the etiologic of migraine in women. Hormonal changes throughout the life cycle (menarche, menstruation, oral contraceptive, pregnancy, menopause and hormone replacement therapy) have an influence on migraine in women (Silberstein, 1999: 919). The trigger factor for menstrual migraine is probably in part due to a significant drop in circulating oestrogen levels in the premenstrual phase, two to three days before menses onset (Martin & Lipton, 2008: 124). A study at Belgrade University of female students found that females with migraine had menstrual-related attacks more frequently than students with non-migraine headaches (67.7% versus 29.5%) (Dzoljic, Sipetic, Vlajinac, Marinkovic, Brzakovic, Pokrajac & Kostic, 2002: 185). Granella and colleagues reported in their study that menstrual migraines differed from non-menstrual migraines in that they tended to be of longer in duration and less responsive to treatment (Granella, Sances, Allais, Nappi, Tirelli, Benedetto, Brundu, Facchinetti & Nappi, 2004: 707).

A controlled prospective study of 17 migraines by Kibler and colleagues (2005) found that reproductive hormones and menstrual-related stress appeared to predict migraine activity. These associations were evident for migraines at each phase of the menstrual cycle as well as perimenstrual (Kibler, Rhudy, Penzien, Rains, Meeks, Bennett & Dollar, 2005: 1181). A diary-based study by Wöber and colleagues (2007) of 327 migraineurs, identified menstruation as a predominate factor increasing the occurrence and persistence of a migraine attack by up to 96% (Wöber, *et al*., 2007: 304). A population-based study by Vetvik and colleagues (2013) on the prevalence of menstrual migraine was carried out in Norway. Results from a group of 237 female migraineurs were that one-fifth of migraineurs had migraines in at least 50% of menstruations. The majority suffered menstrual migraines without aura, but one in eight women suffered from menstrual migraine with aura (Vetvik, *et al.,* 2013: 1).

Studies suggest that the prevalence of migraine tends to peak during late menopause, particularly in those with a history of premenstrual stress disorder (Martin, 2014: 65). Migraine and perimenopause are closely linked with hormonal instability causing an increased incidence of migraine (Ibrahimi, Couturier & MaassenVanDenBrink, 2014: 277). A cross-sectional community-based survey on the prevalence of migraine during the menopausal transition was carried out by Wang and colleagues (2003) in China. The findings from their study indicated that migraine prevalence increased before

menopause and decreased after spontaneous menopause. This trend occurred only in women with a history of premenstrual syndrome (Wang, Fuh, Lu, Juang & Wang, 2003: 470).

Misakian and colleagues (2003) did a cross-sectional study on postmenopausal hormone therapy and migraine. The results were that women with migraine headache were significantly younger, had a younger age at menopause, were more likely to have had surgical menopause and were more likely using hormone replacement therapy. They concluded that patients which were undergoing replacement therapy had a higher prevalence of migraine than those that did not (Misakian, Langer, Bensenor, Cook, Manson, Buring & Rexrode, 2003: 1027). A literature review by Loder and colleagues (2007) suggested that replacement therapy should not be the first-line treatment for women with migraine. A hormonal migraine in menopause is most likely due to oestrogen replacement therapy (Loder, Rizzoli & Golub, 2007: 329).

3.2.7 Smoking as a trigger factor

Medical students at a Spanish university took part in a survey by López-Mesonero and colleagues to determine if smoking was a trigger factor for migraine. Seventeen students were smokers and migraineurs. Twelve migraineurs thought smoking worsened migraine attacks, while 10 perceived smoking as a migraine trigger factor (López-Mesonero, Márquez, Parra, Gámez-Leyva, Muñoz & Pascual, 2009: 101).

As such a large percentage of migraineurs have migraine triggers, it is important for each migraineur to identify their trigger factors. In this way, trigger factors can be avoided thereby helping them to manage their migraine.

3.3 Migraine aura

3.3.1 Introduction

Migraine aura can be defined as a recurrent disorder manifesting in attacks of reversible focal neurological symptoms with a mix of positive and negative features, usually evolving over five to 20 minutes, and may or may not be followed by a headache (ICHD-3, 2013: 644). Auras rarely last longer than one hour. About 30% of migraineurs experience an aura which is believed to be caused by neuronal dysfunction with migraine aura corresponding to a cortical event (Young, , *et al.,* 2011: 1, 30). The classical migraine aura that precede a migraine attack is more often visual, and characterized by an arc of brightly coloured lights that flicker and change shapes. These visual disturbances are often surround an area of dimmed or absent vision (Schmidt & Willis, 2007: 144). The characteristic spread and sequence of symptoms suggest that CSD is the mechanism responsible for the migraine aura (Russell & Olesen, 1996: 335). Migraine auras can be visual, sensory, motor, aphasic or basilar type symptoms (Petrusic, Zidverc-Trajkovic, Podgorac & Sternic, 2013: 861). Visual auras are the most common aura seen in migraine patients who experience an aura. Females are more likely to suffer from auras than males (Kelman, 2004b: 733).

Lane and Davies developed a simple classification of auras that included typical and atypical auras (Lane & Davies, 2006: 95). Table 3.2 represents their classification of auras with examples of the different types of auras that can be experienced.

Visual auras could take the form of visual disturbances that are positive or negative. Positive visual auras could be flashing or bright lights, zig-zag lines or stars in the field of vision, or shapes at the edge of the field of vision called scintillating scotomas. Negative visual auras are a loss of vision, dark spots blind spots or tunnel vision. There could be a mix of negative and positive visual auras (Simon, 2012). The aura could take the form of other neurological symptoms such as unusual sounds being heard or strange smells being smelled. There may be tingling, numbness or weakness on the side of the face or in the extremities on the side where a migraine is developing.

Speech disturbances along with confusion, dizziness and perceptual disturbances and hypersensitivity to touch may also occur in the aura phase (Lane & Davies, 2006: 101).

Table 3.2 Classification of aura

Type of aura	Examples of auras
‘‘Typical’’ auras	
Visual	**Simple** Positive, e.g., phosphenes and teichopsia Negative, e.g., scotoma and hemianopia **Complex** e.g., visual metamorphopsia
Somesthetic	**Simple** Positive, e.g., tingling Negative, e.g., numbness **Complex** Somesthetic metamorphopsia
Aphasic	Expressive dysphasia Receptive dysphasia Dyslexia
‘‘Atypical’’ auras	
Primary sensory	Olfactory Auditory Visceral Kinesthetic Limb pain
Vestibulocochlear	Vertigo Deafness Drop attacks
Motor	Chorea Dystonia Hemiplegia
Higher integrative functions	Memory Mood Perception and planning

(Source: - Lane & Davies, 2006: 95)

3.3.2 Visual aura

Visual auras are the most common type of aura experienced by migraineurs. It is characteristic of all visual auras that the images persist when the eyes are closed. Visual auras are usually confined to one eye and described by the patient as blindness over half the eye. Classification of visual aura by Lane and Davies is given in Table 3.3 (Lane & Davies, 2006: 95).

Table 3.3 Classification of visual auras

Type of aura	Examples of auras
Simple auras	
Positive	Elemental (scintillations, phosphenes, kaleidoscopic)
Negative	Blurring, heat haze, ‘‘water on glass’’ Teichopsia (scintillating scotoma and fortification spectra) Hemianopia Tunnel vision Blindness
Complex auras	
	Visual metamorphopsia Agnosia Distortion of motion and space

(Source: - Lane & Davies, 2006: 96).

As 99% of migraine aura patients experience visual aura, Eriksen and colleagues (2005) decided to develop a Visual Aura Rating Scale (VARS). This would be a supplement to the ICHD for migraine aura as a diagnostic scale based on and qualifying the characteristics of migraine aura. Table 3.4 represents the VARS developed by Eriksen and colleagues.

Table 3.4 Visual Aura Rating Scale (VARS)

Visual symptom characteristic	Risk score
Duration 5–60 mins Develops gradually ≥ 5 mins Scotoma Zig-zag line (fortification) Unilateral (homonymous)	3 2 2 2 1
Maximum VARS score Migraine with aura diagnosis	10 ≥5

(Source: - Eriksen, Thomsen & Olesen, 2005: 807).

“According to VARS an outcome diagnosis of migraine aura depends on a predictive score based on the presence or absence of five specific characteristics of visual aura see Table 3.4. The predictive VARS score is the weighted sum of the number of characteristics present. The maximum score is 10 points. A VARS score of 5 or more diagnoses migraine aura with a sensitivity of 91% and a specificity of 96%” (Eriksen, *et al*., 2005: 807).

In 1870 Dr Hubert Airy provided an illustration of his own visual aura. Figure 3.1 depicts "Airy's drawing showing a teichopsia starting in the left paracentral area and expanding into the left hemifield, eventually obscuring most of the left field of vision. A second aura then begins in its wake". Airy popularised the term "teichopsia" (Greek for "town wall vision") which refers to the distinctive zig-zag edged scotoma that was his visual aura (Lane & Davies, 2006: 11-12). Lashley (1941) mapped and described his own visual auras which numbered more than 100. Over a period of one year, he observed and mapped a large number of scotomas which were uncomplicated by other migraine symptoms. He mapped the figures he observed in time and space and concluded that cortical velocity spread at a rate of three millimetres per minute (Tfelt-Hansen & Koehler, 2011: 756). Figure 3.2 depicts the visual aura experienced by Lashley, mapped in time and space.

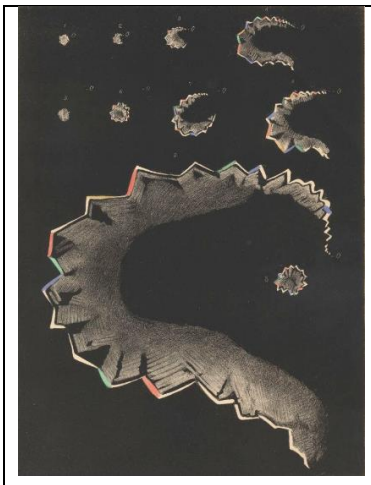


Figure 3.1 Airy's illustration of his visual aura

(Source: - Lane & Davies, 2006: 12)

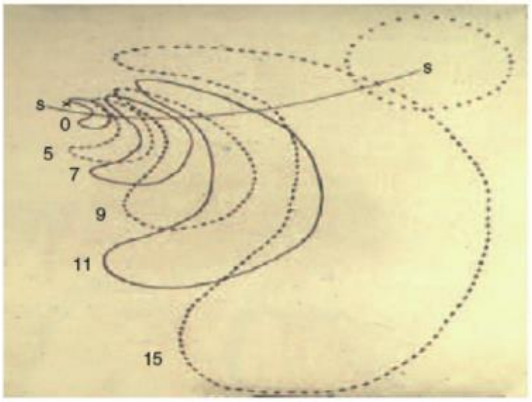


Figure 3.2 Lashley's mapped visual aura

(Source: - Tfelt-Hansen & Koehler, 2011: 756)

A study was carried out by Podoll and Robinson (2000-2002) of art by 562 migraineurs depicting their migraine experience. Six of these migraine art images illustrated illusionary splitting as a visual migraine aura. Illusionary splitting shows objects or people that that appear to be split or displaced into two or more parts along fracture lines of varying form and orientation which may be displaced and separated from each other. Figure 3.3. illustrates the illusory splitting of an image as depicted by a migraine artist. Three of the entries illustrated splitting of the body image as a somesthetic aura

symptom. Figure 3.4 illustrates the illusionary splitting of body image associated with visual aura symptoms as depicted in art by a migraineur (Podoll & Robinson, 2000: 228; Podoll & Robinson, 2002: 62).

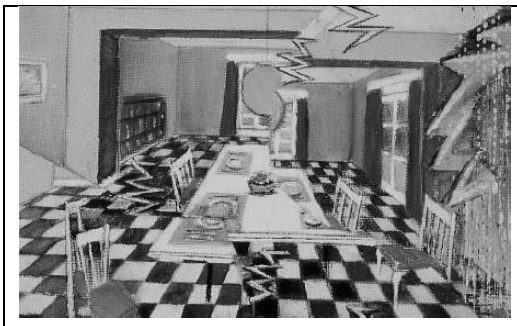


Figure 3.3 illusionary splitting of image

Figure 3.4 illusionary splitting of body

(Source: - Podoll & Robinson, 2000: 229)

Haan and Ferriari (2011) first suggested in 2001 that some of Picasso's paintings resembled migraine aura. They commented on Podall and Robinsons article (2002) and pointed out similar forms of vertical facial splitting in Pablo Picasso's paintings "La femme qui pleurs 1937" Figure 3.5 a) "Weeping Women" and "Portrait de femme au chapeau 1938", Figure 3.5 b). Cubism was originally pioneered by Picasso and Georges Braque with vertical facial splitting an important aspect of the cubist representation of the face. Historians have mentioned African masks as the most likely source for the inspiration drawing of split faces by Picasso. There was no scientific proof that Picasso suffered from migraine with aura although his paintings do resemble those of migraine artists who do suffer from migraine with auras (Haan & Ferrari, 2011: 1057-1058). Van Gogh, a Dutch impressionist, suffered from violent migraines. His painting "Starry Nights", Figure 3.5 c), can be seen as an interpretation of migraine aura. The curved lines and brilliant golden spheres are reminiscent of a migrainous aura (Daniel, 2014). Lewis Carrol's was known to suffer from migraine with aura. In his book "Alice in Wonderland" he made reference to different types of visual hallucinations which could be a projection of the type of migraine auras he experienced. The illusion of bigness (macropsia) and smallness (micropsia) of body size, both psychological features were experienced by Alice after she fell down the rabbit hole. Figure 3.5 d) depicts Alice growing bigger – somesthetic metamorphopsia.

Todd (1955) in his article termed this "the syndrome of Alice in Wonderland" which is used today when referring to this type of aura (Todd, 1955: 701). The wide C shaped of the Cheshire Cat's smile which was all that could be seen, could be based on experience of a migrainous scotoma. See Figure 3.5 e). depicts the Cheshire Cat "all but for a smile" - migrainous scotoma.

a) "Weeping women"

(Source: - Pablo-ruiz-picasso.net, 2016)

b) Portrait de femme au chapeau 1938".

(Source: - Pablo-ruiz-picasso.net, 2016)

c) Starry Night

(Source: Vangoghgallery.com, 2016)

d) the syndrome of Alice in Wonderland

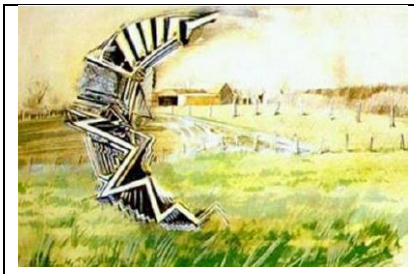
(Source: - Daniel, 2014)

e) Cheshire Cat's smile

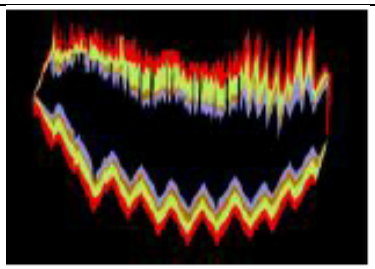
(Source: - Daniel, 2014)

Figure 3.5 Various visual auras

Migraineurs experience a wide range of different visual auras. Figure 3.6 shows representative images of what a migraine aura can look like.

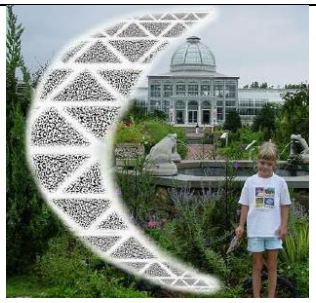


Zig -zag migraine image



Saw tooth orange aura image

Bright migraine with aura and Z image



Boomerang migrainous scotoma

Figure 3.6 Representative images of visual migraine auras
(Source: - Daniel, 2014)**.**

According to Göbel and colleagues (2013) Richard Wagner's opera "Siegfried" might give you a headache as in this composition he "played out his migraine". In Act one scene one of the opera "Siegfried", an extraordinarily concise and strikingly vivid headache episode is portrayed. The music begins with a pulsatile thumping, first in the background, then gradually becoming more intense rising to become a direct tangible almost painful pulsation. In Act one, scene three of "Siegfried," an example of the musical depiction of the visual disturbances of a typical migraine aura can also be found. It is introduced by a scintillating, flickering, glimmering melody line with an underlying zig-zag pattern (Göbel, Göbel & Göbel, 2013: 1-2).

There are varying types of visual migraine auras. Sándor and colleagues (2006) report on the first patient, a 59-year old man with stereotype prosopagnostic aura. He first suffered from migraine without aura which at the age of 52 years developed into migraine with aura, consisting of visual disturbances and prosopagnosia. Prosopagnosia is a condition where a face is recognised as such, but not as the face

of a person known to the observer (Sándor, Morath, Hess, Kaube, Agosti & Regard, 2006: 354). Alonso-Navarro and Jimenze-Jimenze (2009) were the first to report on sensory “pseudoperipheral” migraine aura. They reported on two patients who suffered from typical migraine attacks which were preceded by sensory symptoms that affected one lower limb with a “pseudoperipheral” distribution (Alonso-Navarro & Jiménez-Jiménez, 2009: 1349).

A prospective study of migraine with aura in a headache clinic population in Italy by Cologno and co-authors (2000) found that typical migraine aura (69.1%) was the most frequent type of aura, followed by migraine aura without a headache (29.1%) and then prolonged migraine aura (20%). Their results indicated that migraine aura without a headache was statistically more frequent in males than females and in most cases the frequency of recurrent migraine aura attacks to be relatively low (Cologno, Torelli, Cademartiri & Manzoni, 2000: 925). Oedegaard and colleagues (2005) compared migraine aura without a headache to migraine aura with a headache. The results of their study was that there seemed to be differences in clinical characteristics between the two groups of migraineurs. Those with migraine aura without a headache seemed to have a higher age of onset of migraine to those with migraine aura with a headache (Oedegaard, Angst, Neckelmann & Fasmer, 2005: 368). Aiba and co-authors (2009) investigated the prevalence of typical aura without a headache in Japanese ophthalmology clinics. The results of their study returned 35 patients (3.2%) diagnosed with typical aura without a headache (12 males and 23 females). Migraine with aura was diagnosed in 67 patients (6.3%). The data they collected suggested that typical aura without a headache was not a rare headache type in general ophthalmology clinics and that some migraine with aura patients would transform to typical aura without a headache with ageing (Aiba, Tatsumoto, Saisu, Iwanami, Chiba, Senoo & Hirata, 2010: 962). A 64-year old Chinese man with typical aura without a headache for over 30 years was reported on by He, Li and Nie (2015). The patient mainly experienced episodes of ‘homonymous blurred vision’ or photopsia, which presented as different shapes located at the side or above his visual field, such as, patchy, cord-like, zig-zag, curtain-like or irregular shapes. Although the shape was inconsistent during each attack, the colour was mainly grey or light blue. The visual symptoms lasted about 30 minutes, while no headache was experienced during or after the visual aura (He, Li & Nie, 2015: 1).

Viana and colleagues (2013) did a systematic literature review to determine the typical duration of migraine aura. They found 10 articles that investigated non-hemiplegic migraine aura. Five of these articles reported that 12% to 37% of patients reported aura lasting longer than one hour. Six articles reported on a single non-hemiplegic migraine aura symptom. Aura symptoms which lasted more than one hour were reported to occur as follows: visual aura in six percent to 10% of patients, sensory aura in 14% to 27% of patients and aphasic aura in 17% to 60% of patients. They concluded that the findings indicated that for a significant portion of migraine patients, the duration of non-hemiplegic migraine aura was longer than one hour which was especially true for non-visual aura symptoms (Viana, Sprenger, Andelova & Goadsby, 2013: 483). In 2016 Viana and co-authors (2016) did a diary-based study on aura duration. The results of this study showed that of the 44 patients with three consecutive auras totalling 132 auras: visual symptoms lasted for longer than one hour in 29 out of 129 auras, somatosensory symptoms in 9 of 47 auras and dysphasic symptoms in 3 of 15 auras. Of the 44 patients, six experienced the same aura symptom lasting for longer than one hour in one attack and for less than one hour in another of the three attacks experienced. They suggested that the one hour limit for migraine aura needs to be reviewed (Viana, Linde, Sances, Ghiotto, Guaschino, Allena, Nappi, Goadsby & Tassorelli, 2016: 414). A study was carried out by Zidverc-Trajkovic and co-authors (2013) to identify disturbances of cortical function during visual and/or sensitive aura. They found that the duration of aura was longer in those patients who had cortical function disturbances than in those who did not. In their study, the most frequently reported were motor dysphasia (82.1%), dysnomia (30.7%) and impaired recalling. Those patients who had visual and sensitive aura had a longer duration of an aura than those who only had a visual aura (Zidverc-Trajkovic, Petrusic, Podgorac, Radojicic & Sternic, 2013: 115).

In Kelman's study of 952 migraine patients, 38% reported migraine aura (38.1% female and 33% male). Visual disturbances occurred in 92.1% of reported aura while aura without visual aura was rare. Other aura symptoms reported were, dizziness, numbness and tingling, speech, weakness and blackout. The highest frequency of aura was seen in the more "full blown" migraine attacks (Kelman, 2004b: 728). A study by Jürgens and colleagues (2014) showed that of the migraine patients in their study, 31.9% were diagnosed with migraine with aura. Visual aura symptoms were reported

by 91.4% of patients, 20.0% recorded aphasic aura symptoms, and 22.9% recorded sensory aura symptoms. Other symptoms associated with migraine aura was reported by 8.7% of patients. More than one aura symptom was experienced by 24.6% of migraine with aura patients: four had visual and aphasic aura, six had visual and sensory aura, and seven had visual, aphasic, and sensory aura (Jürgens, Schulte & May, 2014: 1419). Donnet and colleagues did a study of 57 migraineurs in Marseille over 50 years of age who suffered from migraine with aura. All the patients had visual auras, 16 had paresthesic aura and 16 had an aphasic aura. One patient had a sporadic hemiplegic migraine. For most of the patients, the aura was followed by a migraine headache. Typical aura without a headache was experienced by 26 patients and five patients only had typical aura without a headache. The patients were divided into two groups, those who had a migraine with aura before 50 years of age and those who had their first attack after 50 years of age. In the first group 31 patients had migraine with typical aura and 15 patients had typical aura without a headache. In the second group seven patients had typical aura with migraine headache, eight patients had typical aura with a non-migraine headache and 11 patients had typical aura without a headache. They found that when migraine aura beings after 50 years of age the patient is more likely to suffer from typical aura with a non-migraine headache or typical aura without a headache (Donnet, Daniel, Milandre, Berbis & Auquier, 2012: 1869).

The results from a cross-sectional German headache study by Jürgens and colleagues (2015) showed that compared to controls, those patients who suffered from migraine with aura were more likely to have impaired colour vision perception and taste and smell impairment (Jürgens, Berger, Straube & Khil, 2015: 508). A study by Eriksen, Thomsen and Russell (2004) on the prognosis of migraine aura found that the longer the patients suffered from migraine with aura the less likely were the cessation of attacks. They concluded from their results that males who only experienced visual aura and late onset migraine with aura were more likely to have a cessation of migraine with aura attacks. Female migraineurs, however, with sensory or aphasic aura plus visual aura and early onset aura tended to continue with migraine with aura, although attacks were less frequent and severe (Eriksen, Thomsen & Russell, 2004: 22). A retrospective study of the visual aura of 122 migraine patients from Southern Brazil and Northern US, was carried out by Queiroz and co-authors

(2011). In their study there was a gradual onset of the visual aura, usually being peripheral, unilateral and shimmering in nature, lasting five to 30 minutes before the onset of a headache. The visual aura was usually without colour and often described as small bright dots and zig-zag lines. Blurred vision was the most frequently reported visual disturbance. They concluded that a migraine visual aura was heterogeneous and pleomorphic (Queiroz, Friedman, Rapoport & Purdy, 2011: 1652).

The implications of clinical subtypes of migraine with aura were studied by Eriksen and colleagues (2006). The results showed that visual aura was equally frequent across all subtypes (FHM, SHM and non-hemiplegic migraine aura (NHMA)) with scotoma being more frequent and zig-zag lines being less frequent. The sensory aura was unilateral in 99% of patients with FHM and SHM compared to 84% for population-based NHMA. Sensory aura was equally distributed for FHM and SHM. Additional body parts such as the face, an arm, a leg or a foot, were affected in FHM and SHM compared to population-based NHMA. Motor aura was unilateral with equal distribution for FHM and SHM. In 59% of FHM and 50% of SHM of patients, the motor aura affected the ipsilateral arm and leg, the motor aura being hemiparetic. The rest of the patients had unilateral nonhemiparetic motor aura: - affecting only an arm or a leg. Aphasic aura due to impaired language production was equally frequent in FHM and SHM and population-based NHMA. However, impaired language comprehension was less frequent in FHM and SHM compared to population-based NHMA (Eriksen, Thomsen & Olesen, 2006: 288)

3.3.3 Persistent migraine aura

A migraine with aura is usually a benign disease, but can have serious complications associated with the disease. Agostoni and Aliprandi (2006: 91) found the most common complication to be migrainous stroke: - defined as a persistent neurological deficit following the aura with evidence of infarction at neuroimaging with no other alternative explanation. The ICHD-3 (2013) describes a complication of persistent aura without infarcts. Persistent aura is characterised by aura symptoms lasting for more than a week without neuroimaging evidence of infarcts. The aura symptoms could involve the visual or motor systems. This rare condition is more likely to occur in

genetic migraine forms such as FHM (ICHD-3, 2013: 651). Evans and Aurora (2012) reported on four cases of migraine with persistent visual aura. In the first case, the patient had an eight-week history of squiggles in her left field of vision of both eyes inferior more than superior. In the second case, the patient constantly saw what she described as television static which was getting worse and more noticeable. The third patient's visual phenomenon consisted of small "fuzzy holes". Over several minutes the holes slowly became larger and eventually encompassed half his visual field and lasted for a few hours. In the fourth case, the patient suffered from circles of light in the centre of her vision which was bluish intermittent without scotoma lasting for about 40 minutes. A migraine with persistent visual aura is rare with symptoms similar or dissimilar to a migraine visual aura (Evans & Aurora, 2012: 495-496).

Systemic literature searches (1991-2014) were carried out by Thissen and colleagues (2014) to identify cases of persistent migraine aura. Two types of persistent migraine auras have been distinguished: persistent primary visual disturbances and typical aura. Forty-seven cases of persistent migraine aura were identified, of which 27 were persistent migraine aura with persistent primary visual disturbances and 19 were persistent migraine aura with typical aura. The mean age of onset for persistent migraine aura was 30 years with the duration of symptoms varying from nine days to 28 years. The persistent migraine aura with persistent primary visual disturbances group had a longer duration of symptoms (Thissen, Vos, Schreuder, Schreurs, Postma & Koehler, 2014: 1290).

3.4 Migraine treatment

3.4.1 Introduction

In this section, the treatment of migraine with regards to the different types of medication, pharmaceutical complementary, alternative, and practices relating to treatment will be discussed. Treatment will be divided into acute migraine treatment, prophylactic treatment of migraine and complementary, alternative medication and practices used to treat a migraine. Migraine treatment involves treating acute migraine attacks when they occur (acute treatment) and developing preventative strategies for

reducing frequency, severity and duration of migraine attacks (prophylactic treatment). The pain and other symptoms associated with individual migraine attacks are treated with acute medication. Acute and prophylactic treatment help patients to find relief from the debilitating effects of migraine (Sheikh & Mathew, 2012: 19).

3.4.2 Acute/abortive treatment for a migraine attack

The aim of acute treatment is to optimise the use of medication to relieve the pain and symptoms of an individual migraine attack. The effect should be rapid with consistent improvement, resulting in a pain-free state within two hours without reoccurrence within a period of 24 hours, with no use of rescue medication and no adverse effects. Treatment should improve the quality of life and minimise the societal impact of migraine for the migraineur (Monteith & Goadsby, 2011: 2). Abortive therapy, intended to stop a migraine from progressing any further, used alone in the acute management of migraine, could be the appropriate option for those patients who experience fewer than two migraines per month or use acute treatment less than two days per week (DeMaagd, 2008: 405). According to Chang and Rapoport (2009), there are more than 40 different types of treatments available to treat the symptoms of an acute migraine attack. They recommend the use of migraine-specific agents and not analgesics as the first line of treatment. The characteristics of a migraine attack and patient preferences should be taken into account when deciding which medication to use and via which route it should be administered. A patient with severe nausea and vomiting will require an injection, nasal spray or suppository to obtain an adequate dosage of the medication. The best migraine treatment is that which has the highest efficacy, with the least side effects and at the lowest cost (Chang & Rapoport, 2009: 11). Treatment is usually most effective when taken in the early stages of an attack. The severity of migraine attacks and their response to treatment may vary from one attack to another. Patients may require only one drug for one attack and several for more severe attacks (Goadsby, *et al.*, 2002: 261). Acute treatment for migraine can be divided into non-specific medications and migraine-specific medications. Non-specific agents include - simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), opioid analgesics, combination analgesics, and antiemetics and phenothiazines

(Goadsby, *et al*., 2002: 260). Migraine-specific medications for acute treatment can be divided to ergot alkaloids and serotonin HT_1 agonists ("triptans").

3.4.3 Non-specific medications for acute treatment of migraine

Clinical guidelines by Snow and colleagues (2002), state that according to the American College of Physicians–American Society of Internal Medicine (ACP-ASIM) and the American Academy of Family Physicians (AAFP), first-line treatments for migraine are NSAIDs, followed by migraine-specific agents (Snow, Weiss, Wall & Mottur-Pilson, 2002: 842). According to the American Academy of Neurology Guidelines published in 2000, these drugs have Level A evidence as there are at least 2 Class 1 studies to support the efficacy of these drugs in the acute treatment of migraine (Marmura, Silberstein & Schwedt, 2015: 3). A review article by Goadsby and colleagues (2002) reported that the dose of medication should be adequate to treat a migraine attack. Concurrent use of an antiemetic would facilitate the absorption of the drug and therefore increase its effectiveness in relieving the migraine attack. When steroids are added to standard abortive therapy for migraine headaches, they are effective and safe for preventing moderate or severe headache recurrence (Huang, Cai, Song, Tang, Huang, Xie & Hu, 2013: 1184). In the following section, simple analgesic and non-steroidal anti-inflammatory drugs will be discussed.

3.4.3.1 Paracetamol

The simple analgesic paracetamol is a synthetic non-opioid analgesic, with no anti-inflammatory properties, used to treat mild to moderate pain. The updated Cochrane review of 11 studies on paracetamol in the treatment of migraine reported that paracetamol 1000 mg was statistically superior to a placebo but inferior to other commonly used analgesics (Derry & Moore, 2013: 2). Chang and Rapoport (2009: 11) reported paracetamol was not a first-line treatment for migraine. It did, however, have its uses when other medications were contra-indicated (such as in pregnancy).

3.4.3.2 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs, of which aspirin is the prototype, inhibit the synthesis of cyclo-oxygenase-2 (COX-2), the enzyme responsible for prostaglandins synthesis. By blocking the COX-2 enzymes, NSAIDs reduce the production of prostaglandins, thereby reducing inflammation and pain (Rossiter, 2013: 398). Examples of NSAIDs are ibuprofen, naproxen, diclofenac, and indomethacin. Chang and Rapoport (2009: 11) reported that aspirin and NSAIDs may be effective when treating mild occasional migraine without nausea and taken early in an attack. They reported that clinical studies had shown that NSAIDs in the correct dose were effective in the treatment of migraine.

A Cochrane review of 13 studies on aspirin with or without an antiemetic for acute migraine headaches in adults was carried out by Kirthi, Derry and Moore (2013: 2). Their study concluded that aspirin 1000 mg was an effective treatment for an acute migraine. The pain was reduced from moderate or severe to none within two hours in approximately 1 in 4 people (24%) taking aspirin, compared with about 1 in 10 (11%) taking a placebo. A Cochrane review of nine studies by Rabbie, Derry and Moore (2013: 3) involving ibuprofen reported that a single oral dose of ibuprofen 200mg or 400mg was effective in relieving pain in migraine headaches. A Cochrane review involving five studies of diclofenac by Derry, Rabbie and Moore (2013: 4) reported that oral diclofenac potassium 50 mg was an effective treatment for a migraine headache. Moderate to severe pain was reduced to no more than mild pain within two hours in about half (55%) of those treated and no pain at two hours in about one in five (22%) and to no pain sustained to 24 hours in about the same number (19%). Law, Derry and Moore (2013: 2) carried out a Cochrane review of six studies on naproxen for the acute treatment of migraine. The authors concluded that naproxen was statistically superior to a placebo but not clinically useful as a stand-alone analgesic for the acute treatment of migraine as it was effective in less than two in 10 people. Table 3.5 gives an overview of non-specific medications used to abort a migraine attack with reference to the simple analgesic paracetamol and the nonsteroidal anti-inflammatory drugs including aspirin.

Table 3.5 Simple analgesic and NSAIDs used to abort a migraine attack

CLASSIFICATION DRUG /TRADE NAMES ATC CODES	DOSE FOR ADULTS	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
Simple Analgesic **Paracetamol** N02BE01 Panado® Dolorol® Paramed®	650-1000 mg every 4-6 hours. Maximum 4 g per day.	Gastrointestinal disturbances Rash Headache Dizziness	Anticoagulants Chloramphenicol Hepatic enzyme inducers	Hypersensitivity to paracetamol Severe liver function impairment
Non-steroidal anti-inflammatory drugs (NSAIDs)				
Aspirin N02BA01 Disprin® Bayer Asprin®	600-1000 mg up to 4 times per day. Maximum 4 g per day.	Gastrointestinal disturbances Dizziness Bronchospasm Tinnitus Prolonged bleeding times	Corticosteroids Anticoagulants Uricosurics Phenytoin Sodium Valporate	Patients with bleeding disorders Ulcers Asthma Hypersensitivity to aspirin Severe renal impairment
Ibuprofen M01AE01 Nurofen® Brufen®	600-1200 mg up to 4 times per day. Maximum 2.4 g per day.	Gastrointestinal disturbances Dizziness Drowsiness Depression Bronchospasm	Oral anticoagulants Lithium Glucocorticosteroids Methotrexate Probenecid	Patients with bleeding disorders Renal impairment Caution in the elderly asthmatics Impaired cardiac function
Naproxen M01Ae03 Napflam® Synflex®	500-750 mg up to 3 times per day. Maximum 1.5 g per day.	Itching Rash	Agents causing hypoprothrombinemia	
Diclofenac M01AB05 Voltaren® Panamor®	50-100 mg 2-3 times per day. Maximum dose 150 mg per day.			
I**ndomethacin** M01AB01 Flamecid® Arthrexin®	50-100 mg 2-3 times per day. Maximum 200 mg per day			

Adapted from: (Demaagd, 2008: 406; Pesaturo & Wooding, 2009: 154; Rossiter, 2013; Turner, 2010)

3.4.3.3 Opioid analgesics

Rossiter (2013) reported that opioids modulate nociception in the trigeminovascular complex and have no vasopressor or anti-inflammatory effect. Examples of opioid analgesics are morphine, oxycodone, pethidine and pentazocine. Opioid analgesics may be relied on to relieve severe and chronic pain (Rossiter, 2013: 402). The US Headache Consortium Guidelines state “that opioids should only be considered when the potential for abuse has been addressed and sedation will not put the patient at risk”. While the European Federation of Neurologic Societies guidelines on the drug treatment of migraine state, "Opioids are of only minor efficacy; no modern controlled trials are available for these substances” (Da Silva & Tepper, 2012: 836).

The use of opioids in migraine treatment is controversial. Tepper, (2012: 30) in his article stated that opioids should not be used in the treatment of migraine as they precipitate bad clinical outcomes. He reported that there are no randomised controlled studies showing pain-free results with opioids in the treatment of migraine and that opioids could cause progression of the disease transforming migraine into a daily headache from opioid overuse. According to Tepper the “use of opioids is pennywise and pound foolish” (Tepper, 2012: 30). Opioids could be misused and abused leading to opioid abuse or dependence. Even though evidence-based guidelines do not recommend opioids as first-line treatment of migraine attacks their use in clinical practice and even more so in emergency departments is very large, especially in US and Canada (Casucci & Cevoli, 2013: 125). According to the American Academy of Neurology Practice Parameter, opioids are considered second or third-tier treatments for migraine following simple analgesics and migraine-specific medications. Those migraineurs who have a lack of response to simple analgesics and or migraine-specific medications, problems with tolerability or contra-indications such as pregnancy and cardiovascular disease, may require opioids for the management of pain during a migraine attack (Buse, Pearlman, Reed, Serrano, Ng-Mak & Lipton, 2012: 19).

Opioids are used as rescue medication in emergency departments. A study by Kelley and Tepper (2012: 467), reported that three opioids most frequently studied (meperidine, tramadol, and nalbuphine) were superior to a placebo in relieving

migraine pain. However, the rate of headache recurrence within 24 to 72 hours after use of opioids was greater than 50%. Buse and colleagues (2012) reported that opioid use for migraine was associated with more severe headache-related disability, symptomology, comorbidities (depression, anxiety, and cardiovascular disease and events), and greater health care resource utilisation for headache (Buse, *et al*., 2012: 18). The risks of using opioids should be considered but not overestimated. The results coming from small clinical studies suggesting that in expert hands daily long-acting opioids provide an option for the treatment of some individuals with chronic intractable headaches (Finocchi & Viani, 2013: 119). Table 3.6 gives an overview of non-specific opioid analgesics that are used to abort a migraine attack.

3.4.3.4 Combination analgesics

There are many different combination drugs available OTC and on prescription. Only a few are discussed here. Combination therapy making use of the simple analgesics paracetamol and aspirin, to which caffeine has been added (to enhance absorption and to possibly potentiate activity) could be effective in acute migraine treatment. Clinical trials using this combination have reported relief of headache intensity in mild to a moderate migraine (DeMaagd, 2008: 407). Loder reported on Somerville's study of the combination of codeine 10 mg, paracetamol 450 mg, doxylamine 5 mg and caffeine 30 mg versus a placebo. There was a 22% difference in response rate that was deemed clinically significant. According to Loder there is a limited benefit for fixed combination drug therapy for the treatment of migraine, However, those containing NSAIDs are associated with reasonable evidence of efficacy (Loder, 2005: 773, 783). Table 3.7 gives an overview of non-specific, combination analgesics that are used to abort a migraine attack.

Table 3.6 Non-specific opioid analgesics used to abort a migraine attack

CLASSIFICATION DRUG /TRADE NAME ATC CODES	DOSE FOR ADULTS	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
<u>Opioid Analgesics</u> **Morphine** N02AA01 Morphine Sulphate-Fresenius®	10 mg/70 kg 3-4 hourly	Drowsiness Nausea/vomiting Pruritus Constipation Weakness Dizziness	Amitriptyline Antiphyschotics Apraclonidine Cimetidine Ciprofloxcin Clomipramine	Raised intracranial pressure Head injury Respiratory depression Can lead to addiction and abuse
Oxycodone N02AA05 Oxycontin®	5 mg 4-6 hourly	Confusion Difficulty breathing Hypotension	CNS depressants MAOIs Metoclopramide Naloxone	
Pethidine N02AB02 Pethidine®	50-100 mg 4 hourly		Quindine Rifampicin Ritonavir	
Pentazocine N02AD01 Sosenol®	30-60 mg repeated 3-4 hourly Maximum 360 mg/day			

Adapted from: (Demaagd, 2008: 406; Pesaturo & Wooding, 2009: 154; Rossiter, 2013; Turner, 2010)

Table 3.7 Non-specific combination analgesics used to abort a migraine attack

CLASSIFICATION DRUG /TRADE NAME ATC CODES	DOSE FOR ADULTS	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
A few examples of combination analgesics				
Mypaid ® M01AE51 200 mg ibuprofen +250 mg paracetamol	2 capsules every 4 hours. Maximum 6 per day.	Gastrointestinal disturbances Rash Headache Dizziness Bronchospasm	Chloramphenicol Hepatic enzyme inducers Corticosteroids Anticoagulants Uricosurics	Combination preparation are more likely to lead to rebound headaches. Codeine is addictive. Doxylamine has sedative properties
Myblulen ® Gen-Payne ® Myprodol ® M01AE51 200 mg ibuprofen +250 mg paracetamol +10 mg codeine	1-2 capsules every 4 hours. Maximum 12 per day.	Tinnitus Prolonged bleeding times Gastrointestinal Drowsiness Depression Bronchospasm Itching Rash	Phenytoin Sodium Valporate Lithium Glucocorticosteroids Methotrexate Probenecid Agents causing hypoprothrombinemia	
Adco Dol® Syndol ® N02BE01 450 mg paracetamol +10 mg codeine +5 mg doxylamine +30 mg caffeine	1-2 tablets every 4-6 hours. Maximum 8 per day.			

Adapted from: (Demaagd, 2008: 406; Pesaturo & Wooding, 2009: 154; Rossiter, 2013; Turner, 2010)

3.4.3.5 Antiemetic dopamine antagonists

Antiemetic dopamine antagonists such as metoclopramide, droperidol and phenothiazines such as chlorpromazine and prochlorperazine have been used in the treatment of migraine. It has been suggested that these drugs should be used as first-line treatment in the emergency department (Ashina & Portenoy, 2012: 26). According to Gilmore and Michael, (2011: 277), there is evidence to support the role of parental antiemetic in an acute migraine, independent of their antiemetic effects. The authors reported that a meta-analysis of 13 randomised controlled trials reported that intravenous metoclopramide should be considered a primary agent in the treatment of migraine in the emergency department. A review and meta-analysis by Eken (2015: 331) reported that although the studies comparing parenteral metoclopramide to a placebo in easing migraine headache favoured metoclopramide over a placebo and lower rates of rescue drug were needed, methodological quality was not high enough to perform a meta-analysis. However, Eken suggests that further studies with high methodological quality are needed to reveal whether and how much metoclopramide is superior to a placebo. Colman and colleagues (2004) carried out a meta-analysis of randomised controlled trials of parenteral metoclopramide for acute migraine. They concluded that metoclopramide was an effective treatment for migraine headache and could be effective when combined with other treatments. The authors suggested that metoclopramide should be considered a primary agent for emergency department treatment of acute migraine given its non-narcotic and antiemetic properties (Colman, Brown, Innes, Grafstein, Roberts & Rowe, 2004: 1369).

Friedman and colleagues (2008) carried out a randomised controlled trial in an emergency department comparing 10 mg prochlorperazine to 10 mg metoclopramide both administered intravenously. Results were similar at two hours and 24 hours with 77% of patients receiving prochlorperazine and 72% of patients receiving metoclopramide wanted to receive the same treatment for their next visit due to the efficacy of the treatment (Friedman, Esses, Solorzano, Dua, Greenwald, Radulescu, Chang, Hochberg, Campbell, Aghera, Valentin, Paternoster, Biju, Lipton, & Gallagher, 2008: 399). A similar study comparing metoclopramide and prochlorperazine in the emergency department was carried out by Coppola, Yealy and Leibold, (1995: 542).

Their study showed that intravenous prochlorperazine (82%) was better at relieving headache and improving nausea than intramuscular metoclopramide (46%) in the emergency department.

Two studies by Richman and colleagues (2002) reported that intramuscular droperidol was effective in the treatment of acute migraine headache in the emergency department. In the first study over 80% of patients felt well enough to go home without rescue medication. Rescue medications are those medications taken if abortive medications fail or if you are unable to take the abortive medications. Potential advantages of intramuscular droperidol over intravenous prochlorperazine or metoclopramide are the low time of onset three to 10 minutes. No intravenous administration of medication is needed thereby reducing patient discomfort, nursing time and emergency department duration. There was also a low incidence of side effects compared with phenothiazines which were only effective when given intravenously (Richman, Reischel, Ostrow, Irving, Ritter, Allegra, Eskin, Szucs & Nashed, 1999: 398; Richman, Allegra, Eskin, Doran, Reischel, Kaiafas & Nashed, 2002: 41). Jones and colleagues' study (1996), reported that although prochlorperazine intramuscular provided more pain relief than metoclopramide intramuscular, neither were effective in treating acute migraine. The majority of patients required rescue medication after the 60-minute study period (Jones, Pack & Chun, 1996: 262).

Gelfand and Goadsby (2012: 53) reported that the estimated efficacy in the emergency department of dopamine receptor antagonists to treat acute migraine in small randomised double-blind placebo-controlled trials was as follows, chlorpromazine 0.1 mg/kg to 25 mg intravenous or intramuscular was 83% effective at one hour. It appears to have comparable efficacy to injectable sumatriptan. Prochlorperazine 10 mg intravenously or intramuscularly was 67% to 88% effective at 30 to 60 minutes for complete or partial pain relief, while 25 mg per rectal route had a positive outcome at two hours. In another study three-quarters of patients treated with prochlorperazine had complete relief from nausea. Metoclopramide 10 mg intravenously was 34% to 46% effective at 30 to 60 minutes. According to the authors, prochlorperazine and chlorpromazine are the best first-line agents in this class. Table 3.8 gives an overview of the antiemetic dopamine antagonists used to abort a migraine attack.

Table 3.8 Antiemetics used to abort a migraine attack and treat nausea

CLASSIFICATION DRUG /TRADE NAMES ATC CODES	DOSE FOR ADULTS	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
Antiemetic **Domperidone** A03FA03 Motilium®	20 mg 3 to 4 times per day,	Rash/urticarial Abdominal cramps Hypertension Raised serum prolactin levels	Antimuscarinic agents Cimetidine CYP3A4 inhibitors	Gastrointestinal haemorrhage, obstruction or perforation Prolactinoma Hepatic/renal impairment Cardiac disease
Metoclopramide A03FA01 Maxolon® Clopamon®	Oral: 10 mg Rectal: 20 mg IM: 10 mg IV dose: 0.1 mg/kg One dose 30 minutes before taking acute therapy drug when nausea is present	Restlessness Drowsiness Diarrhoea Dystonic reaction Dizziness Weakness Abdominal cramps	Antipsychotic agents CNS depressants / alcohol Digoxin Tetracycline Ampicillin Levodopa	Phaeochromocytoma Seizure Gastrointestinal bleeding, or obstruction
Cyclizine RA6AE03 Valoid® Nauzine®	oral-50mg 3 times per day rectal-100mg3 times per day Maximum 200mg/day	Dry mouth Constipation Urinary retention Constipation Hypotension Depression Stimulation	CNS depressants Tricyclic antidepressants Antipsychotic agents	Closed-angle glaucoma Urinary retention Prostatic hypertrophy Chronis pulmonary disease
Phenothiazines: **Prochlorperazine** NO5AB04 Stemetil® Mitil®	Oral: 5-10mg rectal: 25 mg IM: 5 to 10 mg IV: 2.5 to 10 mg Maximum daily dose: 3 doses in 24 hours	Hypotension Arrhythmias Tardive Dyskinesia Dizziness Constipation Blurred vision Drowsiness	CNS depressants Antiparkinsonian agents metoclopramide	CNS depression Coma Phaeochromocytoma

Adapted from: (Demaagd, 2008: 406; Pesaturo & Wooding, 2009: 154; Rossiter, 2013; Turner, 2010)

3.4.4 Migraine-specific medications for acute migraine treatment

These are drugs which have been developed specifically to abort a migraine attack. Ergot alkaloids and serotonin HT_1 agonists (triptans) will be discussed in this section.

3.4.4.1 Ergot alkaloids

Ergotamine was first used in the acute treatment of migraine by Maier in Switzerland in 1925 and dihydroergotamine (DHE) was introduced as an adrenolytic agent in 1943 (Tfelt-Hansen & Koehler, 2008: 877). Ergotamine and DHE were the only available specific antimigraine drugs until the development of triptans in the 1980s (Baron & Tepper, 2010: 1355).

Ergot alkaloids interact with a broader spectrum of receptors than triptans, interacting with a multitude of receptors pivotal to the genesis and maintenance of a migraine headache (Baron & Tepper, 2010: 1354). Ergotamine and DHE are ergot extracts that share structural similarities with the adrenergic, dopaminergic, and serotonergic neurotransmitters and are highly potent at the $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ antimigraine receptors. The broad spectrum of activity at other monoamine receptors is responsible for their side effects (dysphoria, nausea, emesis, unnecessary vascular effects). The mechanisms of action involved in acute migraine treatment are constricting of the pain-producing intracranial extracerebral blood vessels at the $5\text{-}HT_{1B}$ receptors and inhibiting the trigeminal neurotransmission at the peripheral and central $5\text{-}HT_{1D}$ receptors (Silberstein & McCrory, 2003: 144). Dihydroergotamine can block activation of the trigeminal nucleus caudalis by blocking the release of prostaglandins from the glia and is associated with a low headache recurrence rate (Kelley & Tepper, 2012: 118). Tfelt-Hansen, (2013: 1122) carried out a review of eight randomised controlled trials reported on the relatively slow and long lasting antimigraine effect of DHE. A slow dissociation of a drug from the receptor results generally in a long duration of action but also in a slow onset of action. Although ergotamine has been used for over 50 years in clinical practice for the treatment of acute migraine, there is little agreement on its place in clinical practice (Tfelt-Hansen & Koehler, 2008: 887). A European consensus report in 2000 concluded that ergotamine is not the drug of first choice. It

is limited to a number of migraineurs who have infrequent or long duration headaches and who are likely to comply with dosing restrictions (Tfelt-Hansen, Saxena, Dahlöf, Pascual, Lainez, Henry, Diener, Schoenen, Ferrari & Goadsby, 2000: 9). According to Baron and Tepper (2010: 1359), an American review of ergotamine in 2003 yielded similar conclusions, namely that ergotamine can be considered in moderate to severe migraine with long-lasting attacks or frequent recurrence of a headache as headache recurrence is probably less likely. Ergotamine should be limited to patients with slowly evolving migraine without early onset nausea (Silberstein & McCrory, 2003: 161).

Ergotamine is available in combination with caffeine (Cafergot®) which is widely believed to improve the absorption and effectiveness. Migril® is a combination of ergotamine, caffeine and cyclizine to treat the nausea. Prolonged or excessive use of ergotamine could lead to a cycle of drug tolerance and dependence (Silberstein & McCrory, 2003: 145, 156). Dihydroergotamine can be administered through several routes of delivery. Peak concentration occurs within 6 minutes when administered intravenously, within 34 minutes when administered intramuscularly, within 56 minutes when administered via the intranasal route, within 12 minutes when administered via oral inhalation and within 75 minutes with oral administration, for the different formulations of DHE (Silberstein & Kori, 2013: 385). Efficacy and tolerability vary among the different formulations of DHE. In comparative studies, injectable sumatriptan has a more rapid pain and functional improvement response than DHE, although DHE had a better sustained response. Patients currently failing to achieve consistent or long-lasting relief from their current acute treatment for a migraine should consider using DHE (Silberstein & Kori, 2013: 391). It has been demonstrated that parenteral administration of ergotamine and DHE is associated with a faster onset of action and better efficacy (Dahlöf & Maassen Van Den Brink, 2012: 712).

A review by Bigal and Tepper (2003: 55) reported that in many countries, ergotamine is still widely used as the treatment for severe migraine attacks. Ergotamine, when prescribed for infrequent use, in the correct dose and in the absence of a contra-indications, is generally regarded as a safe and useful drug. Ergotamine is still probably useful in patients with status migraine and patients with frequent recurring headaches. Table 3.9 gives an overview of ergot alkaloids used to abort a migraine attack.

Table 3.9 Ergot alkaloids used to abort a migraine attack

CLASSIFICATION DRUG / TRADE NAME ATC CODE	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA- INDICATIONS
<u>Ergot Alkaloids</u> **Ergotamine** N02CA52 Cafergot ® ergotamine +caffeine Migril ® ergotamine +caffeine +cyclizine	2 mg at onset of migraine symptoms. May be repeated twice at 30-minute intervals. Maximum 6 mg per day.	Ergotamine toxicity Cardiac events Arrhythmias Oedema Pruritus Weakness Vomiting Diarrhoea Dry mouth Numbness	Erythromycin and other macrolides Non-selective beta-blockers Triptans within 24 hours Lithium Phenytoin Cimetidine Antibacterial preparations Antiviral preparations Antifungal preparations	Liver, kidney or cardiac disease Porphyria Bad circulation Hypertension Peripheral vascular disease Hyperthyroidism

Adapted from: (Demaagd, 2008: 408; Pesaturo & Wooding, 2009: 154; Rossiter, 2013; Turner, 2010)

3.4.5 Serotonin HT_1 agonists (triptans)

The triptans were the first class of drugs specifically designed and developed for the acute treatment of a migraine (Humphrey, 2008: 685). In this section the different triptans will be discussed.

3.4.5.1 Introduction

The "triptans" as a class are 5-HT_{1D}- and 5-HT_{1B}-receptor agonists and have 5-HT_{1F} agonist activity. Activation of 5-HT_{1D} receptors inhibits vasodilation and inflammation of the meninges and pain transmission and the release of vasodilator substances such as CGRP in trigeminal neurons. Vasoconstriction of dilated cerebral vessels results from 5-HT_{1B} agonist activity (Rosenfeld & Loose, 2014: 155). Triptans are effective in the treatment of moderately severe to severe acute migraine. Blood vessels dilated by calcitonin gene-related peptide are constricted by $5HT_{1B}$, and 5-HT_{1D} further inhibits calcitonin gene-related peptide release from the activated peripheral nociceptive C-fibres. The triptans also inhibit the release of inflammatory peptides in the meninges and interfere with the transduction of pain signals to the trigeminal nucleus caudalis (Kelley & Tepper 2012: 117).

There are currently seven different triptans available worldwide. In South Africa five triptans are available namely, sumatriptan, rizatriptan, eletriptan, naratriptan and zolmitriptan. All oral triptans are effective and well tolerated at marketed doses (Ferrari, Goadsby, Roon & Lipton, 2002: 633). The different triptan formulations available offer the opportunity to individualise migraine treatment, depending on the patient's attack characteristics, tolerance, and preferences (Adelman & Lewit, 2001: 53). Triptans are available in various formulations that allow for alternative dosing in patients who require alternative modes of drug delivery other than oral (Pesaturo & Wooding, 2009: 151). According to Viana and colleagues (2013), the efficacy and tolerability of triptans vary between the different agents and from patient to patient, with about 30% to 40% of patients not responding adequately to therapy. The failure of one triptan does not predict the failure of another. The authors reported that five clinical studies provided evidence that switching from a triptan that is ineffective to a

second triptan could result in effective treatment in a proportion of patients (Viana, Genazzani, Terrazzino, Nappi & Goadsby, 2013: 891). Although triptans are more alike than different, no one triptan is most effective in all clinical endpoints or outcomes. Some triptans can be more effective at higher doses, especially in patients who are less susceptible to adverse events (Johnston & Rapoport, 2010: 1516). Table 3.10 and Table 3.11 give an overview of migraine-specific medication, triptans, used to abort a migraine attack.

Table 3.10 Triptans used to abort a migraine attack

CLASSIFICATION DRUG / TRADE NAMES ATC CODES	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	PHARMACOKINETICS	DRUG INTERACTIONS	CONTRA-INDICATIONS
Triptans **Sumatriptan** N02CC01 Imigran® Imigen® Migrex® Triptam®	Subcutaneous: 6 mg; repeat in 1 hour if necessary Maximum: 12 mg/day Intranasal: 5–20 mg, 1 spray in 1 nostril per dose; may be repeated 2 hours later if necessary maximum: 40 mg/day Oral: 25–50 mg; may be repeated 2 hours later if necessary maximum: 300 mg/day	Nausea Vomiting Vertigo, Weakness Headache Injection site reaction Chest pain Neck pain Dysphoria	Subcutaneous onset: 10–15 minutes Efficacy: 82% at 20 minutes Bioavailability: 97% Intranasal onset: 15–20 minutes Efficacy: 52-62% at 2 hours Bioavailability: 17% Oral onset: 0.5 to 1.5 hours Efficacy: 67-79% at 4 hours High first-pass metabolism Bioavailability: 15% Half-life (all dosage forms): about 2 hours Most options for drug delivery of all the triptans	Ergotamines MAOIs Other triptans Lithium Macrolides SSRIs	Hemiplegic or basilar Migraine Pregnancy Hepatic impairment Uncontrolled hypertension Cardiovascular disease Ischemic cerebrovascular disease Peripheral vascular disease
Rizatriptan N02CC04 Maxalt® Maxalt RDP®	Oral: 5–10 mg; may be repeated in 2 hours if necessary maximum: 30 mg daily, 15 mg if taking propranolol; RPD product dissolves on the tongue; no need for water	Asthenia Fatigue Dizziness Somnolence Nausea Tachycardia Bradycardia Throat tightness	Onset: 30–120 minutes Half-life 2–3 hours Bioavailability: 45% RDP: perceived to have faster onset Onset of action 30 minutes Efficacy: 71% at 2 hours Fastest onset of action of all triptans	Duloxetine Macrolides MAOIs or within 2 weeks of therapy with a MAOI Grapefruit/juice Ergotamines Other triptans Cimetidine	Hepatic/renal impairment uncontrolled hypertension cardiovascular disease ischemic cerebrovascular disease peripheral vascular disease

Table 3.11 Triptans used to abort a migraine attack continued

CLASSIFICATION DRUG / TRADE NAMES ATC CODES	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	PHARMACOKINETICS	DRUG INTERACTIONS	CONTRA-INDICATIONS
Eletriptan N02CC06 Relpax®	Oral: 40 mg; may be repeated once after 2 hours If a headache recurs. A second dose should not be taken for the same attack. Initial dose can be increased to 80mg in subsequent attacks. maximum: 80 mg daily	Dizziness Nausea Weakness Pain or pressure in throat or chest Asthenia Fatigue Dizziness Somnolence	Onset: 1–2 hours Half-life: 4–6 hours Bioavailability: 50% Efficacy: 71% at 2 hours	Clarithromycin Duloxetine Erythromycin Itraconazole Ketoconazole Macrolides Grapefruit/juice	Severe hepatic impairment Uncontrolled hypertension Cardiovascular disease Coronary/ischemic heart disease Cerebrovascular accident
Naratriptan N02CC02 Naramig®	Oral: 1 to 2.5 mg orally; may repeat in 4 hours maximum: 5 mg per day	Dizziness Drowsiness Nausea Vomiting Fatigue Paresthesias	Onset: 1–3 hours Half-life: 6 hours Bioavailability: 60%–70% Efficacy: 60-68% within 4 hours 50% excreted unchanged by kidneys Slow onset, long duration	Duloxetine Macrolides MAOIs or within 2 weeks of therapy with a MAOI Grapefruit/juice	Severe hepatic impairment Uncontrolled hypertension Coronary vasospasm Ischemic heart disease Cerebrovascular disease Elderly
Zolmitriptan N02CC03 Zomig®	Oral 2.5–5 mg; may be repeated in 1–2 hours, maximum 10 mg/day dispersible product dissolves on the tongue; no need for water Intranasal 5 mg; may be repeated after 2 hours, maximum: 10 mg/day	Nausea Vomiting Vertigo, Weakness Headache Chest pain Neck pain Dysphoria	Onset: 45 minutes to 1 hour Half-life: 3 hours Bioavailability: 40% ZMT: perceived as faster onset Intranasal onset: 15–20 minutes Efficacy: 62% within 2 hours 75-78% within 4 hours	Lithium MAOIs Antidepressants Cimetidine Quinolones Glyceryl nitrate	Uncontrolled hypertension Cardiovascular disease Severe hepatic/renal impairment Cerebrovascular disease Epilepsy

Adapted from: (Demaagd, 2008: 409; Pesaturo & Wooding, 2009: 154; Rossiter, 2013; Turner, 2010)

3.4.5.2 Comparison of triptans

A meta-analysis of 53 triptan trials by Ferrari and colleagues (2002) reported the following results. The mean results for oral sumatriptan 100 mg compared to other triptans are shown in Table 3.12.

Table 3.12 Comparison of oral sumatriptan 100 mg to other triptans

Triptan	% Response	Response	Response explained
Oral sumatriptan 100 mg	59%	Two-hour headache response	Improvement from moderate or severe to mild or no pain
	29%	Two-hour pain-free	Improvement to no pain
	20%	For sustained pain-free	Pain-free by two hours and no headache recurrence or use of rescue medication two to 24-hour post dose
	67%	Consistency	Response in at least two out of three treated attacks
Other triptans compared to the results of oral sumatriptan 100 mg			
Rizatriptan 10 mg	Showed better efficacy and consistency Similar tolerability		
Eletriptan 80 mg	Showed better efficacy Similar consistency Lower tolerability		
Almotriptan 12.5 mg	Showed similar efficacy at two hour Better sustained pain-free response Better consistency Better tolerability		
Sumatriptan 25 mg Naratriptan 2.5 mg Eletriptan 20 mg	Showed lower efficacy Better tolerability		
Zolmitriptan 2.5 mg/5 mg eletriptan 40 mg, and rizatriptan 5 mg	Showed very similar results		

(source: - Ferrari, *et al*., 2002: 633)

The conclusion of their study was that the differences among triptans were very small but clinically relevant for individual patients (Ferrari, *et al*., 2002: 633). The following section gives an overview of the various triptans available in South Africa.

3.4.5.3 Sumatriptan

Sumatriptan is currently available as a subcutaneous injection, nasal spray, oral tablet, rectal suppository and a transdermal patch. Formulations vary from country to country (Johnston & Rapoport, 2010: 1508). In South Africa sumatriptan subcutaneous injection, nasal spray and oral tablet are available. Sumatriptan is the only triptan with generics available in South Africa. A Cochrane review by Derry, Derry and Moore (2012) of 61 studies, reported that oral sumatriptan 100 mg was significantly better than oral sumatriptan 50 mg for pain-free and headache relief after two hours as well as for sustained pain-free during 24 hours after treatment. They reported that early treatment with sumatriptan during the mild pain phase had better results as opposed to treatment when the attack was established with moderate to severe pain. The authors concluded that oral sumatriptan was an effective acute abortive treatment for migraine, relieving pain, nausea, photophobia, phonophobia and functional disability (Derry, Derry & Moore, 2012b: 1-2). Twelve studies on sumatriptan reported that 20 mg intranasal was better than 10 mg intranasal for the three primary efficacy outcomes (Derry, Derry & Moore, 2012a: 2). A double-blind placebo controlled trial, by Cady and colleagues (1998), at 15 clinical centres in the US reported that sumatriptan injection 6 mg, reduced productivity loss during a migraine attack. During a minimum eight-hour shift, productivity loss was reduced by 50% compared to a placebo. Sumatriptan injection 6 mg alleviated headache in three-quarters of migraineurs in their study (Cady, Ryan, Jhingran, O'Quinn & Pait, 1998: 1013).

3.4.5.4 Zolmitriptan

Zolmitriptan was the second triptan on the market and is available as an oral tablet, orally disintegrating tablet and a nasal spray (Johnston & Rapoport, 2010:1509). In South Africa, only the oral and orally disintegrating tablets are available. Tepper and co-author (2013) reported that zolmitriptan nasal spray provides onset of headache

relief within 10 minutes for some patients and quickly abolished some of the major migraine symptoms. According to the authors, good candidates are migraineurs whose episodes rapidly escalate to moderate-to-severe pain and those who have morning migraine, have a quick time to vomiting, or have failed oral triptans. A study was carried out by Shapero and colleagues (2006) in which migraineurs used zolmitriptan orally disintegrating tablet to treat three migraines per month and their usual medications for all other migraine attacks. The authors reported that after six months 75.4% of patients that completed the study wished to continue using zolmitriptan orally disintegrating tablet (Shapero, Dowson, Lacoste & Almqvist, 2006: 1530). A study of the different formulations of zolmitriptan by Dowson and colleagues (2007) reported that after four months patients preferred the newer formulations of orally disintegrating tablet (46.9%) and nasal spray (43.8%) over the conventional zolmitriptan tablet (6.3%). Zolmitriptan nasal spray was preferred due to its' speed and efficacy, while orally disintegrating tablets was a more convenient formulation to take (Dowson, Bundy, Salt & Kilminster, 2007: 1144). The global migraine and zolmitriptan evaluation survey by MacGregor and colleagues (2002) reported that patients desired a medication with high efficacy and rapid onset of action. Zolmitriptan orally disintegrating tablet was a favoured formulation and route of administration (MacGregor, Brandes & Eikermann, 2003: 19).

3.4.5.5 Rizatriptan

Rizatriptan is a second generation triptan developed to be a faster-acting triptan and is available as a tablet and an orally disintegrating tablet (Bigal, Bordini, Antoniazzi & Speciali, 2003: 317). According to Truter (2015: 447), rizatriptan is the most frequently prescribed triptan in South Africa. A study of migraineurs who had not previously taken triptans reported that after taking rizatriptan (tablet or orally disintegrating tablet) there was more rapid effective pain relief, patients were largely symptom free and were able to resume usual activities compared to taking non-triptan medication (Solomon, Frishberg, Hu, Markson & Berger, 2001: 886). Rizatriptan 10 mg is more effective than rizatriptan 5 mg based on results from six large clinical trials. When rizatriptan 10 mg was administered 77% of patients experienced pain relief after two hours, 44% were pain-free and 77% were free of nausea (Dahlöf, Rapoport, Sheftell & Lines, 1999:

823). Bell and colleagues (2006) reported that compared to the usual-care oral migraine medication, rizatriptan 10 mg was associated with a faster time to pain relief and onset of pain relief. Patients reported a preference for rizatriptan due to its greater satisfaction in treating a migraine attack (Bell, Foley, Barlas, Solomon & Hu, 2006: 872). Rizatriptan needs to be administered early when pain is mild rather than moderate to severe for the drug to produce a pain-free response at two hours (Mathew, Kailasam & Meadors, 2004: 669). Göbel and colleagues (2001) reported that there was no evidence of tolerance with repeated administration on rizatriptan with the drug scoring consistently high on efficiency and rapid onset (Göbel, Heinze, Heinze-Kuhn & Lindner, 2001: 264). Rizatriptan has been shown in clinical trials to be superior or as effective as other oral migraine-specific agents in the acute treatment of migraine and has been shown to have more consistent long-term efficacy across multiple migraine attacks (Láinez, 2006: 247).

3.4.5.6 Naratriptan

Naratriptan could be the drug of choice for those migraineurs who poorly tolerate other triptans and have longer duration migraine headaches (Dulli, 1999: 407). A meta-analysis of randomised controlled studies reported that naratriptan was an effective well-tolerated treatment for acute migraine attacks with the incidence of adverse effects similar to those of a placebo (Ashcroft & Millson, 2004: 73). In Germany, naratriptan is available as an OTC medication and a reasonable second or third choice on the step care ladder in the acute treatment of migraine (Tfelt-Hansen, 2011: 399). A study of naratriptan to prevent migraine when taken during the prodrome phase was carried out by Luciani and colleagues (2000). The results of their study showed that naratriptan 2.5 mg appeared to prevent a migraine headache if given early in the prodrome phase of migraine. If a headache did occur, there appeared to be a reduction in the severity (Luciani, Carter, Mannix, Hemphill, Diamond & Cady, 2000: 122). Powers and colleagues (2000) in their study of the evaluation of migraineurs' preference for naratriptan over conventional first-line agents reported that 63% of patients preferred naratriptan over their previous therapy. Satisfaction with migraine therapy increased from 47% to 75% after treating three migraines with naratriptan. Naratriptan was the preferred treatment due to its' ability to "relieve pain effectively"

(86%) and “restore ability to function/perform tasks” (89%) (Powers, Szeto, Pangtay, Bort, Cervi & Cady, 2000: 753). Tolerability and efficacy of naratriptan tablets in the acute treatment of migraine attacks over a period one year were studied by Heywood and colleagues (2000). The results of their study demonstrated that the percentage of patients reporting headache relief did not decrease with duration and frequency of use of naratriptan nor was there an increase in adverse events The authors concluded that naratriptan 2.5 mg was effective and well tolerated for the treatment of an acute migraine over a period of one year (Heywood, Bomhof, Pradalier, Thaventhiran, Winter & Hassani, 2000: 470). Gallagher and Mueller (2003: 991) reported that short-term daily administration of naratriptan could be effective in terminating status migraine.

3.4.5.7 Eletriptan

Landy and colleagues (2014) in their study demonstrated that even if a patient did not achieve a headache or pain free response with the first treatment of eletriptan 40 mg they could respond when a second or third attack was treated with the same dose (Landy, Tepper, Schweizer, Almas & Ramos, 2014: 376). Eletriptan was shown to be consistent and have sustained efficacy in the treatment of migraine when 40 mg or 80 mg of eletriptan was given for three migraine attacks (Almas, Tepper, Landy & Ramos, 2013: 131). A review by McCormack and Keating, (2006: 1130) reported that eletriptan was generally well tolerated, improved patients’ health-related quality of life and reduced time lost from normal activities. Wells and Steiner, (2000: 557) demonstrated that patients who received 40 mg or 80 mg of eletriptan were unable to perform their usual activities for a median period of four hours compared with nine hours experienced by those taking a placebo. The authors concluded that eletriptan produced a significant reduction in loss of usual functioning time associated with a migraine attack. A pooled analysis of the eletriptan data by Dodick and colleagues (2007) demonstrated that eletriptan was effective at reducing the incidence of headache recurrence in high-risk subgroups (female gender, age ≥35 years, and severe baseline headache pain) (Dodick, Lipton, Goadsby, Tfelt-Hansen, Ferrari, Diener, Alma, Albert & Parsons, 2008: 184).

3.4.5.8 Triptans in general

Evans and co-authors (2005) in their study of triptans and migraine aura concluded that, the administration of various triptans during the migraine aura phase did not adversely affect the duration of or characteristic of the aura. However, this early treatment is not significantly effective in preventing progression of a migraine headache. Therefore, there is no benefit in treatment with triptan therapy prior to the development of a mild or a moderate headache (Evans, Seifert & Mathew, 2005: 602). An analysis by Pascual (2002: 10) demonstrated that early intervention with triptans resulted in pain that was less likely to intensify, fewer attacks that required re-dosing, more attacks that remained pain-free for 24 hours post dose, and normal function which returned more quickly. In conclusion, early intervention with triptans could improve outcomes and avoid much of the pain and disability associated with treating moderate or severe attacks. Moschiano and colleagues (2005), however, propose that only patients with particularly severe migraines and in whom attacks are always characterised by rapid progression of pain and other symptoms, should be advised to take a triptan as early as possible (Moschiano, D'Amico, Allais, Rigamonti, Melzi, Schieroni & Bussone, 2005: 108).

Databases from two regions in Italy were used to conduct a study of triptans. The authors reported that their data indicated that approximately 10% of triptan users were potentially at risk to develop medication overuse headaches. Patients below the age of 29 years were less likely to be frequent users, while the 40 to 49-year-old population were the most affected (Da Cas, Nigro, Terrazzino, Sances, Viana, Tassorelli, Nappi, Cargnin, Pisterna, Traversa & Genazzani, 2015: 619). Chu and colleagues (2011) reported that in their study less than one in five patients with migraine in the US used triptans for acute headache treatment over the course of a year. Those migraineurs less likely to use triptans included males, African Americans, older adults, and the uninsured (Chu, Buse, Bigal, Serrano & Lipton, 2012: 213).

3.4.5.9 Conclusion

There are a large number of medication options available to migraineurs. More patients tend to use non-specific medication rather than migraine specific medication. Ease of obtaining non-specific migraine medication and lack of knowledge are some of the reasons why it is used. Patients who used migraine-specific medication were more likely to experience early relief of migraine symptoms. Ergot alkaloids are still widely used in many counties and are generally regarded as a safe and useful drug when prescribed for infrequent use, in the correct dose and in the absence of a contra-indications. The various triptans and formulations make it a drug that is very effective in treating migraine as different triptans and routes of administration can be used, depending on the needs of the migraineur. Triptans have been proven to effect within a few hours and to give sustained relief from a migraine attack.

3.4.6 Prophylactic treatment of migraine

Prophylactic treatment of migraine is used to prevent migraine attacks from occurring. In this section the various classes of drugs used to prevent attacks will be discussed.

3.4.6.1 Introduction

Preventative treatment is recommended for migraineurs who experience two or more migraines per week and attacks lasting longer than 48 hours. They have ineffective responses to abortive treatment, experience side effects and contra-indications are problematic (Demaagd, 2008: 480). The aims of migraine prophylaxis are to reduce migraine frequency by 50% per month, minimise the use of abortive and rescue medications, increase the response of migraine attacks to abortive therapy, reduce migraine intensity and duration and to eliminate or minimise side effects (Pesaturo & Wooding, 2009: 148). Dekker and colleagues (2012) suggested that patients' perspectives and opinions of their migraine need to be considered when advising them about prophylactic treatment. Patients need to be open to advise and information, with intervention being offered at an appropriate time during their migraine (Dekker, Neven, Andriesse, Kernick, Reis, Ferrari & Assendelft, 2012: 1).

Mathew (2011: 84-86) stated that the various effective preventive agents used in migraine prophylaxis (topiramate, valproate, beta-blockers, and tricyclic antidepressants), appeared to have a common effect of suppressing cortical excitability which correlated with the dosages and the duration of treatment. He also stated that the beneficial effect of botulinum toxin in chronic migraine could be due to its antinociceptive effect. The European Federation of Neurological Societies (2009) Guidelines on migraine prophylactic treatment are as follows: drugs of first choice – beta-blockers (propranolol and metoprolol), flunarizine, valproate, and topiramate, and drugs of second choice amitriptyline, naproxen, petasites, and bisoprolol (Evers, Áfra, Frese, Goadsby, Linde, May & Sándor, 2009: 968). Silberstein and Goadsby (2002: 491) in their review of migraine preventative treatment suggested that a drug should be chosen based on its proven efficacy, the patient's preferences and headache profile, the drug's side effects, and the presence or absence of coexisting or comorbid disease. They reported that a drug should be started at a low dose, therapy re-evaluated, with each treatment given an adequate trial while avoiding interfering, overused, and contra-indicated drugs. The authors suggested that to maximise compliance, patients should be involved in decisions with regards to their treatment. According to their review prophylactic migraine drugs that have documented high efficacy and mild to moderate side effects, include beta-blockers, amitriptyline (a tricyclic antidepressant), and sodium valproate (an antiepileptic). While drugs that have lower documented efficacy and mild to moderate side effects include selective serotonin reuptake inhibitors (SSRIs), calcium channel antagonists, gabapentin, topiramate, riboflavin, and NSAIDs. A study in the Netherlands, spanning five years, reported that beta-blockers (53%) were the migraine prophylactic drugs of first choice for general practitioners and neurologists. Amitriptyline (14.6%), pizotifen (13.2%), clonidine (5.2%), valproic acid (5.0%), flunarizine (4.6%) verapamil (3.5%) and methysergide (1.0%) were the following drugs in order of choice to be prescribed (Rahimtoola, Buurma, Tijsse, Leufkens & Egberts, 2002: 151).

Table 3.13 gives an overview of drugs used as first line treatment in the prophylactic treatment on migraine. Table 3.14 gives an overview of drugs used as second line treatment in the prophylactic treatment on migraine.

Table 3.13 First line of treatment used in the prophylactic treatment of migraine

CLASSIFICATION DRUG / TRADE NAMES ATC CODES	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
First line of treatment				
Beta-blockers C07AA05 Propranolol Inderal®	40-80 mg twice a day	Dizziness Drowsiness Hallucinations Confusion Nausea	Chlorpromazine Phenothiazines Cimetidine Verapamil Phenobarbital	Asthma Severe obstructive pulmonary disease Diabetes Congestive heart failure
Atenolol C97AB03 Tenormin®	25 mg to 100 mg twice a day	Abdominal pain Constipation Sexual dysfunction (males) Fatigue Depression Insomnia	Rifampicin Fluvoxamine	Heart block Depression Impotence
Calcium channel blockers Verapamil C08DA01 Isoptin®	240–360 mg daily in divided doses	Somnolence Weight gain Constipation Lethargy Fatigue Mental depression Sexual dysfunction (males)	Digoxin Beta-blockers Quinidine Carbamazepine Colchicine	Asthma Severe obstructive pulmonary disease Bradycardia Sick sinus syndrome Atrioventricular block Shock Severe hypotension
Flunarizine N07CA03 Sibelium®	10 mg at night		Phenothiazines Phenytoin Carbamazepine	Pre-existing Parkinson's disease History of mental depression

Table 3.13 First line of treatment used in the prophylactic treatment of migraine - continued

CLASSIFICATION DRUG / TRADE NAMES ATC CODES	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
First line of treatment				
Antidepressants Tricyclic agents Amitriptyline N06AA09 Trepiline® Tryptanol® Imipramine N06AA16 Tofranil®	10-25 mg (usually given at night)	Urinary retention Weight gain Glaucoma Drowsiness Orthostatic Hypotension Headache Decreased libido	Hepatic enzyme inducers MAOIs Depressants Antihistamine Cisapride Serotonergic agents Protease inhibitors Alcohol	Early post myocardial infarct Impaired hepatic/renal function Arrhythmias Hyperthyroidism Prostatic enlargement Closed-angle glaucoma History of suicide
Selective serotonin reuptake inhibitors Fluoxetine N06AB03 Prozac®	10 mg per day	Headache Gastrointestinal disturbances Nervousness Insomnia Drowsiness	CNS depressants Antidepressants Highly protein bound medication MAOIs Lithium Serotonergic agents	Renal failure Hepatic impairment Epilepsy diabetes

Table 3.14 Second line of treatment used in the prophylactic treatment of migraine

CLASSIFICATION DRUG / TRADE NAMES ATC CODES	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
Second line of treatment				
Antiepileptics				
Valproate N03AG01 Epilim® Convulex®	300 mg per day in divided doses, increased to 600-900 mg per day	Sedation Fatigue Ataxia Nausea Vomiting Diarrhoea Constipation	CNS depressants Carbamazepine Ethosuximide Lamotrigine Phenobarbital Phenytoin Warfarin Aspirin Dipyridamole Zidovudine	Liver disease Porphyria
Topiramate N03AX11 Topamax® Epitoz® Adco-Topiramate® Piramax® Sandoz Topiramate® Toplep®	50-200 mg per day	Renal stones Paraesthesia Dizziness Fatigue Nausea Anorexia Somnolence Difficulty with memory	Phenytoin Carbamazepine CNS depressants Antiretrovirals Digoxin Oral contraceptives	Renal impairment Porphyria

Table 3.14 Second line of treatment used in the prophylactic treatment of migraine – continued

CLASSIFICATION DRUG / TRADE NAMES ATC CODES	ADULT DOSE FOR MIGRAINE	SIDE EFFECTS	DRUG INTERACTIONS	CONTRA-INDICATIONS
Second line of treatment				
Other Drugs				
Pizotifen N02CX01 Sandomigran®	1.5 mg per day in three, divided doses or as a single dose at night, reduced, gradually to a maintenance dose of 0.5 to 1 mg per day Maximum 4.5 mg/24 hours	Dry mouth Sedation CNS effects Gastrointestinal disturbances Tight chest Changes in urination	Anticholinergics CNS depressants Aminoglycosides	Asthma Glaucoma Prostatic Hypertrophy Pregnancy Lactation
Clonidine N02CX02 Dixarit® Menograine®	25 mcg twice daily increased after 2-4 weeks if necessary to 50 mcg twice daily Maximum 150 mcg/24 hours in divided doses	Dry mouth Nausea Drowsiness Insomnia Bradycardia	CNS depressants Beta-blockers Tricyclic antidepressants	History of depression Peripheral vascular disease Cerebral/coronary artery insufficiency
NSAIDs Naproxen Naprosyn®	550–1.100 mg daily in divided doses			

Adapted from: (Demaagd, 2008: 481; Pesaturo & Wooding, 2009: 154; Rossiter, 20 13; Turner, 2010)
(CNS: - central nervous system; MAOIs: - monoamine oxidase inhibitors)

3.4.6.2 The main preventive medication treatments for migraine

The main preventive medication treatments for migraine include:

- beta-blockers - propranolol, atenolol;
- calcium channel blockers – verapamil flunarizine;
- tricyclic antidepressants – amitriptyline, and imipramine;
- other antidepressants – fluoxetine;
- antiepileptic agents - valproate, topiramate, gabapentin and pregablin;
- triptans - frovatriptan for a menstruation-associated migraine;
- centrally acting antihypertensive – clonidine;
- NSAIDs – naproxen;
- pizotifen; and
- botulinum toxin type A.

3.4.6.2.1 Beta-blockers

Demaagd (2008) reported that the effectiveness of beta-blockers in migraine prophylaxis was first recognised in the 1960s. The beta-blocker, propranolol is considered a first-line prophylactic agent in migraine and reported to be effective in approximately 70% of patients (Demaagd, 2008: 480). An updated review by Linde and Rossnagel (2012: 2) of 58 trials comparing propranolol to a placebo reported clear evidence demonstrating the effectiveness of propranolol in short-term migraine prophylaxis. Limmroth and Michel (2001: 240) reported that propranolol reduced migraine activity on average by 44% when daily headache recordings were used to assess treatment outcome, and there was a 65% reduction of migraine activity when clinical ratings of improvement and global patient reports were used. Holroyd and colleagues (2010) reported that when combined as opposed to on their own, a beta-blocker and behavioural migraine management could improve outcomes in the treatment of frequent migraines (Holroyd, Cottrell, O'Donnell, Cordingley, Drew, Carlson & Himawan, 2010: 1). Atenolol has limited evidence to support its use in migraine prophylaxis (Modi & Lowder, 2006: 73).

3.4.6.2.2 Antiepileptic agents

Antiepileptic drugs have been used in migraine prophylaxis since the 1970s (Frediani, Cominelli & Sgarzi, 2001: 121). Migraine prevention using antiepileptic drugs is well known and the effectiveness of these medications has been demonstrated in several clinical trials. The antiepileptic drugs, valproate and topiramate, are effective and well tolerated in migraine prevention and are suitable first-line agents (Shahien & Beiruti, 2012: 40).

3.4.6.2.2.1 Valproate

Silberstein and Collins (1999: 633) reported that valproate was effective for long-term migraine prophylaxis with improvements seen in four weeks and change from baseline migraine rates seen during each of the three and six-month time intervals. These initial benefits were maintained for periods in excess of three years. A review by Linde and colleagues (2014) of 10 relevant valproate trials, concluded that, compared with placebo, valproate reduced the frequency of migraine headaches by approximately four per month. They found that patients were also more than twice as likely to reduce the number of their migraine headaches by 50% or more with valproate than with a placebo (Linde, Mulleners, Chronicle & McCrory, 2013: 2).

3.4.6.2.2.2 Topiramate

Topiramate is an appropriate first-line drug for migraine prophylactic treatment (Sinert, & Epstein, 2009). Ruiz and Ferrandi (2009: 419) reported in their review article that recent evidence showed that topiramate, by reducing migraine frequency and use of acute medication, could prevent the migraine progression. They reported that in those patients that had already progressed to chronic migraine, or had difficult to treat conditions associated with medication overuse, 100 mg/day of topiramate was both effective and well tolerated. The authors concluded that topiramate by acting at different levels in the migraine cycle could reduce the frequency of episodic migraine, prevent a migraine as well as treat chronic migraine. A review of 20 papers on topiramate by Linde and colleagues (2014) returned the same results. They concluded

that this provided good evidence to support its use in routine clinical management of migraine (Linde, Mulleners, Chronicle & McCory, 2014: 2).

A randomised control study in 52 North American clinical centres concluded that topiramate showed significant efficacy in migraine prevention within the first month of treatment, an effect which was maintained for the duration of the double-blind phase (Brandes, Saper, Diamond, Couch, Lewi, Schmitt, Neto, Schwabe, Jacobs & Group, 2004: 965). When comparing the response of migraine with and without aura to topiramate prophylaxis, Reuter and colleagues (2010) found that topiramate appeared to reduce the number of migraine auras in parallel with headache reductions. Headache reduction with topiramate was similar in patients with and without aura (Reuter, Del Rio, Diener, Allais, Davies, Gendolla, Pfeil, Schwalen, Schäuble & Van Oene, 2010: 543).

According to Diener, Holle and Dodick (2011: 64) only two pharmacological agents, topiramate and the local injection of botulinum toxin, have been shown to be effective chronic migraine treatments in placebo-controlled randomised trials. However, Lipton and colleagues (2010) in their study found that topiramate 100 mg/day did not prevent the development of chronic daily headache at six months in patients with high-frequency episodic migraine. They did report that topiramate was generally well tolerated and effective in reducing headache days and migraine headache days (Lipton, Silberstein, Dodick, Cady, Freitag, Mathew, Biondi, Ascher, Olson & Hulihan, 2011: 18). Carmona and Bruera (2009: 661) reported that models both in the US and the UK have shown that topiramate prophylaxis offers a cost benefit when direct and indirect costs are evaluated, by reducing work loss, improving the quality of life and reducing the use of increasingly scarce health resources.

3.4.6.2.2.3 Gabapentin

Mathew and colleagues (2001) reported that gabapentin was an effective prophylactic agent for patients with migraine. Gabapentin appeared generally well tolerated and showed at least a 50% reduction in migraine with mild to moderate adverse effects (somnolence and dizziness) (Mathew, Rapoport, Saper, Magnus, Klapper, Ramadan,

Stacey & Tepper, 2001: 119). A Cochrane review by Mulleners and Chronicle (2008) reported that in small trials gabapentin was statistically superior to a placebo in reducing migraine frequency. They reported that studies indicated that gabapentin 2000 mg was more effective than gabapentin 1200 mg. The authors concluded that with some reservations gabapentin could be used for migraine prophylaxis for those cases which were difficult to manage with currently available strategies as gabapentin has a reasonable tolerability and safety profile (Mulleners & Chronicle, 2008: 588, 595, 596). Gabapentin is a second choice anticonvulsant drug with poorer evidence of efficacy for migraine prophylaxis (Evers, 2008: 2565). However, a study in Croatia reported that gabapentin significantly reduced the number of migraine days from 15.6 to 7.2 days in a four-week cycle. Their study also reported a significant reduction in pain intensity and use of acute medication indicating that for some migraineurs gabapentin does have efficacy as a migraine prophylactic (Vuković, Lovrencić-Huzjan, Bosnar-Puretić & Demarin, 2009: 145**).** Silberstein (2006: 413) reported that gabapentin might be effective in migraine prophylaxis, but the trial results are not conclusive.

3.4.6.2.2.4 Pregabalin

Sun-Edelstein and Rapoport (2016: 6) reported that open-label studies had suggested that pregabalin could be effective in chronic migraine prevention. A study by Garcia-Leiva, Calandre and Rico-Villademoros (2008: s570) reported that severe intensity of migraine attacks decreased from 6.4 to 4.2 per month, however, there was no relevant changes in moderate and mild intensity attacks. They reported that 46.4% of patients reverted from chronic migraine to episodic migraine. They concluded that in highly refractor patients pregabalin reduced both the frequency and severity of attacks, and decreased the amount of analgesics used. The findings of an open-label study of pregabalin in the treatment of chronic migraine were that pregabalin was associated with a significant decrease in headache frequency, severity and medication intake (Calandre, Garcia-Leiva, Rico-Villademoros, Vilchez & Rodriguez-Lopez, 2010: 35). A study by Pizzolato and colleagues (2011) reported a statistically significant reduction in migraine frequency, compared to baseline, after one to three months of treatment (Pizzolato, Villani, Prosperini, Ciuffoli & Sette, 2011: 521). The findings of these

studies suggest that for those who suffer from chronic or refractory migraine pregabalin could be a useful alternative prophylactic medication. According to the Cochrane review (2016), there is no published evidence of controlled trials of pregabalin for the prophylaxis of episodic migraine in adults (Linde, Mulleners, Chronicle & McCrory, 2016: 3).

3.4.6.2.3 Antidepressants

Antidepressants are classified according to their different chemical structures or depending on which central neurotransmitters they act upon (Sweetman, 2009: 372). In this section the tricyclic antidepressant amitriptyline and the selective serotonin reuptake inhibitors fluoxetine will be discussed. Tricyclic antidepressants inhibit the reuptake of serotonin and noradrenaline and dopamine into nerve terminals in the brain (Moini, 2009: 62). Selective serotonin reuptake inhibitors block the presynaptic amine reuptake pump, primarily affecting serotonin reuptake (Moini, 2009: 64).

3.4.6.2.3.1 Tricyclic antidepressants – amitriptyline

The class of antidepressants with the most proven efficacy are the tricyclic antidepressants, of which amitriptyline has the most data to support its use in migraine prophylaxis (Sheikh & Mathew, 2012: 22). Amitriptyline has been used for migraine prophylaxis since the 1970s (Pesaturo & Wooding, 2009: 155). Clinical trials with amitriptyline 10 mg to 100 mg daily have reported a 50% to 70% reduction in the number and intensity of migraine attacks (Demaagd, 2008: 481). A comparative meta-analysis of prophylactic migraine drugs showed weak evidence supporting amitriptyline's superiority over other prophylactic drugs (Jackson, Cogbill, Santana-Davila, Eldredge, Collier, Gradall, Sehgal & Kuester, 2015: 2). In a study by Couch (2011: 33) using headache frequency as the primary metric, amitriptyline was superior to a placebo in migraine prophylaxis at eight weeks but, because of a robust placebo response, not at subsequent time points.

3.4.6.2.3.2 Other antidepressants – fluoxetine

Steiner and colleagues (1998) reported that fluoxetine had greater efficacy than a placebo (Steiner, Ahmed, Findley, MacGregor & Wilkinson, 1998: 285). According to Evers and colleagues (2009), fluoxetine in doses between 10 and 40 mg was effective in three placebo controlled trial and not effective in one placebo controlled trial (Evers, Áfra, Frese, Goadsby, Linde, May & Sándor, 2009: 973). A small double-blind study showed that there was no significant benefit from amitriptyline plus fluoxetine over amitriptyline alone in the treatment of chronic daily headache/transformed migraine (Krymchantowski, Silva, Barbosa & Alves, 2002: 510).

3.4.6.2.4 Calcium channel blockers

Calcium channel blockers block the entry of calcium into smooth muscle cells as well as myocytes. They produce arterial vasodilation and thereby reduce arterial blood pressure (Moini, 2009: 173). In this section the calcium channel blockers verapamil and flunarizine will be discussed.

3.4.6.2.4.1 Verapamil

Limmroth and Michel (2001: 240) reported that the calcium channel blocker, verapamil, is frequently used as a migraine prophylactic in the US. Two studies dating from the early 1980s had reported verapamil to be superior to a placebo. They reported that the scientific basis of the frequent use of verapamil was weak due to a lack of comparison studies with established prophylactic drugs. According to the authors, only the calcium channel blocker flunarizine can be considered suitable for migraine prophylaxis.

3.4.6.2.4.2 Flunarizine

A randomized controlled trial showed that flunarizine 10 mg was an effective prophylactic treatment in patients with migrainous vertigo who suffer from considerable vestibular symptoms. The authors of this trial recommended that flunarizine be used

as a first-line prophylactic treatment in patients with migrainous vertigo as the compliance was good and side effects were minimal (Lepcha, Amalanathan, Augustine, Tyagi & Balraj, 2013: 2931).

3.4.6.2.5 Other drugs

There are a number of other drugs used in the prophylactic treatment of migraine. In this section clonidine and pizotifen will be discussed.

3.4.6.2.5.1 Clonidine

Clonidine is a selective alpha$_2$ presynaptic agonist that acts specifically on alpha$_2$ receptors. A double-blind trial (1978) concluded that 0.15 mg clonidine daily, significantly reduced headache severity (50%) and appeared to reduce the duration of a headache in some patients. However, there did not appear to be a reduction in the frequency of a headache. There was some suggestion that the effects of clonidine persisted after the drug was withdrawn (Adam, Gore & Price, 1978: 590). A migraine prophylactic study in the Netherlands (1992-1998) reported that 7.8% of migraineurs on the preventative medication used clonidine (Rahimtoola, Buurma, Tijssen, Leufkens & Egberts, 2003: 295). A study of anti-migraine drug prescribing in South Africa for 2011 in the private medical sector, reported that clonidine was the most frequently prescribed drug, accounting for 49% of prescriptions (Truter, 2015: 447). Silberstein and colleagues (2012) reported that clonidine is a medication that is possibly effective in the prevention of migraine and could be considered. However, an update on their guidelines reported that the data to support or refute clonidine for migraine prophylaxis was inadequate or conflicting (Silberstein, Holland, Freitag, Dodick, Argoff & Ashman, 2012: 871).

3.4.6.2.5.2 Pizotifen

Pizotifen is a 5-HT$_2$ receptor antagonist. Silberstein (2014: 5) reported that pizotifen for migraine prevention was of benefit to 40% to 79% of patients in Europe in controlled and uncontrolled studies. A study by Chitsaz and colleagues (2012) confirmed the

efficacy of pizotifen as an available choice in migraine prevention. Pizotifen showed a statistically significant reduction in headache frequency, duration, and severity (Chitsaz, Najafi, Zangeneh, Norouzi & Salari, 2012: 320).

3.4.6.2.6 Comparison studies

Demirkaya and colleagues' (2000) comparative study showed that there was no significant difference between amitriptyline and flunarizine in the reduction of migraine attack frequency and severity (Demirkaya, Dora, Topcuoglu, Ulas & Vural, 2000: 179). A study using flunarizine 5 mg and 10 mg compared to propranolol 160 mg reported that 10 mg flunarizine daily, with a drug-free weekend, was at least as effective as 160 mg propranolol in the prophylaxis of migraine for all evaluated parameters. However, propranolol 160 mg was more effective than flunarizine 5 mg (Diener, Matias-Guiu, Hartung, Pfaffenrath, Ludin, Nappi & De Beukelaar, 2002: 209). A randomised controlled trial of amitriptyline versus valporate showed that valproate extended release was more effective at three months than amitriptyline. However, at six months, both were equally effective in migraine prophylaxis (Kalita, Bhoi, & Misra, 2013: 65). The results of a study comparing pizotifen and sodium valproate by Chitsaz and colleagues (2012), were that in the short-term pizotifen was a safe and effective option for migraine prophylaxis that was superior to sodium valproate. Both drugs showed a significant improvement in all evaluated headache parameters (frequency, severity and duration). In some patients, complete remission of symptoms was observed (Chitsaz, *et al*., 2012: 322).

3.4.6.2.7 OnabotulinumtoxinA treatment

OnabotulinumtoxinA is a toxin produced by *Clostridium botulinum* that has the ability to block neuromuscular transmissions. Patients with intractable migraine that fails to respond to at least three conventional preventative medications could benefit from onabotulinumtoxinA injections. Injections of this toxin are administered to the scalp and temples. This treatment may reduce the frequency and severity of migraine attacks after two to three months of injections (Chawla, 2015). A standard dose and treatment regimen has not yet been established for onabotulinumtoxinA treatment

(Pesaturo, & Wooding, 2009: 156). A pooled analysis of onabotulinumtoxinA treatment in two phase 2 and two phase 3 double-blind, placebo-controlled trials, reported that doses of 72 to 260 units administered every 12 weeks for up to five treatment cycles were well tolerated in adults with chronic migraine as a prophylactic treatment (Diener, Dodick, Turkel, Demos, Degryse, Earl & Brin, 2014: 851). Silberstein and colleagues (2014) looked at the onabotulinumtoxinA treatment for chronic migraine prophylaxis. Their results showed that 50% reduction in headache-day frequency was reported by 43.3% of patients, first responding during cycle one, 11.3% during cycle two and 10.3% during cycle three. Fifty percent reduction in cumulative hours of headache, was 54.2%, 11.6% and 7.4% for cycles one, two and three respectively. The authors concluded that a meaningful number of chronic migraine patients who did not respond in the first cycle responded in the second and third cycle of onabotulinumtoxinA treatment (Silberstein, Dodick, Aurora, Diener, DeGryse, Lipton & Turkel, 2015: 996). According to Robertson and Garza (2012: 46), based on available data, episodic migraine has not been effectively prevented with onabotulinumtoxinA. However, prophylactic treatment of chronic migraine has been effective with onabotulinumtoxinA.

3.4.6.2.8 Complementary and alternative prophylactic treatment

Complementary and alternative medications that are used for prophylactic treatment of migraine include – butterbur, feverfew, magnesium, coenzyme Q10 and zinc (Silberstein & Goadsby, 2002: 492). Behavioural treatments include biofeedback therapy, relaxation techniques and cognitive behavioural therapy (Simon, 2012). Manual therapies such as massage, physiotherapy, chiropractic treatments and acupuncture are also used (Chaibi, Tuchin & Russell, 2011: 132). For those migraineurs who do not benefit from or do not want to take daily medication, exercise could be an option for prophylactic treatment of migraine (Varkey, Cider, Carlsson & Linde, 2011: 1428).

3.4.6.2.8.1 Complementary and alternative medications

In this section, alternative medicines such as herbal medicines and mineral and vitamin supplements are discussed.

3.4.6.2.8.1a Butterbur/feverfew

Butterbur and feverfew are herbal remedies that have been proven to be effective in migraine prophylaxis. The antispasmodic, anti-inflammatory and vasodilatory properties of butterbur make it an attractive treatment option for migraine prevention (Sutherland & Sweet, 2010: 706). Feverfew has anti-inflammatory and antispasmodic properties and inhibits excessive aggregating of platelets, which also normalises blood flow. These properties could be responsible for the reduction in migraine frequency and severity (Meschino, n.d.: 1). Meschino reported that clinical studies showed that a feverfew supplement reduced migraine attacks by 50% in chronic migraine sufferers**.**

The American Headache Society and American Academy of Neurology (AHS/ANN) in their 2012 Migraine Prophylaxis Guidelines listed butterbur extract (50-75 mg twice a day) as having Level A evidence while feverfew (50-300 mg twice a day) has Level B evidence. The AHS/ANN guidelines assign treatments to 1 of 5 levels based on the strength of evidence for their efficacy: Level A, Level B, Level C, Level U, and an "Other" group. According to their evidence-based report, butterbur is Level A "established as effective and should be offered for migraine prevention" while feverfew is Level B "probably effective and should be considered for migraine prevention" (Loder, Burch & Rizzoli, 2012: 933). A systemic review by Agosti and colleagues (2006) summarised that there was only moderate evidence for a three to four month daily treatment with butterbur being effective in migraine prevention (Agosti, Duke, Chrubasik & Chrubasik, 2006: 745). Lipton and co-authors (2004) reported that 75 mg butterbur (*Petasites hybridus* root) extract was more effective than a placebo while 50 mg butterbur was not significantly more effective than a placebo as a migraine preventative (Lipton, Gobel, Einhaupl, Wilks & Mauskop, 2004: 2240).

3.4.6.2.8.1b Magnesium, riboflavin (vitamin B2), and coenzyme Q10

According to the 2012 AHS/ANN guidelines for prevention of episodic migraine, magnesium 600 mg daily and riboflavin are Level B evidence ("probably effective and should be considered for migraine prevention") while coenzyme Q10 100 mg three times per day is Level C evidence "possibly effective and may be considered for patients requiring migraine prophylaxis" (Loder, *et al*., 2012: 933). Demirkaya and colleagues (2000) results show that oral magnesium was an effective and well-tolerated drug in the prophylaxis of migraine and compared well to established drugs like flunarizine and amitriptyline both in effectiveness and occurrence of side effects. Magnesium could be an alternative drug for migraine prophylaxis (Demirkaya, *et al.*, 2000: 179). According to Tepper, trials with magnesium supplementation for migraine prophylaxis have yielded mixed results. There have been positive studies in patients with aura and with perimenstrual migraine. A migraine can be terminated using parenteral magnesium (1g intravenously) in migraine patients with low ionised magnesium levels, and in those with aura. The recommended migraine prophylactic dose is 400 mg to 600 mg/day of chelated magnesium for at least three to four months (Tepper, n.d.: 1).

A review of riboflavin evidence between 1994 and 2014 reported that migraine symptoms were probably reduced when treated with high doses (400 mg) of riboflavin (Sadeghi, Askari, Nasiri & Maghsoudi, 2015: 110). A randomised control trial of the efficacy of coenzyme Q10 in migraine prophylaxis reported the following results, coenzyme Q10 100 mg three times per day was superior to a placebo and the effect began after the first month and maximised after the third month. The 50%-responder-rate for headache frequency was higher for coenzyme Q10 than for the placebo (Sándor, Di Clemente, Coppola, Saenger, Fumal, Magis, Seidel, Agosti & Schoenen, 2005: 714).

A study by Gaul, Diener and Danesch (2015: 1, 8) showed that migraineurs who were treated with a supplement of magnesium, riboflavin and coenzyme Q10 showed a significant reduction in migraine pain intensity. They reported that treatment for three months with this nutritional supplement combination could reduce the number of days

with migraine by almost 2 days (1.8) compared to a placebo (1.3 days). However, the reduction in migraine days was not statistically significant.

3.4.6.2.8.2 Behavioural treatments

Behavioural migraine management is clearly effective, with headache activity being reduced by 50% or more for some patients. However, one-third to one-half of behavioural treatment patients does not achieve such success (Holroyd & Drew, 2006: 204). Multimodal behavioural treatment together with drug treatment can lead to a decreased and more efficient drug consumption (Hedborg & Muhr, 2012: 298).

3.4.6.2.8.2 Cognitive behavioural treatment, biofeedback and relaxation

Seng and Holroyd's (2014: 1479) behavioural migraine management study indicated that the reductions in catastrophising with cognitive behavioural treatment for migraine demonstrate a strong relationship with the effect of cognitive behavioural treatment on migraine-related disability. However, changes in behavioural coping appeared to play a less significant role in this treatment effect. The authors suggested that reducing catastrophising is likely an important component of cognitive behavioural treatments for migraine. A meta-analysis by Nestoriuc and Martin (2007: 111) reported a medium effect on all biofeedback interventions, which proved stable over an average follow-up phase of 17 months. According to the authors, frequency of migraine attacks and perceived self-efficacy demonstrated the strongest improvements with biofeedback. Stokes and Lappin (2010: 1) in their study showed that a combination of biofeedback, neurofeedback interventions and medication was more effective in reducing the frequency of migraine in patients than medication alone. Relaxation training has been shown to improve pain severity in migraineurs relative to a control group (D'Souza, Lumley, Kraft & Dooley, 2010: 21). A small study on meditation in migraine demonstrated that there was a beneficial effect on headache duration and disability in migraineurs (Wells, Burch, Paulsen, Wayne, Houle, & Loder 2014: 1148).

3.4.6.2.8.3 Manual therapies

A study of the effectiveness of a Self-Administered Behavioural Intervention using message techniques develpoed for migraine patients was carried out by Nicholson, Nash and Andrasik, (2005: 1124). Their results showed that 62% of patients reported at least 50% reduction in headache frequency. Nicholson and colleagues (2011) carried out a structured review of data that reported that physical treatment was more effective than massage therapy. However, physical treatment was most effective when combined with biofeedback. They suggested that physical treatment was not a first-line treatment for migraine prevention (Nicholson, Buse, Andrasik & Lipton, 2011: 36). However, other authors suggested that physiotherapy and massage therapy could be comparable to some preventative drug treatments (Gantenbein, Afra, Jenni & Sándor, 2012: 79).

A patient treated for 12 weeks with a regimen, consisting of, spinal manipulation and active and passive therapeutic care, reported a reduction in duration, frequency and intensity of their migraine attacks. The author suggested that this case is an example of the potential for chiropractic and rehabilitation treatment for migraine suffers (Harris, 2005: 25). A randomised control study by Tuchin and colleagues (2000) reported that migraineurs reported a significant improvement after chiropractic manipulation. They reported that these results could be due the result of chiropractic care on the high stress reported in migraine. The reduction in stress by the treatment lead to a reduction in migraines (Tuchin, Pollard & Bonello, 2000: 91).

Wang and colleagues (2011) suggested that acupuncture was more effective than flunarizine in decreasing days of migraine attacks, whereas no significantly differences were found between acupuncture and flunarizine in reduction of pain intensity and improvement of the quality of life (Wang, Zhang, Guo, Liu, Zhang, Liu, Yi, Wang, Zhao & Li, 2011: 1864). A study by Li and colleagues (2012) reported that acupuncture appeared to have a clinically minor effect on migraine prophylaxis compared with pretence acupuncture (Li, Zheng, Witt, Roll, Yu, Yan, Sun, Zhao, Huang & Chang, 2012: 401). However, Linde and colleagues (2005) reported that acupuncture was no more effective than “sham” (placebo) acupuncture in reducing migraine headaches (Linde, Streng, Jürgens, Hoppe, Brinkhaus, Witt, Wagenpfeil, Pfaffenrath, Hammes &

Weidenhammer, 2005: 2118). Chaibi and colleagues, (2011: 132) reported that current randomised control trials suggest that massage therapy, physiotherapy, relaxation and chiropractic spinal manipulative therapy might be equally efficient as propranolol and topiramate in the prophylactic management of migraine.

3.4.6.2.9 Menstrual migraine prophylaxis

For those women who suffer from menstrual migraine and do not get relief from acute medications, short-term premenstrual prevention treatment could be employed. Treatments that could be used are NSAIDs, triptans or hormonal containing preparations (Newman & Yugrakh, 2014: 47). A comparison study by Guidotti and colleagues (2007) reported that short-term prophylaxis of menstrual migraine with frovatriptan could be more effective than transdermal oestrogens or naproxen sodium. Frovatriptan had a shorter duration of treatment (Guidotti, Mauri, Barrilà, Guidotti & Belloni, 2007: 283). A systematic review of six trials which compared frovatriptan, naratriptan and zolmitriptan at different doses with placebo in preventing menstrual migraine was carried out by Hu and colleagues (2013). The authors reported that all three triptans were effective short-term prophylactic treatments for menstrual migraine. Considering menstrual migraine frequency, severity and adverse events, frovatriptan 2.5 mg twice a day and zolmitriptan 2.5 mg three times per day, tend to be the preferred regimens (Hu, Guan, Fan & Jin, 2013: 1). In randomised controlled trials and 12-month open-label studies, frovatriptan was well tolerated for the treatment of menstrual migraine. This held true for acute therapy and short-term prophylaxis (MacGregor, Pawsey, Campbell & Hu, 2010: 88). Frovatriptan is not available in South Africa.

3.4.6.2.10 Conclusion

A study in the US by Lipton and colleagues (2007) found that approximately 38% of migraineurs need prevention, but only 13% of this group used preventive therapy for their migraines. The authors of this study reported that only six percent of migraineurs in France and two percent in Latin America used preventative medication even though the migraine disability was similar to that in the US (Lipton, Bigal, Diamond, Freitag,

Reed & Stewart, 2007: 348). A five-year study in the Netherlands found that only 12% of their migraine population were on prophylactic treatment (Rahimtoola, *et al*., 2002: 149). An analysis of preventative treatment duration by Silva-Néto, Almeida and Bernardino (2014: 38), reported that the best results were obtained when migraine prophylaxis was maintained for 24 months after patients became pain-free. An adequate prophylaxis intervention is crucial in reducing disability and preventing the evolution of migraine into a chronic progressive illness (Pompili, Serafini, Innamorati, Serra, Dominici, Fortes-Lindau, Pastina, Telesforo, Lester, Girardi, Tatarelli & Martelletti, 2010: 107).

Prophylactic treatment must be tailored to the individual migraineur so as to take into account their preferences and needs. The migraineur will be more compliant in taking their medication if they are informed about their treatment. Medication taken as prescribed could lead to a reduction in frequency and severity of migraine attacks. If one medication does not work another can be tried until an effective treatment is found.

3.5 Summary of chapter 3

More than 60 trigger factors are recognised as being precipitating factors that could trigger a migraine attack. Migraineurs need to be aware of and avoid the factors that affect them, thereby decreasing the chance of having an attack. There are a sub-group of migraineurs that experience an aura, that could be visual or sensory. This aura can be seen for some as a warning and therefore the migraine can be treated early, reducing the duration of the migraine. There are a large number of medications that can be used to treat and/or prevent migraine. Effective treatment with acute medication and/or prophylactic medication can reduce the frequency and severity of migraine.

Chapter 4

Methodology

4.1 Introduction

Research methodology is "*the general approach the researcher takes in carrying out the research project; to some extent, this approach dictates the particular tools the researcher selects*" (Leedy & Ormrod, 2010: 12). Therefore, research methodology can be defined as the tools, instruments, step-by-step processes and procedures followed while conducting research (Kothari, 2004: 8).

In this study, the instruments utilised were two structured self-administered questionnaire surveys. The pharmacist questionnaire survey involved data collection through completion of a questionnaire on migraine patients by corporate and independent retail community pharmacists, to be discussed in Section 4.6.2.1. The migraine patient questionnaire survey involved data collection from migraine patients about their disease, to be discussed in Section 4.6.2.2.

4.2 Ethical approval for the study

Before commencing data collection, the research proposal was submitted to the Faculty of Health Science Postgraduate Studies Committee at NMMU and the NMMU Research Ethics Committee (Human) for approval. The application was successful and approved on 28 May 2014 (reference number: H14-HEA-PHA-003). A copy of the letter of approval for the study is attached and marked Appendix F.

This study was conducted in accordance with the Declaration of Helsinki, 2008 (World Medical Association, 2013) which is a declaration of ethical principles applied to medical research involving human subjects and identifiable human data and material.

4.3 Study design

The study consisted of an exploratory descriptive design. Exploratory research is the development of insights or hypotheses. The purpose of which is to formulate a problem for more precise investigation leading to the discovery of ideas and insights (Kothari, 2004: 4,36). Exploratory research examines the relevant data in detail to arrive at a

complete description of an existing situation (Brink & Wood, 1998: 284). This entail the collection, analysis and interpretation of data (WHO, 2001). The resources used to conduct exploratory research are:

- in depth literature reviews;
- discussions with experts; and
- attending workshops/seminars (Mouton & Marais, 1990: 43).

This study was quantitative in nature, implying the extent to which something either does or does not occur in terms of amount, number, frequency that can be statistically analysed (Jonker & Pennink, 2010: 65). An open-ended question was included at the end of the patient questionnaire which was directed towards discovering or uncovering new insights, meaning and understanding. The responses to this question was analysed using content analysis, which is a qualitative data analysis technique. Data collected in this manner could then be analysed (Brink & Wood, 1998: 337). Ritchie and Lewis (2003) reported that, according to Denzin and Lincoln "qualitative researchers study things in their natural settings, attempting to make sense of, or to interpret, phenomena in terms of the meanings people bring to them" (Ritchie & Lewis, 2003: 3). There was a drug utilisation component to this study which was used to determine the pattern of drug use. Drug utilisation research was defined by WHO in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO, 2003: 9).

4.4 Literature review

A literature review was conducted which served to provide knowledge about migraine and different study methodologies. This knowledge was used to design the chosen data collection tools. Appropriate reference books, internet websites and journal articles were consulted during this process. Electronic information, including local and international journal articles, were obtained through the use of the NMMU Library databases such as EBSCOhost®, PubMed Central® Sage® ScienceDirect®, Springerlink®, Web of Science®, Web of Science® and Google™ Scholar BETA search

engines. As the history of migraine was included in the literature review, no time limits were set for the literature search.

4.5 Data collection

The foremost method of collecting data for academic research is by conducting surveys using questionnaires as the data collection tool (Sheth & Malhotra, 2011). A questionnaire "is simply a list of printed questions that is completed by or for a respondent" (WHO, 2001). Questionnaires are a form which are prepared and distributed for the purpose of securing responses. Thereby collecting data/answers which are recorded by respondents (Singh, 2006: 190; Kothari, 2004: 240). Questionnaires are employed to collect primary data and provide accurate reliable information when correctly designed. Both qualitative and quantitative information can be collected by means of a questionnaire survey (Pruzan, 2016: 151, 262). Descriptive research includes surveys which are used to gather information and data that can be analysed and the observed results reported (Kothari, 2004: 2,18)**.**

In social research both open-ended and closed questions or a combination thereof, are commonly used. In an *open-ended question* the possible response categories are not provided in the questionnaire and the respondent records the answers in his/her own words. In a *closed question* the possible answers are set out in the questionnaire and the respondent ticks the applicable category that best describes the respondent's answer. Closed questions are useful for eliciting factual information and open-ended questions for seeking opinions, attitudes and perceptions (Kumar, 2014: 247, 249).

In this research study, data was collected by means of two self-administered questionnaire surveys:

- a questionnaire that was completed by pharmacists; and
- a questionnaire that was completed by migraine patients.

The pharmacist questionnaire consisted of open-ended questions and the patient questionnaire consisted of a combination of closed questions, open-ended questions and a rating scale. Self-administered instruments are used to obtain information about individuals and are subjective according to each respondents' personal interpretation. Questionnaires are typically designed to be self-administered (Colton & Covert, 2007: 7, 321). There are advantages and disadvantages to using a questionnaire.

Advantages of questionnaire surveys are: -

- a quick way of obtaining data from a large group of people as they are easy to administer and distribute;
- relatively low cost in terms of time and money;
- one of the easiest research instruments to test for reliability and validity;
- subjects feel a greater sense of anonymity and are more likely to provide honest answers;
- the format is standard for all subjects and is not dependent on input from the interviewer/researcher; and
- respondents can complete and return the questionnaire in their own time.

Disadvantages of questionnaire surveys, however, are: -

- low response rate due to inability, reluctance or unwillingness to complete the questionnaire survey;
- the respondents who respond may not be representative of the population;
- respondents may provide socially acceptable answers;
- respondents may fail to answer some of the questions;
- there is no opportunity to clarify any questions that may be misunderstood by subjects;
- subjects must be literate;
- questions must be concise and comprehensive; and
- questionnaires are retrospective and rely on accurate recall of information.

(Brink, van der Walt & van Rensberg, 2006: 147; Research and Consultation Guidelines – Questionnaires: 2).

4.6 Study Instruments – questionnaire-based surveys

The primary aim of this study was to determine if there was any relationship between migraine triggers, auras and the treatment that were effective as reported by migraineurs whether self or professionally diagnosed. The survey instruments used were two structured self-administrated questionnaires consisting of:

- a structured pharmacist (as the facilitators' of pharmacies) questionnaire which was used to determine prevalence and information relating to migraine patients frequenting their facility (see Appendix A); and
- a structured questionnaire for migraine patients which was used to determine information related to the respondents' migraine (see Appendix B).

4.6.1 Target population

The research population identified for this study were adults (both male and female) of all ethnic groups who lived in the Port Elizabeth area that met the eligibility criteria. The eligibility criteria specified what characteristics the adults in the population had to meet in order to participate in the study. The eligibility criteria for participants were as follows:

- they had to be 20 to 60 years of age;
- suffer from migraine whether self or professionally diagnosed; and
- pregnant women were excluded from the study.

The survey used non-probability purposive sampling together with snowball sampling to collect data. Non-probability sampling is the selection of sampling participants from a population using non-random procedures. Purposive sampling on the other hand is a non-probability sampling method in which the researcher selects participants based on personal judgment about who in the researchers opinion will be most representative (Polit & Beck, 2004: 729). In snowball sampling, the researcher starts by identifying a few respondents that match the eligibility criteria for inclusion in their study, and then

request those respondents identified, to recommend others they know who also meet the selection criteria (Bhattacherjee, 2012: 79).

Pharmacists willing to participate in the study were asked to complete a questionnaire. Migraine patients who fitted the eligibility criteria for inclusion in the study were asked to complete a questionnaire. Migraine patients obtained the questionnaires from participating pharmacies, health shops or physiotherapist practices in the Port Elizabeth area. To overcome the potential problem of a low response rate, snowball sampling was utilised.

Permission for the study to be conducted through corporate retail pharmacy groups was obtained from their respective head offices. Whilst permission to conduct the study at independent pharmacies, physiotherapy practices and health shops was obtained either from the owner or the responsible person in charge.

4.6.2 Development of the questionnaires

The questionnaires were developed after the literature review. There were no standardised questionnaires available to measure specifically what this study aimed to measure, hence the questionnaires were designed by the researcher for the specific purpose of this study, namely to collect and record the relevant information relating to migraineurs and their disease state. The pharmacist questionnaire consisted of nine questions to record and collect relevant information pertaining to migraine patients that consulted their pharmacies and migraine cocktails/kits sold by pharmacies. The patient questionnaire consisted of six questions which were used to establish relevant information pertaining to migraine attacks. After feedback from the research committee and the pilot studies, the relevant changes were made to both questionnaires. Detailed development of each data collection questionnaire will be discussed in Section 4.6.2.1 and Section 4.6.2.2 and will reflect the final composition of the questionnaires.

4.6.2.1 Questionnaire survey of community pharmacies

This questionnaire was designed for the pharmacists, as the facilitators of pharmacies, to complete. It was designed to collect information about the migraine patients who visited the pharmacy, the type of medication they purchased and whether the pharmacy sold a migraine cocktail/kit. The facilitator questionnaire measured variables such as:

- the average number of male and female patients that consulted the pharmacy staff per month that fitted the criteria for participation in this study;
- the average age of migraine patients and what their gender distribution was;
- the percentage migraine patients with prescriptions as opposed to “walk in” migraine patients and their average age;
- the percentage and average age of migraine patients with doctors’ prescriptions as opposed to specialist prescriptions;
- how often patients were referred to confirmed diagnosis and improve treatment; and
- if the pharmacy sold a migraine cocktail/kit, ingredients of the cocktail/kit, what the demand for such a product was and what the price for the migraine cocktail/kit was at the time of completing the questionnaire.

4.6.2.2 Questionnaire survey of migraine patients

This questionnaire to migraine patients was designed to collect relevant information on factors relating to migraine and the medication used to treat migraine attacks. The following data was collected in the patient questionnaire:

- Section one: demographics - gender, age and race;
- Section two: the respondents’ migraine history;
- Section three: special section for female migraine sufferers – focussing on hormonal influence and hormonal treatment;
- Section four: information on the auras, triggers, comorbid conditions and other medical conditions that a respondent suffered from;

- Section five: the different type of medications and treatments that the participants had tried or were using. In this section information was also obtained as to whether use was being made of alternative treatments for migraine; and
- Section six: a question requesting the respondent to describe how they experience a typical migraine attack.

Questionnaires were well prepared, based on factors identified in the literature review, in order to provide effective collection of the relevant data required for the study.

4.6.3 Pilot study

A pilot study is a small scale version, or trial run, undertaken in preparation for the major study (Polit & Beck, 2004: 729). Any weaknesses or limitations in the questionnaires are revealed by the pilot study. In May 2014, a draft pharmacist questionnaire was distributed to one pharmacist and draft patient questionnaires were distributed five random individuals to determine the feasibility of the questionnaires. All the volunteers to whom patient questionnaires were distributed, suffered from migraine and came from different levels of education. Participants from the pilot study were asked to note the time it took to complete the questionnaire and if the language used was understood. Results from the pilot study did not form part of the final data reviewed.

In general, the questionnaire was reported to be understandable and relatively easy to complete. There was a slight problem with terminology in some instances. The identified problems were taken under review and the questionnaire was adjusted accordingly.

4.6.4 Distribution

Facilitators for the distribution of questionnaires in the Port Elizabeth area were pharmacists (from the selected sample of pharmacies), physiotherapists (from the selection of physiotherapy practices) and the person in charge of health shops. Pharmacists would distribute questionnaires to migraine patients and the pharmacist

in charge would be asked to complete a short questionnaire. Physiotherapists and the person in charge of the health shops were only asked to distribute questionnaires to migraine patients.

According to the South African Pharmacy Council, there were 3041 Community Pharmacies in South Africa in 2013, of which 369 were located in the Eastern Cape. A list of pharmacies in the Port Elizabeth area were obtained from the Pharmaceutical Society of South Africa (Cape Midlands Branch). The 68 pharmacies in Port Elizabeth in 2013 were used for the study. In South Africa pharmacies, could be private enterprises owned by businessmen, private enterprises which are owned by individuals and part of an amalgamated pharmacy chain, or corporate enterprises. Twenty-nine-point five percent of the pharmacies in Port Elizabeth were corporate pharmacies. Every second pharmacy in Port Elizabeth were contacted and depending on the response received, other pharmacies on the list were selected. An attempt was made to include pharmacies from all areas in Port Elizabeth. A list of physiotherapy practices (34) and Health Shops (five) were sourced from The Yellow Pages Directory of Port Elizabeth. All physiotherapy practices and health shops were contacted.

Facilitators were approached telephonically to determine if they would be prepared to participate in the study. The facilitators were asked as to whether they consulted migraine patients and on average how many migraineurs they consulted with per month, thereby determining the feasibility of using their premises for distribution of questionnaires. Those facilitators that consulted on average at least six to eight migraineurs per month were asked to participate in the study. Certain pharmacies were excluded due to a number of factors, namely, insufficient migraine patients consulted per month, pharmacist indicating that there would be a language/literacy problem, head office of corporate pharmacies not granting permission, pharmacy was closing down, the pharmacist was retiring, and when no response was received after an average of four attempts to contact them telephonically had failed. A number of physiotherapists and health shop personnel also indicated that they did not see many migraine patients and were accordingly excluded.

4.6.4.1 Distribution to facilitators

Facilitators who were prepared to participate in the study, were requested to sign a permission form, thereby giving permission to use their premises for questionnaire distribution and collection. An appointment was made with the facilitator to deliver questionnaires and sign the facilitator's consent form. Pharmacists were also asked complete the shorter questionnaire. All questionnaires were delivered to the study sites in July and August 2014. Questionnaires were handed out to migraine patients who come into the pharmacy either with a prescription or to get OTC medication and/or pharmacist-initiated therapy (where the pharmacist assisted in what medication to use) for their migraines. At health shops and physiotherapist practices, questionnaires were provided to patients who frequented the facilities for migraine-related treatment. Consent was obtained from participating facilitators (see Appendices C and D) together with informed consent from participating respondents in this study (see Appendix E).

4.6.4.2 Distribution to migraine patients

Migraine patients were consulted as to whether they were prepared to participate in this migraine research study. If they agreed to participate, they were requested to fill in and sign the consent form and were provided with a questionnaire. They were informed that they could fill in the questionnaire in their own time and either return it to the premises from which it was obtained or fax or email the questionnaire to the number or email address provided by the researcher on the questionnaire. The consent form advised that participation was voluntary and would in no way affect their treatment.

A period of three months was allowed for patients to receive, complete and return questionnaires. Progress was monitored regularly and completed questionnaires collected on a monthly basis. Due to a slow response, snowball sampling was initiated. Persons known to suffer from migraine were approached by the researcher and asked if they had friends or family who fitted the inclusion criteria for participation in the study. If they did, they were asked to distribute questionnaires to respondents who were

prepared to participate. Friends and family were also asked to distribute questionnaires to respondents that fitted the criteria for inclusion in the study. These respondents in turn distributed to their friends and family who fitted the criteria. In this way completed questionnaires were collected.

4.6.5 Response rate

Each of the 25 pharmacies that agreed to participate in the study received a pharmacist questionnaire of which 18 were returned. Although the response appeared to be low, it was roughly representative, as pharmacies were located in the following socio-economic class areas: in lower (three pharmacies), middle (10 pharmacies) and upper (five pharmacies) socio-economic class areas of Port Elizabeth. A total of 281 migraine patient questionnaires were delivered to the 25 pharmacies for distribution to migraine patients. Relative to the number of migraine patients seen monthly, between five and 20 questionnaires were provided to each pharmacy. The response rate for pharmacies amounted to 12 pharmacies retuning 35 migraine patient questionnaires in total. Thirty-three questionnaires were delivered to five physiotherapy practices. Relative to the number of migraine patients seen monthly, between one and 10 questionnaires were provided to each physiotherapy practice. The response rate for physiotherapy practices were that four questionnaires were returned from two of the five participating physiotherapy practices. Two health shop were identified, receiving five and 10 questionnaires respectively. Only one health shops returned two migraine patient questionnaires. Due to the nature of the method of distribution, the number of migraine patient questionnaires distributed though snowball sampling was unknown. A total of 132 questionnaires were completed and returned.

4.7 Data analysis

Data collected from the migraine patient questionnaire and pharmacist questionnaire were captured and coded onto a purpose-designed spreadsheet using Microsoft Excel®. The results were analysed using descriptive and inferential statistics and compared with literature findings.

Specific data obtained from the open-ended migraine patient question six “Describe a typical migraine” was analysed by means of conventional content analysis. Coding categories were derived directly and inductively from the raw data (Zhang & Wildemuth, 2009: 2) with the following steps being followed:

- data was prepared;
- a unit of analysis defined;
- themes were developed;
- data was coded according to themes;
- conclusions were drawn from coded data; and
- the analysing process and results were reported (Elo & Kyngäs, 2008: 110; Zhang & Wildemuth, 2009: 2-4).

Key words from the ICHD-3 criteria for a headache to be classified as a migraine were used to analyse the responses to the question “Describe a typical migraine” (ICHD-3, 2013). The key words were “sensitivity to light”, “aura” (blurred vision, any other visual aura, pins and needles, numbness, vertigo, tinnitus and speech impairment), “nausea and vomiting”, “pain description”, “trigger factors”, “medication” used and “sleep” (whether respondent woke up with a migraine or if sleep and a dark room helped to resolve a migraine). Content analysis was carried out using these key words. Only questionnaires answered in English (three were completed in Afrikaans) were analysed.

4.8 Statistical analysis

Descriptive and inferential statistics were calculated. References regarding difference or association significance imply fulfilment of both statistical and practical significant criteria, thus $V > 0.30$ (i.e. at least medium practical significance) for Chi-square tests where the minimum of rows and columns is 2, and $V > 0.21$ (at least medium practical significance) for Chi-square tests where the minimum of rows and columns is 3. When comparing the means of a numerical variable for two groups, the *t*-test for independent sampling was used. Microsoft Excel® and SPSS® were used for statistical analyses.

4.9 Confidentiality

No patient would be linked to data received. Confidentiality and anonymity were maintained at all times. Anonymity means the “responses given by a particular respondent can never be identified or tied to that particular person”. Confidentiality means that “although the researcher can identify who completed a particular survey, the researcher pledges to keep that information confidential and never reveal the identity of the respondent*”* (Clow & James, 2014: 343). Confidentiality was maintained in the questionnaire surveys through separation of the informed consent forms from the questionnaires. Questionnaire and informed consent documents were stored separately at the researchers’ home.

4.10 Reliability of study

A result is said to be reliable, if the study, repeated under the same conditions obtains the same results. Random error is the natural variability in observations among individuals in the population. If the standard deviation is small, repeated studies from this population are bound to come up with similar results. On the other hand if the standard deviation is large, substantial differences will be seen in different samples from the same population (World Health Organization, 2001: 13). The research design ensured the reliability and ability to reproduce the study.

4.11 Validity

Validity is the degree to which a study accurately measures the specific concept that the researcher is attempting to measure (Barry, *et al*., 2014: 13). Careful detail in the design of the questionnaire ensured that the information required was obtained from respondents. This enabled the researcher to accurately report the findings of the study.

4.12 Limitations of the study

The questionnaire was designed as a self-administered questionnaire, therefore it afforded participants no opportunity to clarify any question that were misunderstood. The questionnaire was also retrospective and relied on accurate recall of information. The information sought in the questionnaire was specific and respondents may not have been able to report accurate information, leaving some questions unanswered. The respondent had to be literate to complete the questionnaire. These factors may have led to the inability, reluctance and unwillingness of respondents to complete the questionnaire.

Distribution of questionnaires was carried out by facilitators at pharmacies, physiotherapy practices and health shops and not the researcher. Therefore, it was not possible to ensure that all potential respondents received questionnaires. As staff at the various distribution points were not constant, it was possible that they were not informed about the distribution procedure of the questionnaires. The respondents were instructed to complete the questionnaire in their own time and questionnaires to be returned to distribution points. These factors or a combination thereof may have led to the questionnaires being misplaced and forgotten or simply not completed or returned timeously.

4.13 Conclusion

In this study two questionnaire surveys were carried out to collect information on migraine patients in Port Elizabeth. The pharmacist questionnaire collected information on migraine patients that consulted them and the patient questionnaire collected information on migraine as experienced by the respondent. Information collected was captured, analysed and the results were reported. The aim of this study was to determine if there was a relationship between migraine aura, triggers and the type of medication used. In the next chapter the results of the study will be reported and discussed.

Chapter 5

Results and discussion

5.1 Introduction

In this chapter, the results of both the survey for pharmacists and the survey for migraine patients will be discussed. The *pharmacist survey* collected data to gather information about migraine patients visiting pharmacies. The survey also investigated whether migraine cocktails/kits were offered by the pharmacies to patients to treat a migraine attack. The *migraine patient survey* collected data to gather information about migraine as experienced by the patients. As the questionnaires used in the study were completed by pharmacists or patients without the assistance of the researcher, certain fields were occasionally left blank, and for this reason, the number of respondents varied within results presented in this chapter. The results of the migraine survey for pharmacists will be discussed in Section 5.2 (the questionnaire is provided in Appendix A). The results of the migraine survey for patients will be discussed in Section 5.3 (the questionnaire is provided in Appendix B).

5.2 Results of the pharmacist survey

The aim of the pharmacists' survey was to determine how many patients suffering from migraine consulted with a pharmacist per month. Data was collected on the average percentage and average age of patients who used: OTC medication/pharmacist-initiated therapy, had prescriptions from general practitioners or had prescriptions from specialists. Pharmacists were also asked to specify if migraine cocktails/kits were available at their pharmacy. If the pharmacy did sell migraine cocktails/kits, information was requested pertaining to their migraine cocktails/kits.

A total of 18 pharmacists responded. Although the response rate seemed to be low, it was roughly representative, of the location of pharmacies in the different socio-economic areas of Port Elizabeth, namely: lower socio-economic area (three pharmacies), middle socio-economic area (10 pharmacies) and upper socio-economic area (five pharmacies). On average, pharmacists reported that 22 (average=22.4; SD=15.3) patients consulted them per month about migraine. The average age of these patients was 33.4 (SD=6.0) years, with most patients being female (72.2%).

Table 5.1 gives an overview of the source of the medication used by migraine patients as reported by pharmacists in response to the questions asked in Appendix A. Pharmacists had to give an average percentage per month as a response. Most migraine patients (80.0%) came into the pharmacy for OTC medication/pharmacist-initiated therapy (where the pharmacist-assisted in what medication to use). On average, only 19.7% of patients came to the pharmacy with prescriptions for their migraine. Pharmacists indicated that most prescriptions (58.9%) were from general practitioners, with 23.5% patients having prescriptions from specialists. Migraine patients with prescriptions from a specialist were generally older (average age: 35.4 years) than those with prescriptions from a general practitioner (average age: 33.3 years). On average, pharmacists referred eight patients per month to general practitioners to assist with the treatment of their migraine. According to the literature, migraineurs often rely on non-prescription medications to treat themselves. These medications are effective for some individuals and are easily accessible (Unger, 2006: 374, 376). This is consistent with the findings in this study.

Table 5.1 Source of medication used by migraine patients (n=18)

Type of treatment	**Migraine patients per month (percentage)**				**Age of migraine patients (in years)**			
	Average	Standard deviation (SD)	Minimum	Maximum	Average	Standard deviation (SD)	Minimum	Maximum
Pharmacist-initiated therapy/OTC medication	80.0%	13.4%	50.0%	95.0%	33.0	5.4	25	45
All prescriptions	19.7%	14.1%	5.0%	50.0%	35.4	6.2	25	35
Prescriptions by general practitioners	58.9%	31.4%	10.0%	95.0%	33.3	7.2	20	45
Prescriptions by specialists	23.5%	15.0%	5.0%	50.0%	35.4	8.0	25	50

Fifteen of the 18 pharmacies reported that they sold migraine kits. An average of 30 (average=30.4; SD=21.3) migraine cocktails/kits were reported to be sold per month. Fourteen pharmacists were willing to indicate what medications were included in their migraine cocktails/kits. Migraine cocktails/kits were comprised of three to five

medications. Table 5.2 gives an overview of the medications and the percentage of migraine kits which contained these medications. Combination analgesics which were included in migraine cocktails/kits all contained codeine phosphate.

Table 5.2 Medications and percentage migraine kits which contained each medication (n=14)

Medication class	Percentage (number)
Anti-inflammatory	85.7% (12)
Anti-emetic	85.7% (12)
Combination analgesic	57.1% (8)
Alpha$_2$-adrenergic agonist	42.9% (6)
Analgesic	35.7% (5)
Vitamin supplement	35.7% (5)
Anti-spasmodic	28.6% (4)
Ergot alkaloid	21.4% (3)
Dopamine antagonist	7.1% (1)

Medications with the highest possibility of being included in a migraine cocktail/kit were: an anti-inflammatory (85.7%), an anti-emetic (85.7%), followed by a combination analgesic (57.1%). These medications would treat the pain and nausea associated with migraine. The price of a migraine kit varied from R8.00 to R30.00 (average price=R18.40; standard deviation=R6.42; mode=R15.00; median=R17.00 and interquartile range=R5.00). No specific literature references to migraine cocktails/kits were found in the literature.

The exact ingredients included in migraine cocktails/kits, as reported by the pharmacists, are listed in Table 5.3. Each pharmacy had their own combination of medications which could have had an influence on the price. The combination of medications a patient received would depend on which pharmacy the patient bought his or her migraine cocktail/kit from. Thus, the number of migraine cocktails/kits sold by a pharmacy could be influenced by the type of medications contained in the migraine cocktails/kits.

Table 5.3 Medications in migraine cocktails/kits as reported by pharmacists

Migraine kit	*Ingredient 1*	*Ingredient 2*	*Ingredient 3*	*Ingredient 4*	*Ingredient 5*
Kit 1	*Paracetamol 500 mg codeine 8 mg x2*	*Naproxen 250 mg*	*Clonidine HCL 25 ug*	*Cyclizine 50 mg*	
Kit2	*Spasmed® x2*	*Menograine® x1*	*Domperidone/ Aculoid® x1*	*Multivitamin 2x*	
Kit3	*Adco-Dol®*	*Ibuprofen 400 mg*	*Dixarit*	*Valoid®*	
Kit 4	*Diclofenac 50 mg x1*	*Acurate x2*	*Valoid ® x1*		
Kit 5	*Ergotamine 2 mg*	*Orphenadrine 35mg*	*Cyclizine 50 mg*	*Ascorbic Acid 500mg*	*Paracetamol 1000 mg*
Kit 6	*Adco-Dol® x2*	*Inza® 400 mg x1*	*Menograine® x1*	*Cyclizine 50 mg x1*	
Kit 7	*Ibuprofen 400 mg x1*	*Adco-Dol ® x1*	*Medazine x1*	*Multivit x2*	*Vit B Co x1*
Kit 8	*Migril® x1*	*Ibuprofen 400 mg x1*	*Vit B*	*Spasmed®*	
Kit 9	*Paracetamol 500 mg*	*Cyclizine 50 mg*	*Ibuprofen 400 mg*		
Kit 10	*Ibuprofen*	*Paracetamol*	*codeine*	*Cyclizine*	*Methocarbamol*
Kit 11	*Cyclizine 50 mg x1*	*Migril® x1*	*Paracetamol 500 mg Codeine 8 mg x2*	*Diclofenac 50 mg x1*	
Kit 12	*Pain tablets x2*	*Anti-inflammatory x1*	*Anti-nausea x1*	*Dopamine antagonist x1*	
Kit 13	*Codoxal® (Syndol®) x2*	*Ibuprofen 400 mg x1*	*Menograine x1*	*Vit B Co x2*	
Kit 14	*Cyclizine*	*Ibuprofen*	*Clonidine*		

5.3 Results of the migraine survey for patients

The aim of the migraine patient survey was to collect data and thereby gather specific information about migraines as reported by migraine patients. Information gathered would be used to determine if a relationship existed between migraine trigger factors, aura and the type of medication that was effective in treating migraine. In this section, information about migraine from migraine patients will be reported on.

A total of 173 migraine patients responded. The source of these respondents is illustrated in Figure 5.1. As can be seen from this figure, there was a poor response from health care providers (pharmacies, physiotherapists and health shops). Twelve pharmacies, two physiotherapy practices and one health shop returned completed questionnaires. The bulk of respondents were sourced through snowball sampling (132 respondents). One of the limitations of snowball sampling is that it is open to bias.

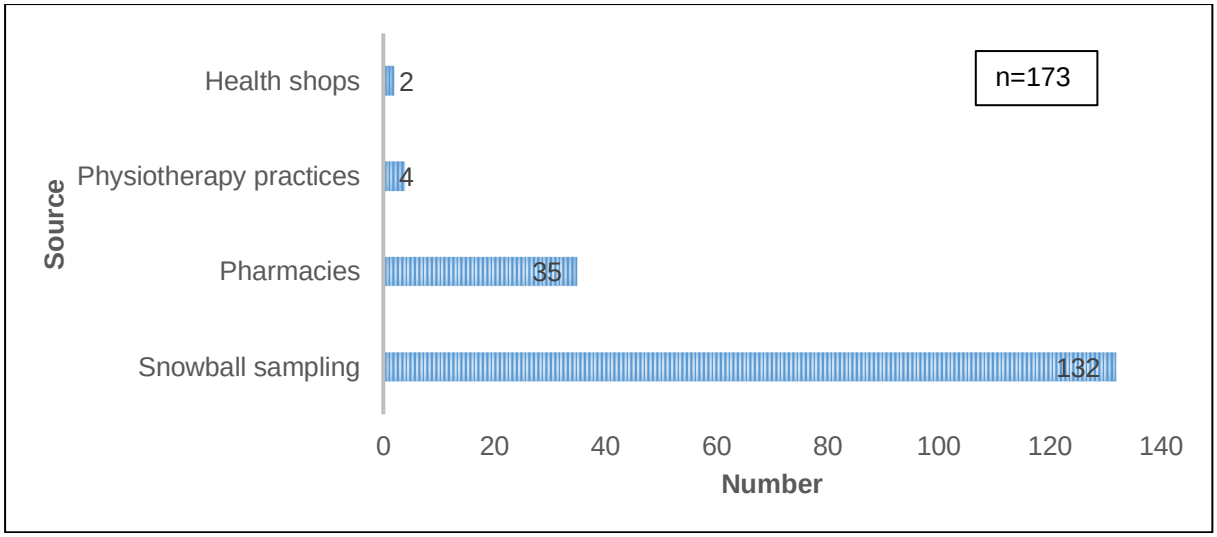


Figure 5.1 Number of questionnaires returned in relation to the source

5.3.1 Demographic Information

Of the 173 migraine respondents, 10.7% (n=18) were male and 89.3% (n=151) female (gender n=169). Table 5.4 gives an overview of the age distribution of respondents with reference to the percentage of male and female respondents. As can be seen from the table the largest age group of respondents were in their third decade (31.0%) of life.

Table 5.4 Age and gender distribution of respondents (n=168)

Age group (in years)	**Male** (n=18)	**Female**** (n=150)	**All respondents*** (n=168)
20-29	16.7% (3)	24.0% (36)	23.2% (39)
30-39	33.3% (6)	30.7% (46)	31.0% (52)
40-49	27.8% (5)	27.8% (41)	27.4% (46)
50-60	22.2% (4)	18.0% (27)	18.5% (31)
Total	100.0% (18)	100.0% (150)	100.0% (168)

*Each age group had one respondent who did not indicate gender
**One female respondent did not indicate age

Most respondents in this study were female. Literature reports that migraine is more prevalent in females than males. Bigal and colleagues (2004) reported that migraine prevalence was highest in women, in persons between the ages of 25 and 55 years in the US (Bigal, Lipton & Stewart, 2004: 98). Prevalence rates of IHS-defined migraine

were reported by Leonardi and colleagues (2005) to be relatively consistent in Western countries, varying from 4% to 9.5% in men and from 11.2% to 25% in women (Leonardi, *et al.*, 2005: 433-434).

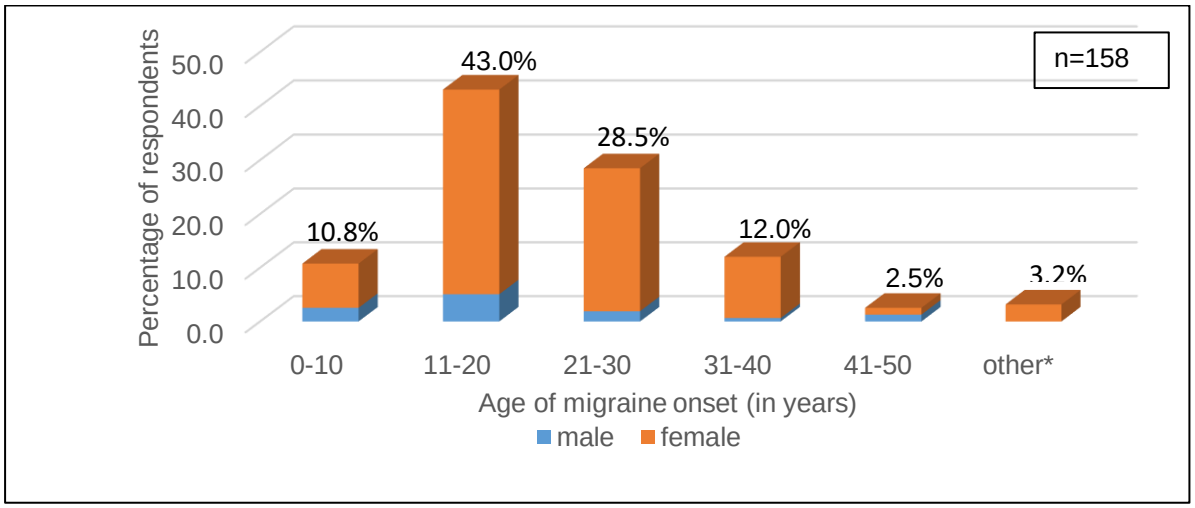
The largest ethnic group in this study were White respondents (81.5%), followed by Coloured (10.6%), Black respondents (4.0%) and Indian respondents (1.2%). “Other” ethnic groups were reported as follows: one African, one Muslim (n=170). The largest group of respondents in this study were White. Literature, reports that Caucasians are more likely to suffer from migraine than other ethnic groups. A study of Americans in Maryland on the variation of migraine prevalence by race reported that the prevalence of migraine was lower in African Americans and Asian Americans than among Caucasians (Stewart, Lipton & Liberman, 1996: 52). African Americans were reported to have less trust in the medical community and are less likely to have ever been seen by a doctor for their migraine or to have been prescribed migraine medication (Nicholson, *et al.*, 2006: 754). Another study in the US, using statistics from National Survey Studies, reported that migraine prevalence was highest amongst Native Americans, then Caucasians, followed closely by Hispanics and Blacks with Asians reporting the lowest prevalence (Loder, *et al.*, 2015: 214). A prevalence study in England reported that Caucasians were twice as likely to suffer from migraine than other races (Steiner, *et al.*, 2003: 519). No studies reporting on the racial demographics of migraineurs in South Africa could be found. The findings for the various ethnic groups in this study could be influenced by a number of factors such as, genetics, mistrust of the health care system, making use of traditional healers, ignorance of the disease in part due to illiteracy and a large percentage of the Black population in Port Elizabeth not having access to private medical aids.

5.3.2 Migraine history

Information about respondents’ migraine such as: age of onset, frequency of migraines, migraine duration, migraine intensity, work days lost due to migraine and family history of migraine will be reported in this section.

5.3.2.1 Age of migraine onset

The onset of migraine can occur at any age. In this study, 43.0% of respondents who reported their age at onset of migraine, indicated that their migraine started in the age range 11 to 20 years (84.5% of these respondents were female). These findings reiterate the literature which reports that menses increases the prevalence of migraine in females with the onset of puberty (Gupta, *et al*., 2007: 321). Figure 5.2 shows the frequency distribution of the age of migraine onset. Most respondents (82.3%) reported that the onset of their migraines was before 30 years of age. No respondents reported onset of migraine after the age of 50 years. Stewart and colleagues (2008) reported that the median age of onset for migraine was 25 years among women and 24 years among men. The onset of migraine in 50% of cases occurred before age 25 years and in 75% of age 35 years (Stewart, Wood, Reed, Roy & Lipton, 2008: 1170). The findings in this study were slightly higher, with 53.8% reporting onset of migraine before the age of 20 years and 82.3% before the age of 30 years.



*These respondents indicated: “unknown”, “very young”, “not sure”, “1990” and “2014”

Figure 5.2 Percentage distribution of respondents according to age of migraine onset

Table 5.5 illustrates the frequency distribution of respondents within gender for age of migraine onset. The frequencies are displayed in brackets and the percentages are *column percentages.* Within gender, more male respondents (22.2%) reported onset of migraine before the age of 10 years than female respondents (9.3%). This finding is consistent with what is reported in the literature. Before puberty, migraine prevalence is higher in boys than girls (Leonardi, *et al.*, 2005: 434).

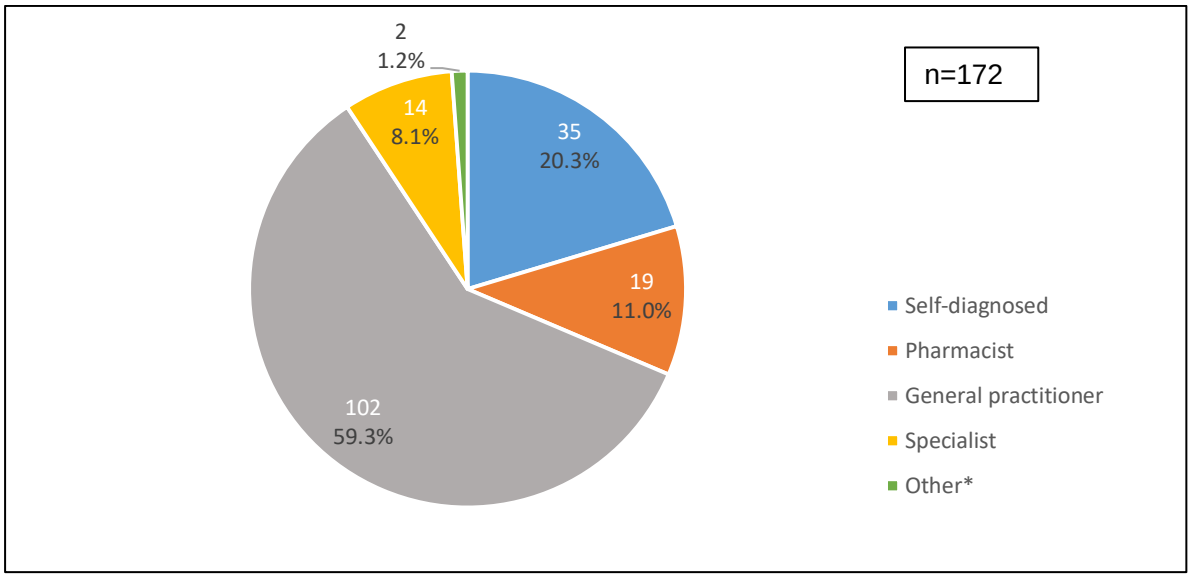
Table 5.5 Frequency distribution of respondents in relation to age of migraine onset within gender

Age on migraine onset (in years)	**Male** (n=18)	**Female** (n=140)	**All respondents** (n=158)
0 to 10	22.2% (4)	9.3% (13)	10.8% (17)
11 to 20	44.4% (8)	42.9% (60)	43.0% (68)
21 to 30	16.7% (3)	30.0% (42)	28.5% (45)
31 to 40	5.6% (1)	12.9% (18)	12.0% (19)
41 to 50	11.1% (2)	1.4% (2)	2.5% (4)
Other	0.0% (0)	3.6% (5)	3.2% (5)
Total	100.0% (18)	100.0% (140)	100.0% (158)

In this study there was only a slight difference in the percentage respondents within gender for the onset of migraine in the age range 11 to 20 years. In the age range 21 to 40 years within gender more female respondents reported onset of migraine than male respondents. Leonardi and colleagues (2005) reported that after puberty, the prevalence of migraine is higher (2.5 to 3 times) in females than males, with the sex ratio varying with age. Hormonal changes associated with the onset of menses could account for much of the sex ratio variation (Leonardi, *et al.*, 2005: 434). However, Lipton and colleagues (2001) reported that the sex ratio variation held true even at the age of 80 years well after cyclic hormonal factors could be a contributing factor. Migraine prevalence is highest during the economic productive years (25 to 35 years), increasing from age 15 years, peaking between the late 30's to early 40's and declining thereafter (Lipton, *et al.,* 2001: 1-3). A Chi-square test was performed, which indicated a significant relationship between gender and age of migraine onset at the 10% level (Chi-square = 10.742; d.f = 5; p-value =0.057). Cramér's *V* showed a small practical significance at 0.261. No studies were found reporting specifically on the age of onset of migraine in South Africa.

5.3.2.2 Person who diagnosed the respondents' migraine

A general practitioner diagnosed migraine in 59.3% of migraineurs in this study. There was a high percentage (20.3%) of a self-diagnosed migraine. Figure 5.3 illustrates the distribution of who diagnosed that the respondent suffered from migraine. A respondent could diagnose their own migraine and then seek medical help if their attacks were not well managed by themselves. Each health care professional in turn could concur with the migraine diagnosis and improve the medical management of migraine attacks.



*These respondents indicated "mother" and "chiropractor"

Figure 5.3 Percentage distribution of persons who diagnosed respondents' migraine

A study by Bigal and colleagues (2008) reported that most patients (87.6%) whose migraine had progressed from episodic to chronic migraine had previously sought care from health care professionals. The most commonly used health care professional was a family practice doctor (80.1%), followed by a neurologist (41.6%) and this was followed by consultation with a headache or pain specialist (26.9%) (Bigal, Serrano, Reed & Lipton, 2008: 562). Some migraine prevalence studies, such as one in Austria, reported low doctor attendance rates (Zebenholzer, *et al.,* 2015: 1). Similarly, in Japan a study reported that 64.4% of patients had not consulted a doctor, with another study reporting that only 7.3% of those with migraine with aura and 5.3% of those with

migraine without aura had consulted a physician (Sakai & Igarashi, 1997: 15; Takeshima, *et al.,* 2004: 8). The findings of this study are much higher than the studies in Austria and Japan for the number of respondents consulting a general practitioner.

5.2.2.3 Migraine initiated by illness or injury

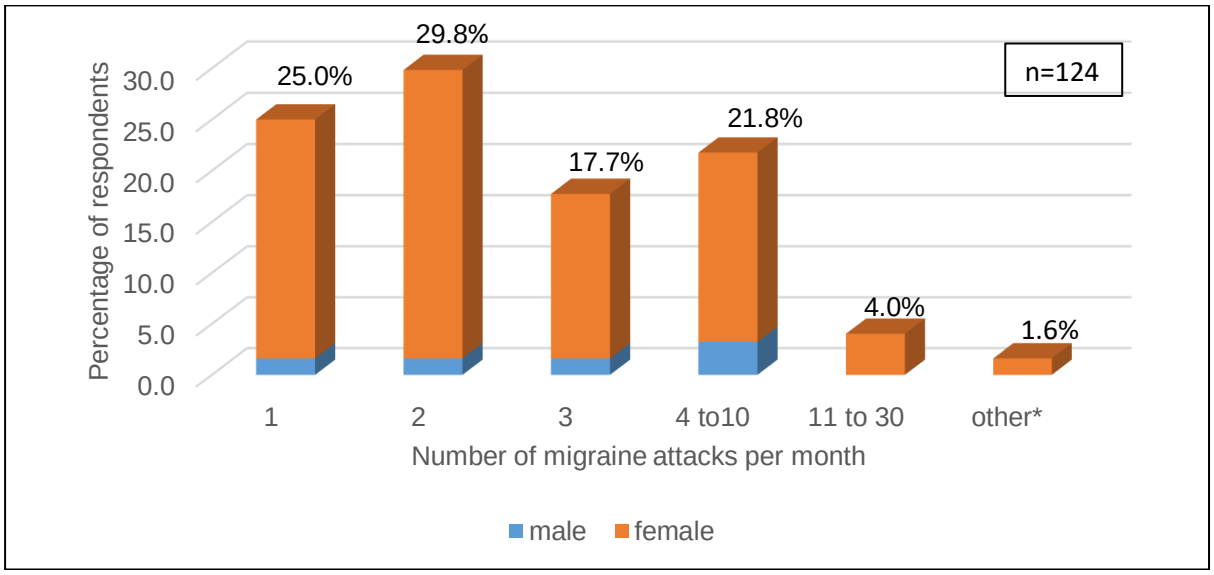
Injury or illness has been reported to be a possible origin of migraine attacks for some patients. Only 6.4% of respondents reported that injury or illness were the cause of their migraines. However, there were 69 respondents who were unsure. The following were reported as the cause of respondents' migraine attacks: one patient reported that their migraine was as a result of meningitis; two respondents reported changes in hormone levels; while three respondents, respectively, reported stress, depression and Meniere's disease as the cause of their migraine. Neck/back injury and concussion were reported by eight respondents as the cause of their migraine. These findings indicated that injury was more likely to be the cause of migraine than a specific illness for respondents in this study.

5.3.2.4 Frequency of migraine attacks per month and per year

Seventy-four percent (128) of respondents indicated how many migraines on average they experienced per month. Figure 5.4 details the number of migraines per month as experienced by respondents with male and female percentages (four respondents did not indicate gender). Twenty-five percent of respondents experienced one migraine per month and 29.8% experienced two migraines per month. Most of the respondents (72.5%) experienced one to three migraines per month.

The largest group of male respondents (40.0% of males) reported that they experienced on average four to 10 migraines per month, while the largest group of female respondents (30.7% of females) reported that they experienced two migraines per month. More female respondents (73.7%) than male respondents (60.0%) experience one to three migraines on average per month. There was a small percentage (4.0%) of respondents, all female, who experienced between 11 to 30

migraines per month. This may suggest that they could fall into the category of “chronic migraine”.



*These respondents indicated “depends” and “every second month”

Figure 5.4 Percentage distribution of respondents according to the number of migraine attacks experienced per month

A smaller percentage of respondents (65.3%) reported on the number of migraines that they experienced per year than had reported on the number of migraines per month (74.0%). Figure 5.5 displays the number of migraines experienced per year by respondents with male and female percentages (two respondents did not indicate gender). One to twelve migraines per year were experienced by 60.4% of respondents.

When comparing the number of migraines experienced by respondents per month to the number of migraines experienced per year, there is a trend towards experiencing more migraines per month than calculated per year. This could be due to respondents not experiencing migraine every month or due to reliance on memory not being accurate. Variations of migraines on average per year as experienced by respondents within gender groups were reported as follows: one to 12 - a higher percentage was reported in female respondents (62.8%) than male in respondents (47.1%), 13 and more - a higher percentage was reported in male respondents (52.9%) than female respondents (37.3%). These results indicated that within gender groups, male respondents tend to experience more migraines on average per year than female

respondents. The results are retrospective and thus reliant on the respondents' memory.

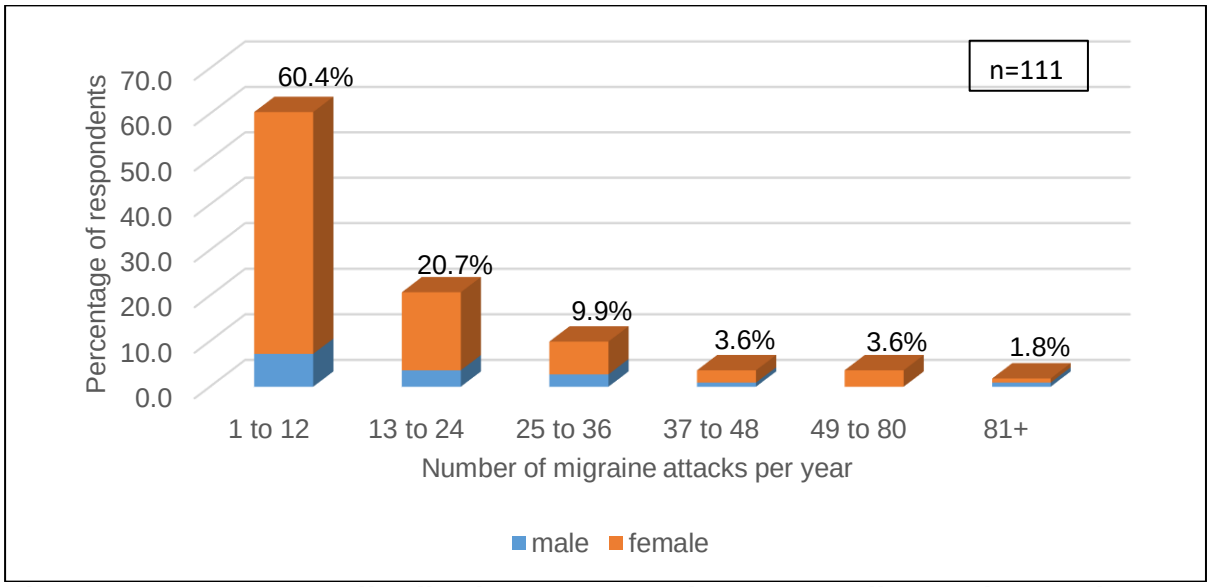


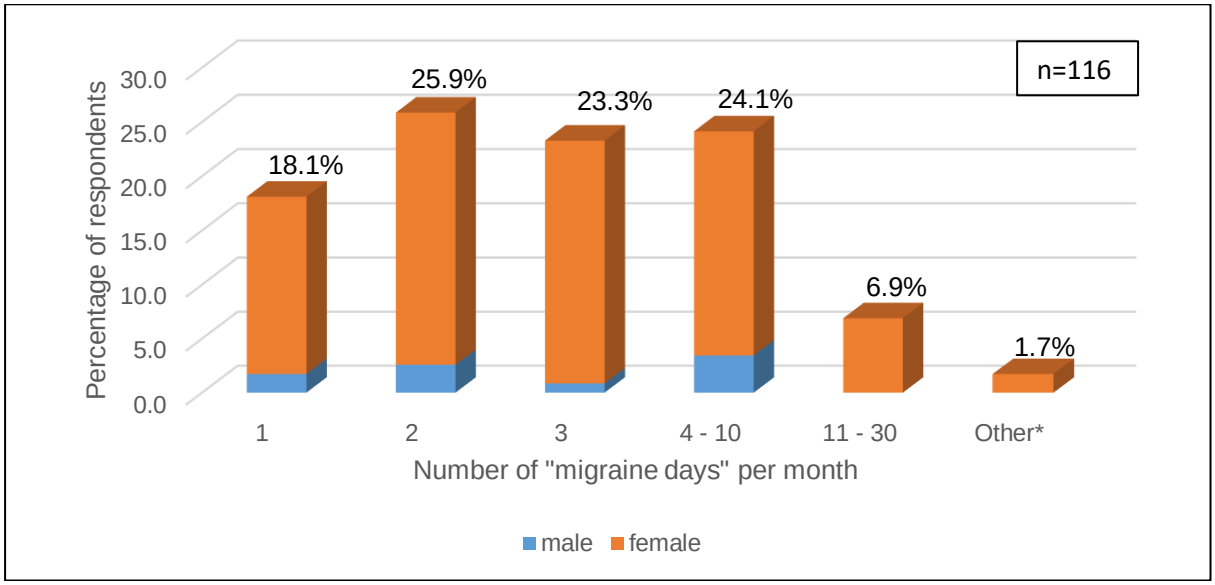
Figure 5.5 Percentage distribution of respondents according to the number of migraine attacks experienced per year

Landy and colleagues (2012) reported in their study an average of 3.6 migraines per month with a standard deviation of 1.87 (Landy, Runken, Bell, Higbie & Haskins, 2012: 366). A study in the US by Lipton and colleagues (2001) reported that frequency of migraine as follows: 14.4% reported two to six migraines per week, 10.8% reported one migraine per week, 36.8% reported one to three migraines per month and 38.0% reported one to 12 migraines per year (Lipton, *et al.*, 2001: 653). The number of migraines per month and per year as experienced by respondents are higher in this study compared to the results of Liptons' study.

5.3.2.5 Number of "migraine days" per month and per year

Nearly 70% of respondents (120) reported on how many "migraines days" on average they experienced per month. Figure 5.6 details the number of "migraine days" experienced per month by respondents with male and female percentages (four respondents did not indicate gender). Nearly 70% of respondents experienced migraine on one to three days per month, while 24.1% of respondents reported

migraine on four to 10 days per month. Within gender groups, one to three “migraine days” per month were experienced by more female respondents (67.9%) than male respondents (60.0%). However, more male respondents (40.0%) experienced four to 10 “migraine days” per month than female respondents (22.6%). There was a small group of female respondents (6.9%) who reported migraine on 11 to 30 days per month.



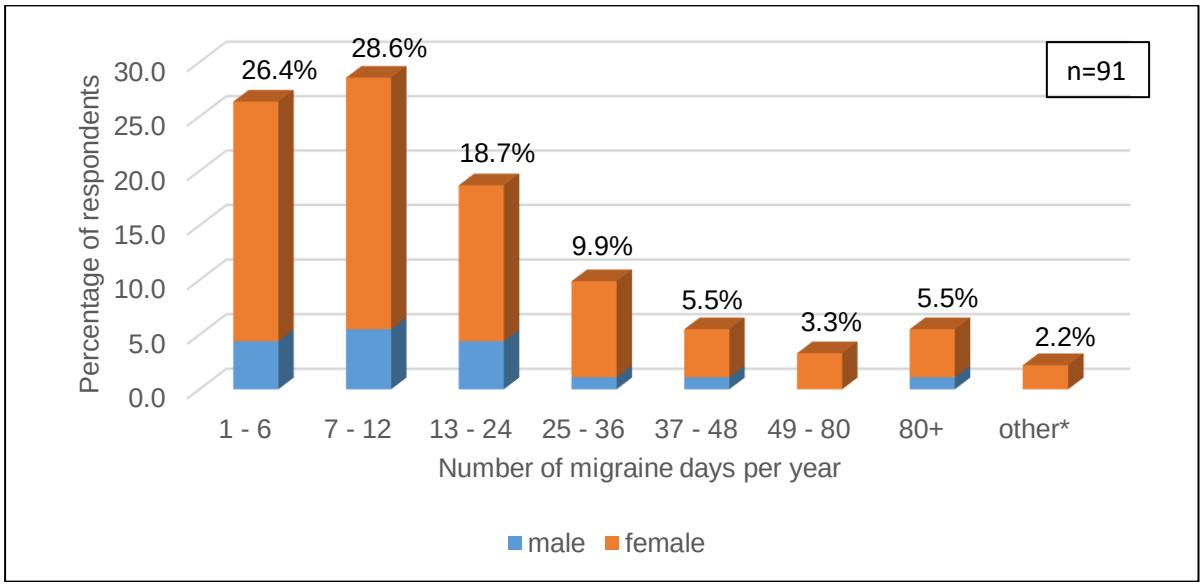
*These respondents indicated “depends” and “every second month”

Figure 5.6 Percentage distribution of respondents according to the number of migraine days experienced per month

Buse and colleagues in a study in the US reported that the majority of migraineurs experienced one to four days of headache per month. In their study, males were more likely than females to have a higher migraine frequency (headache ≥ 10 days per month) (Buse, *et al.*, 2013: 1288). The findings of this study are similar to their findings. However, the following two studies reported a higher number of migraine days on average per month than this study. A study by Wöber and colleagues (2007) reported that the mean number of migraine days per month was 6.1 ± 5.5 (Wöber, *et al.*, 2007: 307). Landy and colleagues reported an average of 6.4 migraines days in a typical month with a standard deviation of 3.10 (Landy, *et al.*, 2012: 366).

Slightly more than half (53.2%) of the respondents indicated the number of “migraine days” per year that they experienced. Figure 5.7 details the number of “migraine days” per year as experienced by respondents with the male and female percentages (one

respondent did not indicate gender). One to six “migraine days” per year were reported by 26.4% of respondents.



*These respondents indicated “depends” and “every second month”

Figure 5.7 Percentage distribution of respondents according to the number of migraine days experienced per year

These result indicates that respondents do not experience migraine every month. Migraine on 24 days or less per year was reported by 73.7% of respondents. The variation in the results of the number of migraines per month compared to the number of migraines per year could be attributed to the fact that migraine varies from person to person as well as from attack to attack. There was a small group of respondents (5.5%) who experience migraine on more than 80 days per year. Migraine is disabling, the more days on which migraine is experienced the more disabling the disease. A survey in the US reported that the mean number of days with a headache was higher in female migraineurs (7.6) than in male migraineurs (7.0) (Lipton, *et al*., 2001: 651).

5.3.2.6 Duration of migraine

The International Classification of Headache Disorders states that a “migraine lasts four to 72 hours with or without medication”. Figure 5.8 gives an overview of the percentage distribution of respondents in relation to the duration of migraine. Migraines lasting less than four hours were reported by 15.9% of respondents in this

study. Effective migraine medication and/or medication taken early in a migraine attack could be responsible for the short duration of attacks reported.

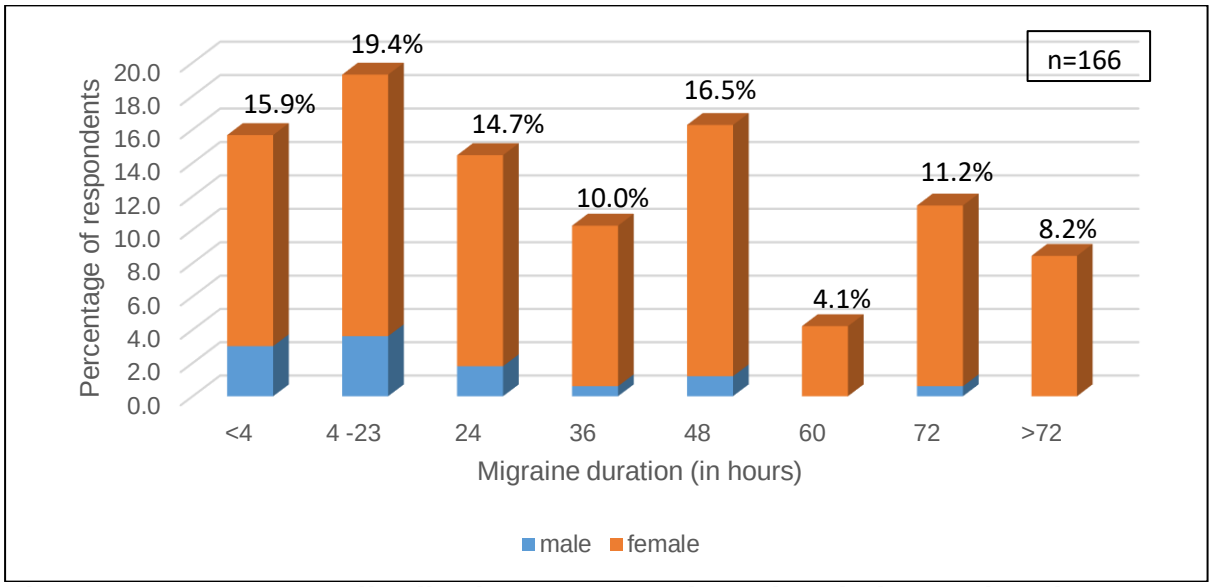


Figure 5.8 Percentage distribution of respondents in relation to duration of migraine

Landy and colleagues (2012) reported that migraines treated within one hour were significantly shorter (less than four hours) than those treated after one hour in a proportion of migraine attacks (Landy, *et al*., 2012: 368). A small percentage of respondents (8.2%, all female) had migraine attacks lasting longer than 72 hours. Fifty percent of respondents' migraines resolved before 24 hours, 60.0% before 36 hours, 76.5% before 48 hours and 91.8% within 72 hours. Male respondents tended to have migraines of shorter duration than female respondents.

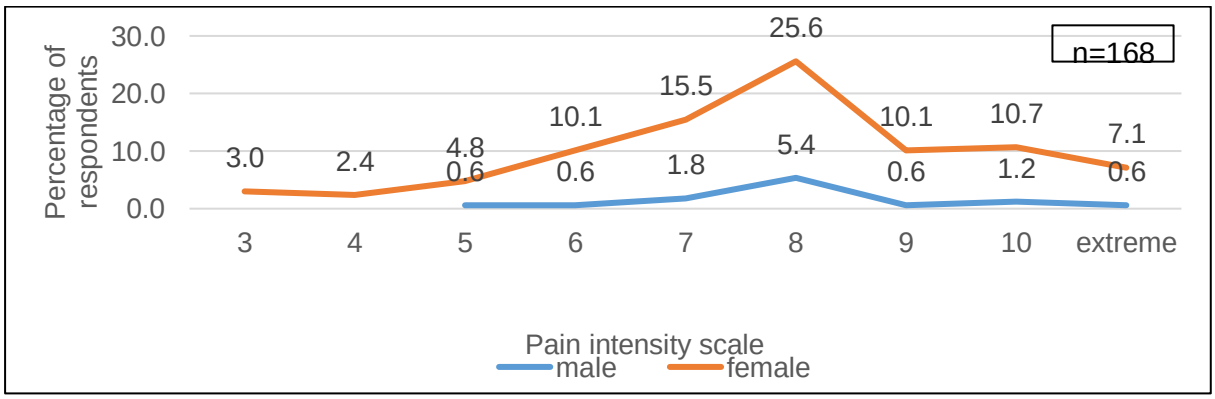
Table 5.6 gives an overview of the percentage distribution of respondents (within each age group) according to migraine duration in hours. The frequencies are displayed in brackets and the percentages are *column percentages.* Nearly half (48.9%) of the respondents, for all age groups, indicated that their migraine resolved within 24 hours. Migraine duration of longer than 72 hours was reported by more respondents in the age group 20 to 29 years (15.0%) than within any other age group. More respondents in the age group 50 to 60 years (18.8%) had migraines of 72-hour duration than for any other age group.

Table 5.6 Percentage distribution of respondents (within each age group) in relation to migraine duration in hours

Migraine duration (in hours)	**Age group** (in years) (n=169)			
	20-29 (n=40)	**30-39** (n=51)	**40-49** (n=46)	**50-60** (n=32)
<4	20.0% (8)	11.8% (6)	17.4% (8)	15.6% (5)
4-23	25.0% (10)	17.6% (9)	15.2% (7)	18.8% (6)
24	5.0% (2)	21.6% (11)	19.6% (9)	10.7% (3)
36	2.5% (1)	15.7% (8)	15.2% (7)	3.1% (1)
48	15.0% (6)	19.6% (10)	15.2% (7)	15.6% (5)
60	5.0% (2)	2.0% (1)	2.2% (1)	10.7% (3)
72	12.5% (5)	3.9% (2)	13.0% (6)	18.8% (6)
>72	15.0%(6)	7.8% (4)	2.2% (1)	10.7% (3)
Total	100.0% (40)	100.0% (51)	100.0% (46)	100.0% (32)

5.3.2.7 Intensity of migraine pain

Respondents were asked to rate the pain intensity of a migraine attack on a scale of one to 10. Figure 5.9 gives an overview of the percentage distribution of respondents according to migraine pain intensity. Eleven percent of respondents reported experiencing pain of three to five on the pain intensity scale. The largest group of respondents (30.2%) reported that the intensity of their migraine pain was eight on the pain intensity scale. Severe pain (upwards of eight on the pain intensity scale) was experienced by 60.5% of respondents. The mean pain intensity for male respondents (7.94; SD = 1.305) was slightly higher than for female respondents (7.67; SD = 1.782). A *t*-test was performed to determine whether there was a relationship between pain intensity and gender. The test showed no significant result ($t = 0.625$; p-value = 0.533).

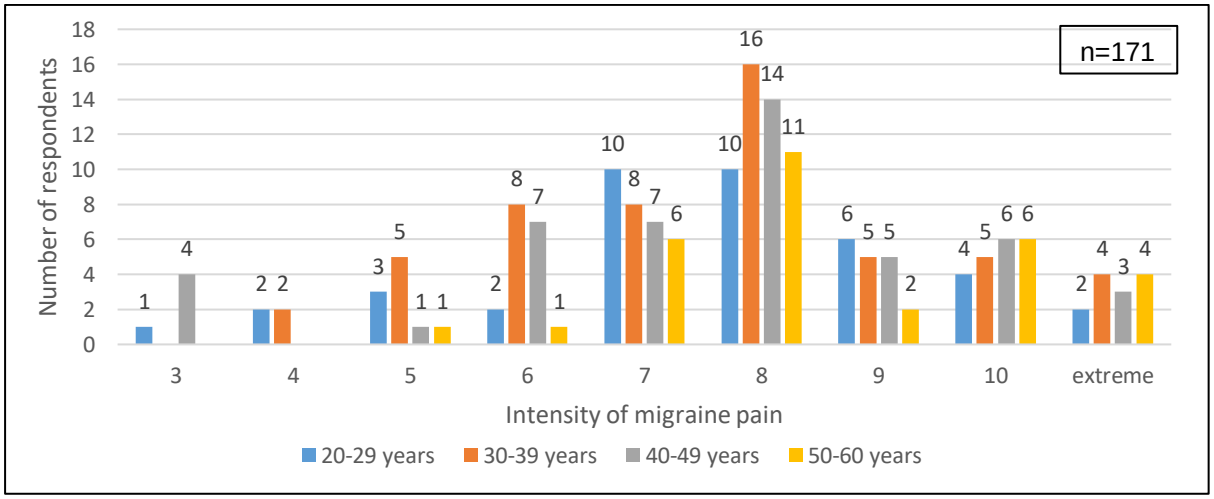


Four respondents did not indicate gender

Figure 5.9 Percentage distribution of respondents in relation to the migraine pain intensity

A study in Austria reported pain intensity to be severe in 38.2%, moderate in 48.3% and mild in 13.5% of migraine attacks (Lampl, *et al.*, 2003). In Unger's (2006: 375) study, 80% of migraineurs reported their pain as being severe (39% for women, 46% for men) or very severe (43% for women, 32% for men), whereas the rest of the subjects reported mild to moderate pain. The pain intensity experienced by respondents in this study is similar to that reported in the literature.

When looking at pain intensity across the various age groups it is clearly seen in Figure 5.10 that eight on the pain intensity scale was reported by the largest percentage of respondents for all age groups. This was followed by seven on the pain intensity scale. Respondents between the ages of 50 to 60 years tended to experience pain of greater intensity compared to respondents in their 20's.



One respondent did not indicate age

Figure 5.10 Number of respondents in relation to the pain intensity scale across the various age groups

5.3.2.8 Frequency distribution of who diagnosed migraine in relation to pain intensity

The pain intensity scale was simplified to three categories, namely low (1 to 5), medium (6 to 8) and high (9 to extreme). Migraine pain is intense so less than five is low intensity pain. Table 5.7 gives an overview of the frequency distribution of who diagnosed respondents' migraine in relation to pain intensity pain experienced by a migraineur. Sixty-one percent of respondents who suffered from medium intensity pain and 65.4% who suffered from high intensity pain were diagnosed by their general

practitioners. Respondents who were diagnosed by a specialist experienced medium or high intensity pain. There was a large number of respondents who experienced high pain intensity (19.2%) who diagnosed their own migraine. The question asked was "who diagnosed your migraine", not who is treating your migraine. Therefore, the group of self-diagnosed high intensity pain respondents could have diagnosed their own migraine but were being treated by a medical professional. These results indicate that the greater the pain intensity the greater the likelihood of a general practitioner having diagnosed that the respondent suffered from migraine. The Chi-square test indicated that there was a statistical significant relationship between who diagnosed respondents' migraine and the pain intensity at the 10% level (Chi-square =14.076, d.f.=8, p-value = 0.080). Cramér's *V* showed a small practical significance at 0.203.

Table 5.7 Frequency distribution of who diagnosed respondents' migraine in relation to pain intensity (n=171)

Person who diagnosed respondents' migraine	Intensity of migraine pain				
	Low (n=19)	**Medium** (n=100)	**High** (n=52)	**All Respondents** (n=171)	
				%	Number
Self-diagnosed	31.6%	19.0%	19.2%	20.5%	35
Pharmacist	31.6%	10.0%	5.8%	11.1%	19
General Practitioner	36.8%	61.0%	65.4%	59.6%	102
Specialist	0.0%	9.0%	7.7%	7.6%	13
Other	0.0%	1.0%	1.9%	1.2%	2
Total	100.0%	100.0%	100.0%	100.0%	171

5.3.2.9 Change in migraine frequency and intensity over time

Migraines can change in frequency and intensity over time. Figure 5.11 gives an overview of the change in migraine frequency for male and female respondents over time. Half of the male respondents reported a decrease in migraine frequency over time, however, only 24.8% of the female respondents reported a decrease in migraine frequency over time. Both percentages for increase in migraine frequency and migraine frequency staying the same were slightly lower for male respondents (22.2%:27.8%) than female respondents (29.5%:32.9%).

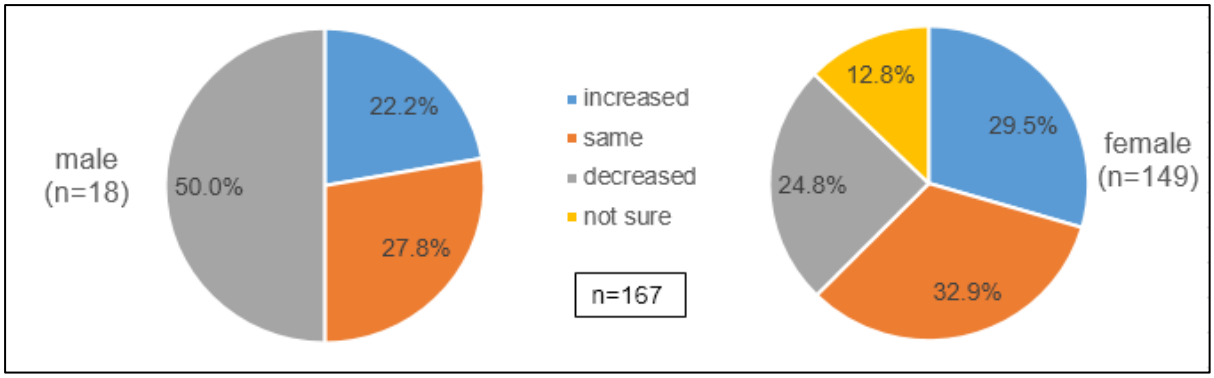


Figure 5.11 Percentage distribution of respondents in relation to change in migraine frequency over time within gender

The percentage distribution of respondents in relation to change in migraine frequency for the various age groups over time is illustrated in Figure 5.12. Older respondents in this study were more likely to report a decrease in the frequency of their migraine attacks, with half of the respondents in their 50's reporting a decrease in migraine attacks. Respondents in their 20's (35.9%) were more likely to report that migraine frequency stayed the same than those in their 50's (21.9%). An increase in migraine frequency was more likely to be reported by respondents in their 40's (31.9%) than for any other age group.

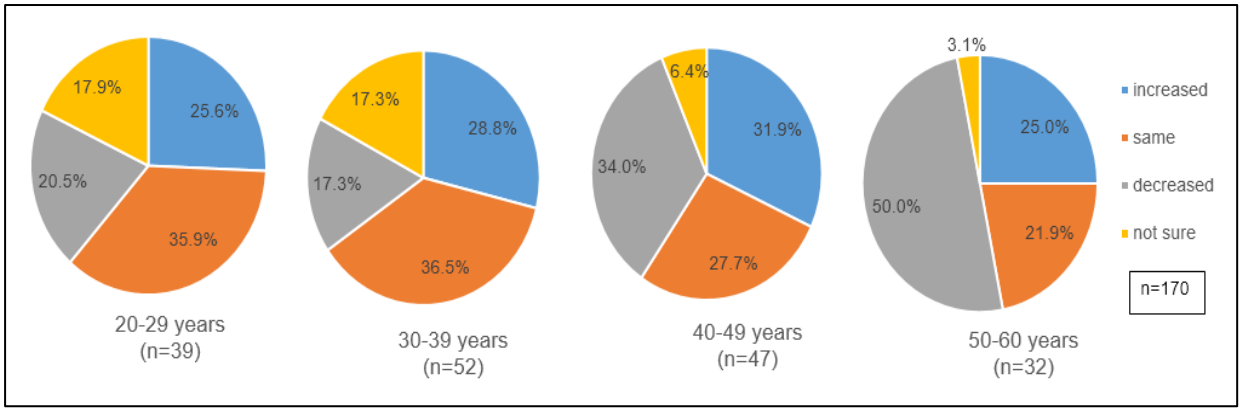


Figure 5.12 Percentage distribution of respondents in relation to change in migraine frequency over time for the various age groups

Figure 5.13 gives an overview of the change in migraine intensity of male and female respondents over time. Migraine intensity stayed the same for approximately 50% of respondents in this study. Male respondents (27.8%) reported a decrease in migraine intensity over time, while female respondents (27.5%) reported an increase in migraine intensity over time.

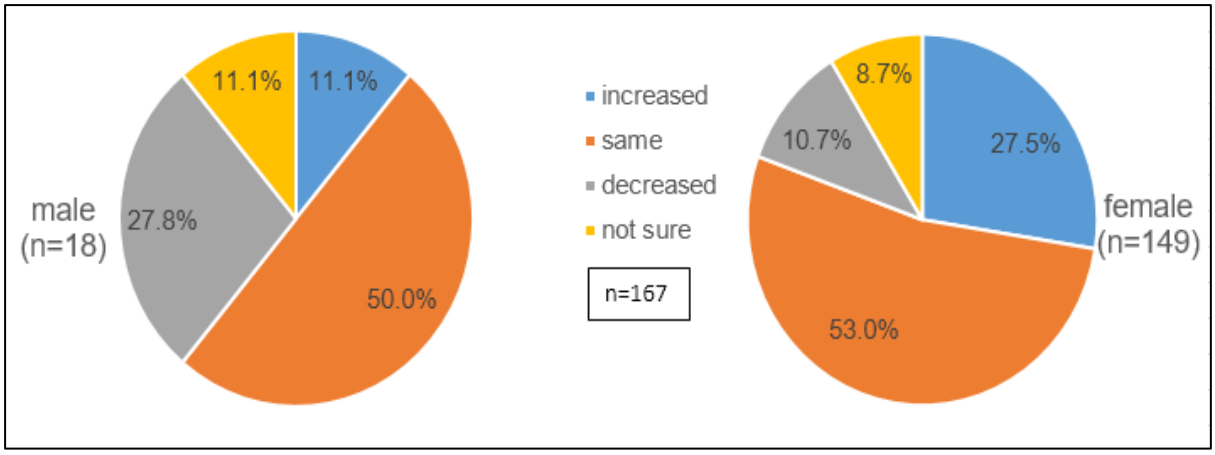


Figure 5.13 Percentage distribution of respondents in relation to change in migraine intensity over time within gender

The percentage distribution of respondents in relation to change in migraine intensity for the various age groups over time is illustrated in Figure 5.14. As with gender, nearly 50% of respondents from all age groups reported that their migraine stayed the same over time. With increase in age, more respondents reported a decrease in migraine intensity while an increase in migraine intensity was reported by younger respondents.

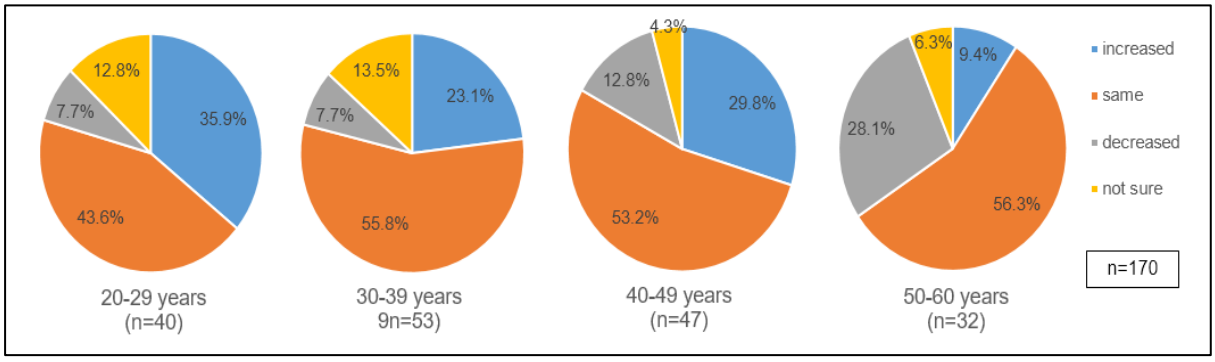


Figure 5.14 Percentage distribution of respondents in relation to change in migraine intensity over time for the various age groups

5.3.2.10 Work days lost due to migraine

The South African Department of Labour, states that a worker may take up to six weeks of sick leave on full pay in a three-year period. Employers may insist on proof of illness before paying a worker for sick leave (Labour.gov.za, 2016). In this study respondents reported migraine sick leave as follows: 16.8% did not report on sick leave taken, 33.5% reported no days taken and 49.7% reported on the number of sick leave days taken. Figure 5.15 gives an overview of the percentage distribution of

respondents in relation to sick leave taken per year (two respondents did not indicate gender). Slightly more than half (51.2%) of respondents who reported sick leave indicated that they took one to seven days per year and 26.2% indicated that they took eight to 14 days per year. Respondents who took more than 14 sick leave days per year were all female. “Other” as an option was reported by five respondents as follows, “one day per attack”, “not sure”, “40%”, “went home if attacks were bad” and “monitored sick leave”. One respondent being on “monitored sick leave” and 16.7% taking more than 14 days per year, showed that migraine could take up a large portion of a person’s sick leave, leaving few days for other illnesses. A study by Lipton and colleagues (2001) reported that approximately 31% of all migraineurs missed at least one day of work in a study in the US (Lipton, *et al*., 2001: 651).

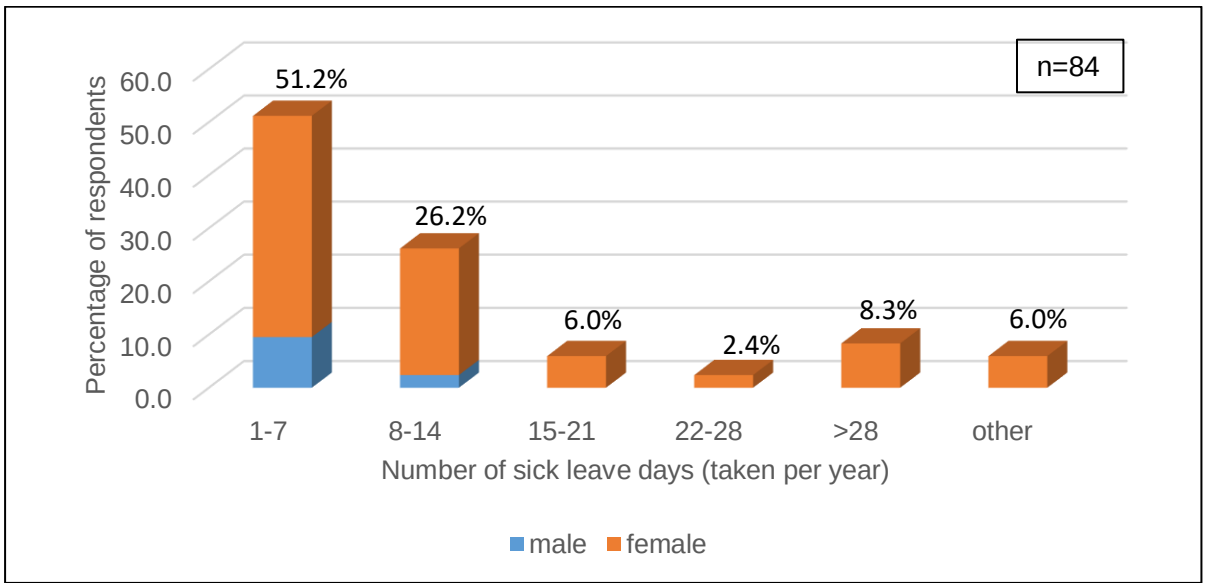


Figure 5.15 Percentage distribution and gender ratio of respondents in relation to work days lost due to migraine

An overview of the percentage of respondents in relation to sick leave days, taken per year, due to migraine for the various age groups is reported in Figure 5.16. More respondents within the 30 to 39 years of age group (37.8%) reported sick leave days due to migraine which was closely followed by respondents within the age group 20 to 29 years of age (29.3%). Those respondents within the 50 to 60 years of age group (13.4%) reported the least sick leave days per year. These findings are in keeping with the decrease in frequency of migraine with age.

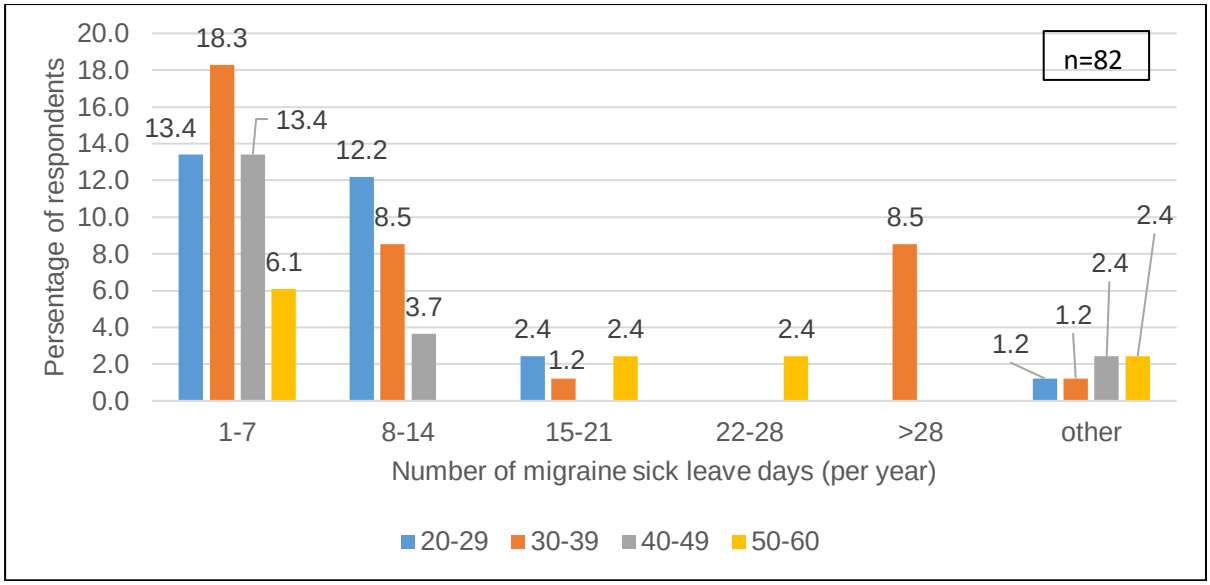


Figure 5.16 Number of respondents in relation to sick leave days due to migraine across the various age groups

5.3.2.11 Family members with migraine

A family history of migraine was reported by respondents as follows: 52.3% of respondents reported a positive family history, 14.0% of respondents were unsure and 33.7% reported no family history of migraine. Table 5.8 gives an overview of the percentage distribution of respondents in relation to having a family member who suffers from migraine. The percentage male (55.6%) and female (52.0%) respondents who reported a positive family history of migraine were similar. Similar to the findings of this study, Low, Cui and Merikangas (2007: 939) reported that in their study, gender of migraineurs did not have an influence on relatives having migraine. Asuni and colleagues (2010) reported that 81% of patients in their study presented a positive family history for headache, which is much higher than the 52.3% of this study (Asuni, Manchia, Deidda, Stochino, Cherchi & Del Zompo, 2010: 1315).

Table 5.8 Percentage distribution of respondents in relation to having a family member who suffers from migraine

Family member with migraine	**Male** (n=18)	**Female** (n=150)	**All respondents** (n=168)
Family member	55.6% (10)	52.0% (78)	52.4% (88)
No family member	33.3% (6)	34.7% (52)	34.5% (58)
Not sure	11.1% (2)	13.3% (20)	13.1% (22)
Total	100.0% (18)	100.0% (150)	100.0% (168)

The total number of relatives reported to suffer from migraine added up to more than the 88 respondents who indicated a positive family history of migraine. The reason for this was that some of the respondents had more than one affected relative. Figure 5.17 gives an overview of the percentage distribution of respondents in relation to family members of respondents who also suffer from migraine. More respondents reported female family members with migraine, with 47.3% of respondents having mothers who also suffered from migraine. One to four family members were reported by respondents to also suffer from migraine in this study. The number of family members with migraine per respondent were as follows: 71% reported one family member, 15.1% reported two family members, 11.8% reported three family members and 2.2% reported four family members. Lemos and colleagues (2012) reported that gender was a risk factor for migraine, with mothers of migraineurs being more frequently affected than expected (Lemos, Alonso, Barros, Sequeiros, Pereira-Monteiro, Mendonça & Sousa, 2012: 3).

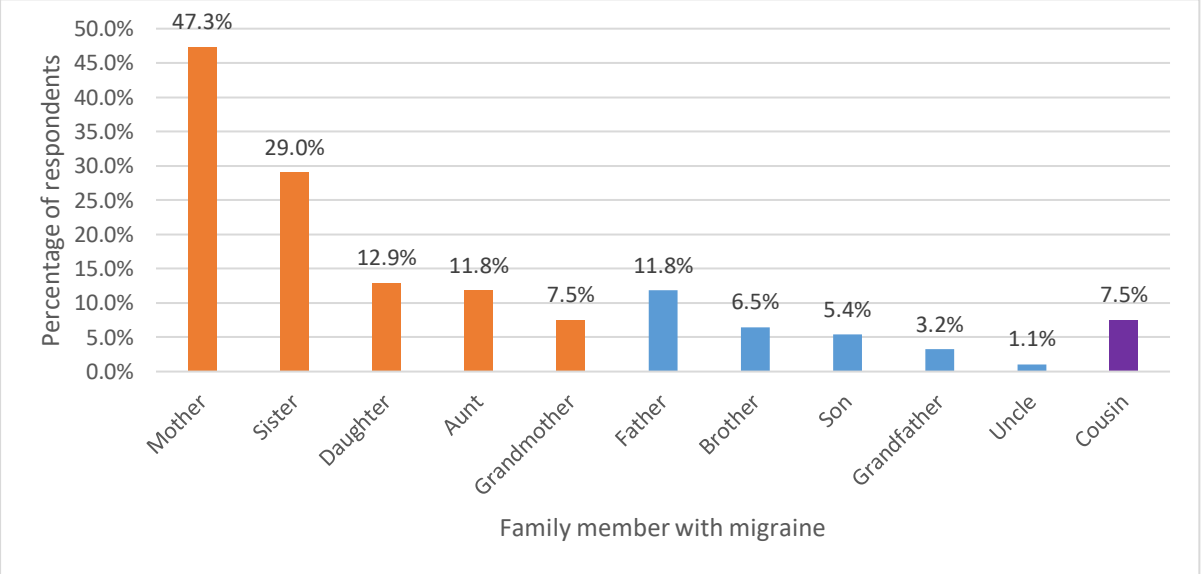


Figure 5.17 Percentage distribution of respondents in relation to family members of respondents who also suffer from migraine

A survey of female students with migraine reported a 53.9% positive family history of migraine (Dzoljic, Vlajinac, Sipetic, Marinkovic, Grbatinic & Kostic, 2014: 82). A study by Vlajinac and colleagues (2004) reported in their study of female students that those who suffered from migraine had a significantly higher frequency of or one or more first-degree and/or second degree relatives who also suffered from migraine. They reported that compared to other migraine subtypes, menstrual migraine had two or

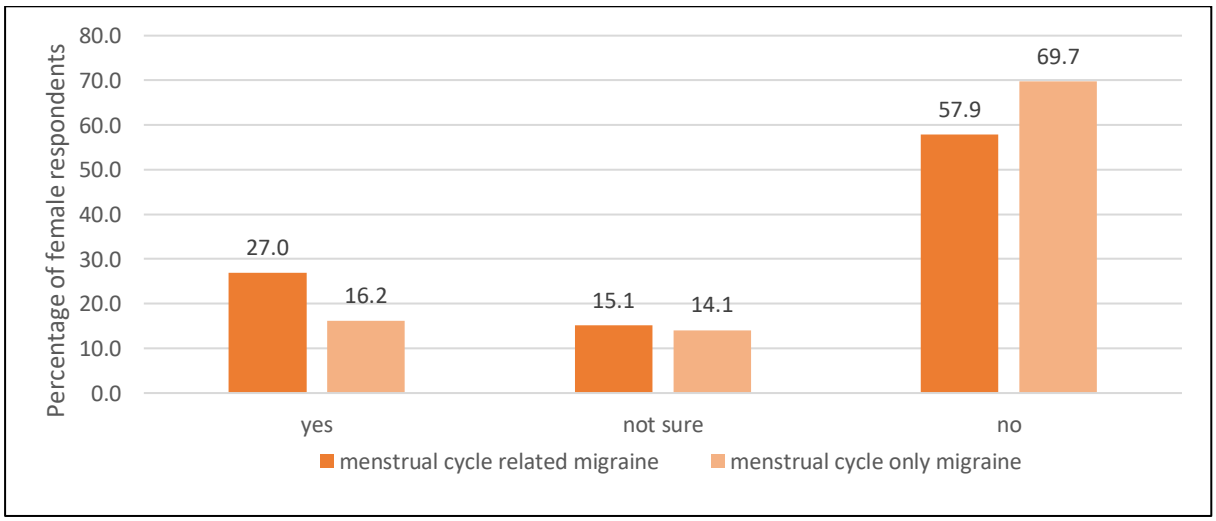
more relatives with migraine (Vlajinac, Dzoljic, Sipetic & Kostic, 2004: 973). Russell (2008: 52) reports that migraine is a genetic illness with a significantly increased familial risk of migraine. The results of this study were in line with literature showing a high frequency of positive family history for migraine among migraineurs.

5.3.3 Female migraineurs

Female respondents reported on the effects that their menstrual cycle, contraceptives/hormone replacement therapy and menopause had on their migraine attacks. Literature reports that the onset of menstruation, taking contraceptive pills, menopause and taking hormone replacement therapy can trigger, worsen or improve migraine in female migraineurs (Paulino & Griffin, 2001: 125).

5.3.3.1 Menstrual cycle and migraine

A large number of female migraineurs develop their headaches at the onset of their first period or sometime during their early teenage years. Menstrual migraine can be divided into pure menstrual migraine and menstrual-related migraine. Figure 5.18 gives an overview of the percentage respondents in relation to migraine related to menstrual cycle and menstrual cycle only migraine.



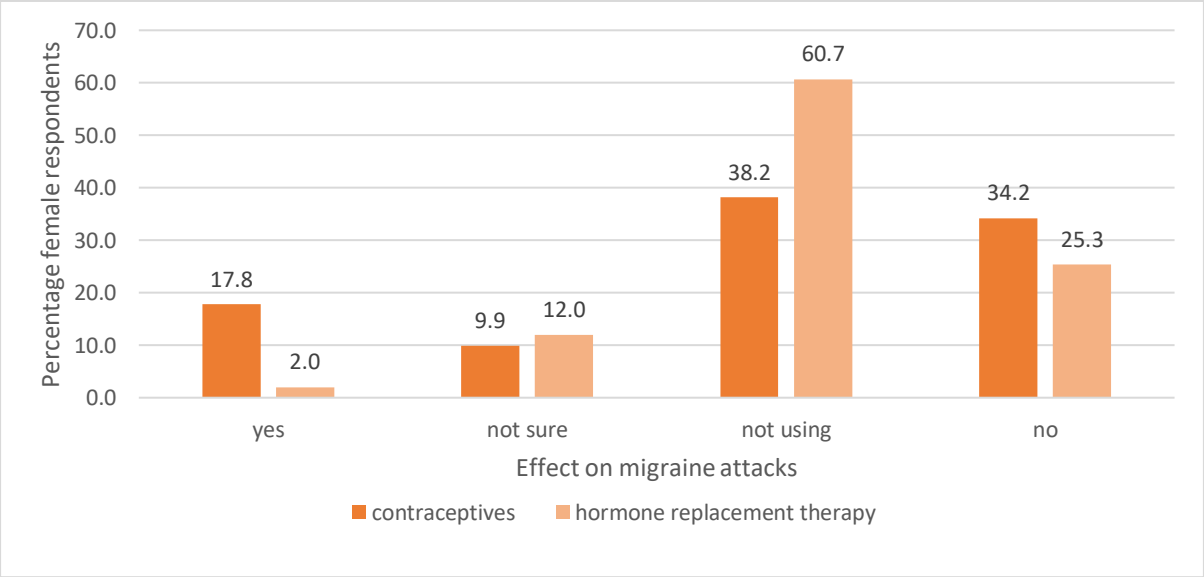
*One respondent did not indicate gender

Figure 5.18 Percentage respondents in relation to migraine related to menstrual cycle (n=152*) and menstrual cycle only migraine (n=142)

Twenty-seven percent of female respondents reported having migraine related to their menstrual cycle and migraine on additional days of the month. About 16% of female respondents reported that they only had migraine related to their migraine cycle. These results are much lower than those reported by Pavlović and colleagues (2015) who reported that for nearly 60% of women there was an association between migraine and menses. Women who experienced menstrual only migraine were more impaired by migraine attacks while those who experienced menses related migraine and migraine on additional days had a higher overall burden, due to more days of migraine per month (Pavlović, *et al.,* 2015: 1).

5.3.2.2 Effect of contraceptives and hormone replacement therapy on migraine

Contraceptive pills and hormone replacement therapy could be responsible for a number of women developing migraine for the first time, due to the fluctuations in hormone levels associated with these pills. These migraines usually stop once the person stops taking the pill (Paulino & Griffin, 2001: 45). Figure 5.19 gives an overview of the percentage of female respondents in relation to the affects of contraceptives and hormone replacement therapy on migraine. Contraceptives were reported by 17.8% of respondents to affect their migraines, while 34.2% indicated that their migraines were not affected by taking contraceptives.



*****One respondent did not indicate gender

Figure 5.19 Percentage distribution of respondents according to contraceptives (n=152*) and hormone replacement therapy (n=150) and migraine

More than half the female respondents in this study (68.1%) were not yet menopausal, thus not using hormone replacement therapy. Two percent of respondents reported that hormone replacement therapy did affect there migraines, while 25.3% reported that hormone replacement therapy did not affect their migraines. Martin (2014: S68) reported that cross-sectional studies suggested that hormone replacement therapy was associated with an increased prevalence of migraine.

5.3.3.3 Menopause and migraine

Female migraineurs could experience various changes (such as an increase or decrease in frequency and intensity) in their migraine patterns with the onset of menopause. Figure 5.20 gives an overview of the effects of menopause on migraine. Migraine attacks stayed the same for 11.1% of female respondents, with 5.6% of female respondents reported increase in migraine attacks, and 5.6% of female respondents reported a decrease in their migraine attacks. A small number of women develop their first migraines around the time of menopause (Paulino & Griffin, 2001: 67). Migraine symptoms can worsen during the premenopausal and menopausal phases for some women, with the majority of women reporting a marked reduction or complete resolution of their migraine after menopause (Paulino & Griffin, 2001: 107). In this study more respondents indicated that their migraine stayed the same at the time of menopause.

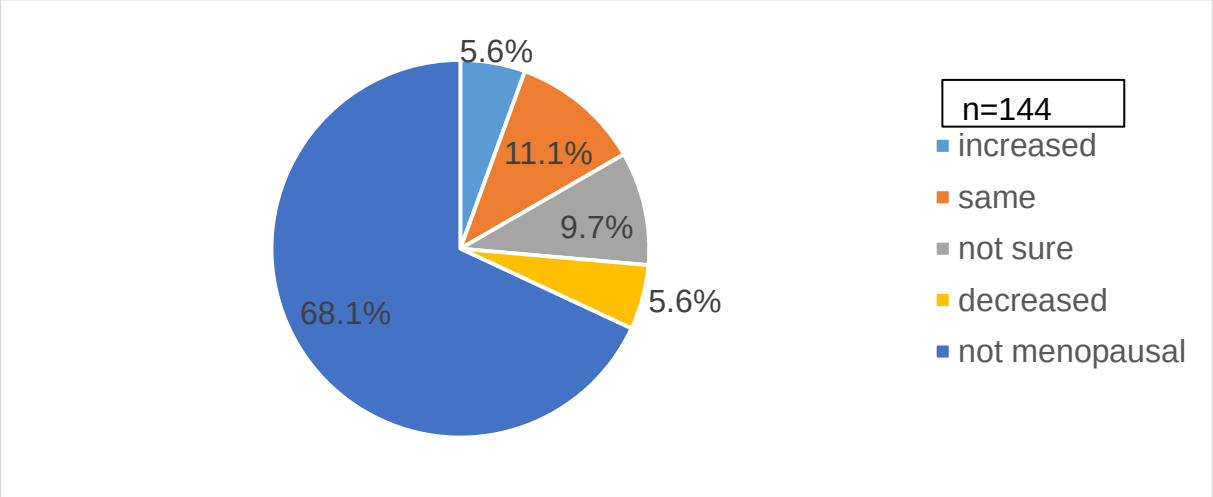


Figure 5.20 Percentage distribution of female respondents in relation to menopause and migraine frequency

5.3.4 Migraine aura

Experiencing an aura before a migraine attack was reported by 43.9% of respondents and only “sometimes” by 22.5% of respondents. Table 5.9 shows the breakdown of how respondents reported whether they experienced an aura before a migraine attack or not. As can be seen from this table, respondents were not sure about auras as there were respondents who reported aura symptoms but did not indicate that they experienced an aura. A higher percentage (79.2%) of respondents in this study reported experiencing an aura than is reported in the literature. Kelman (2004b: 728) in her study of 952 migraine patients reported that 38.0% of patients reported aura symptoms. Jürgens and colleagues (2014: 1419) reported that 31.9% of patients in their study were diagnosed with migraine with aura. All 18 male respondents in this study reported that they experienced auras.

Table 5.9 Experience of auras as reported by respondents (n=173)

Aura experienced	Aura symptoms	No aura symptoms	All respondents	Percentage respondents
Yes	76	0	76	43.9%
Sometimes	38	1	39	22.5%
Not Sure	7	9	16	9.2%
No	10	19	29	16.8%
No response	6	7	13	7.5%
Total	137	36	173	100.0%

Aura was subdivided into various visual auras and sensory auras. Visual auras were experienced by 92.0% of respondents with auras and sensory auras were experienced by 71.5% of respondents, with 62.8% of respondents experiencing both visual and sensory auras. Figure 5.21 gives an overview of the percentage of respondents in relation to the various visual and sensory auras experienced. The ICHD-3 reports that visual auras are the most commonly experienced aura followed by sensory aura and less frequently speech disturbances which are usually aphasic (ICHD-3, 2013: 646).

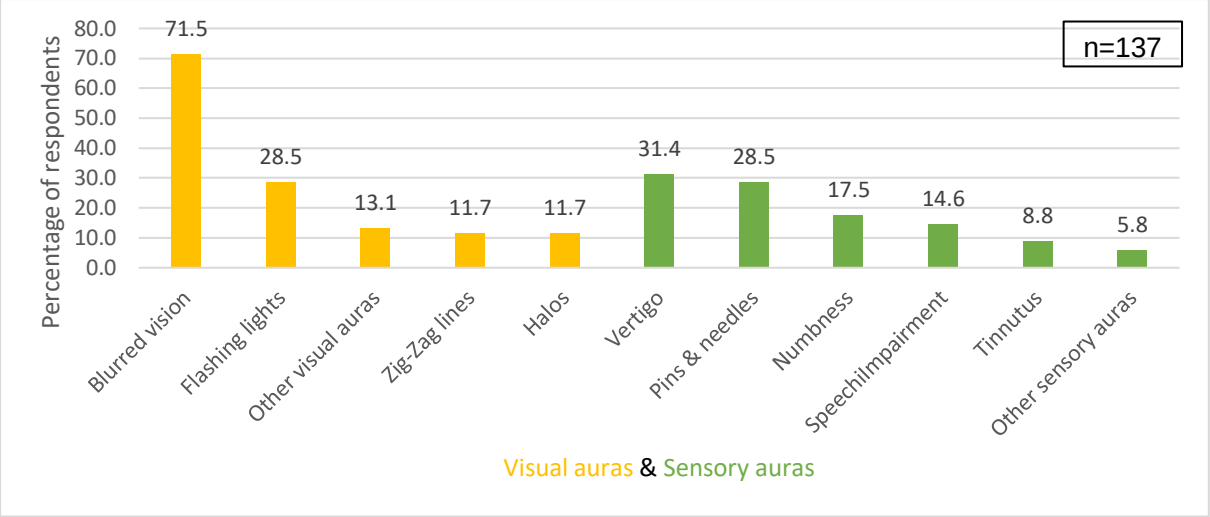


Figure 5.21 Percentage of respondents in relation to various visual and sensory auras

A study of migraine aura symptoms by Viana and colleagues (2016) reported that out of 162 auras evaluated, 97% were visual auras, 32% were sensory auras and 11% dysphasic symptoms (Viana, *et al*., 2016: 416). Russell and Olesen (1996: 355) reported that visual aura symptoms were the most frequent (99%), followed by sensory (31%), aphasic (18%) and motor (6%) symptoms experienced by migraineurs. In their study of 4000 people, migraine with aura was experienced by 163 people, 62 had migraine with aura and headache as well as migraine aura without headache, and seven had exclusively migraine aura without headache. A study by Erikson and colleagues (2003) reported the following findings: 64% of patients had migraine with aura in every attack, 30% had attacks of both migraine auras with and without headache, and 6% had exclusively aura without headache. Males were more likely to have exclusively aura without headache than females (Eriksen, Thomsen, Andersen, Nazim & Olesen, 2004: 567).

In this study blurred vision (71.5%) was the most commonly experienced type of aura followed by vertigo (31.4%). As in this study, a study of visual aura of 122 migraine patients from Southern Brazil and Northern US by Queiroz and colleagues (2011), reported that blurred vision (which is not typically considered an aura phenomenon) was the most frequently reported visual type of aura. The authors reported that visual aura is heterogeneous and pleomorphic (Queiroz, *et al*, 2011: 1652).

5.3.5 Trigger factors for migraine

The response rate for trigger factors was 161 of respondents. Respondents reported on whether they had migraine trigger factors as follows: - 62.4% indicated that they experienced trigger factors, 23.1% were not sure and 6.4% indicated that they did not have trigger factors. When a list of 24 trigger factors was presented to choose from, 89.0% indicated that they experienced trigger factors. Therefore, there was a percentage of respondents who were not sure or familiar with trigger factors. The result of 89.0% of respondents with trigger factors was similar to results seen in some other studies, as can be seen in Table 5.10. There were, however, some studies that report lower percentages in the 70's.

Table 5.10 Summary of studies reporting percentage of migraineurs who reported trigger factors

Country	% migraineurs reporting trigger factors in studies	References
Croatia	77%	(Zivadinov, *et al.*, 2003: 339)
US	75.9%	(Kelman, 2007: 400)
Brazil	100%	(Fukui, *et al*., 2008: 498)
India	87.9%	(Yadav, *et al*., 2010: 44)
US	91%	(Andress-Rothrock, *et al*., 2010: 1366)
US	89%	(Theeler, *et al*., 2010: 790)
Brazil	90%	(Rockett, *et al.*, 2012: 483)
China	80.2%	(Wang, *et al*., 2013: 689)
Italy	72.5% spontaneously 100% specific list	(Baldacci, Vedovello, Ulivi, Vergallo, Poletti, Borelli, Nuti & Bonuccelli, 2013: 834)
India	99%	(Menon & Kinnera, 2013: 221)

The following section gives an overview of the findings related to the different trigger factors identified in this study. Table 5.11 gives the list from the questionnaire of trigger factors which were divided into different categories with sub-categories.

Table 5.11 Categories with sub-categories for trigger factors

Trigger factor	Sub-category of trigger factor
Stress	Emotional stress Work based stress Financial stress Environmental stress
Weather	Heat Wind Cold Thunderstorms
Excessive stimuli	Flashing lights Strong odours Exercise
Food	Caffeine Cheese Chocolate Red wine Skipping meals Processed foods Monosodium glutamate Yeast Artificial sweeteners
Sleep	Insufficient sleep Excessive sleep
Hormonal factors	
Smoking/smoke	

The average number of trigger factors reported per migraineur in this study was five. This differed from Kelman's (2007) study which reported an average of seven triggers per migraineur (Kelman, 2007: 402). Rockett and colleagues (2012) reported that most patients were susceptible to five or more triggers of the 36 triggers offered in their study (Rockett, *et al*., 2012: 483).

5.3.5.1 Stress as a trigger factor

Of the 89.0% of respondents who reported having migraine trigger factors, the most commonly reported factor was stress (78.0%). Stress as a trigger factor was sub-divided into different types of stress. Emotional stress (50.3%) was the most commonly reported stress, followed by in descending order by, work-based stress (45.9%),

financial stress (25.8%), environmental stress (8.8%) and other stress factors (3.1%). Those that reported “other” stress factors reported the following, their studies, being woken suddenly, long exposure to a PC/TV screen, fluorescent lights and the stress of avoiding trigger factors. There were respondents who reported more than one type of stress as a trigger factor.

In the literature, stress is cited as the most common migraine trigger factor with similar percentages to this study being reported for some studies. There are, however, other studies that report much lower figures for stress as a trigger factor. Table 5.12 gives a summary of studies in literature that report stress as a trigger factor.

Table 5.12 Summary of studies reporting stress as a trigger factor

Country	Description of stress as trigger factor	%	Rank in study	References
US	stress	79.9%	first	(Kelman, 2007: 339)
Turkey	emotional stress	79%	first	(Mollaoğlu, 2013: 984)
US	physical and emotion stress	77%	first	(Rothrock, 2008: 499)
Italy	stress	75.8%	first	(Baldacci, *et al*., 2013: 3)
Denmark	relaxation after stress acute stress	70% 59%	first third	(Hauge, *et al*., 2010: 349-350)
Austria	Stress	66.7%	second	(Wöber, Holzhammer, Zeitlhofer, Wessely & Wöber-Bingöl, 2006: 188)
India	emotional stress	70%	first	(Yadav, *et al*., 2010: 44)
Review	stress	58%	first	(Peroutka, 2014: 2)
Croatia	stress	57.8%	first	(Zivadinov, *et al*., 2003: 339)
India	mental stress	42.3%	fourth	(Menon & Kinnera, 2013: 223)

5.3.5.2 Weather as a trigger factor

Weather as a trigger for migraine was the second most common trigger factor reported by respondents in this study. Of the 89.0% of respondents that indicated that they had trigger factors, 43.4% reported being sensitive to weather factors. The most common weather factor was heat (35.2%) followed in descending order by, wind (10.1%), cold

(3.8%) and thunder storms (1.9%). Other weather trigger factors were reported by 3.1% of respondents. They reported mist/change of season, berg winds, lighting and very bright light as trigger factors. The findings of this study are in keeping with the literature as results are similar to some studies. The percentage respondents that reported heat (35.2%) is similar to that reported by Baldacci and colleagues who reported 31.7% for heat as a trigger factor.

According to studies reported in the literature, weather as a migraine trigger factor differs greatly (seven to 60%) (Bolay & Rapoport, 2011: 1426). Variation in reported results can be seen in Table 5.13 which gives a summary of studies that report weather as a trigger factor.

Table 5.13 Summary of studies of reporting weather as a trigger factor

Country	**Description of weather as trigger factor**	**%**	**Rank in study**	**References**
Austria	weather	82.5%	first	(Wöber, *et al*., 2006; 191)
US	weather	53.2%	fourth	(Kelman, 2007: 339)
Croatia	weather conditions and temperature	44.7%	fourth	(Zivadinov, *et al*., 2003: 339)
Italy	weather seasonal variation heat cold	40% 40% 31.7% 29.2%	seventh	(Baldacci, *et al*., 2013: 3)
Review study	weather	39%	seventh	(Peroutka, 2014: 3)
China	weather wind heat cold	31.1% 23.9% 14.2% 13.7%	fourth	(Wang, *et al*., 2013: 689)
India	weather	10.1%	sixth	(Yadav, *et al*., 2010: 44)
Turkey	weather	1.0%		(Kutlu, *et al.*, 2010)

5.3.5.3 Sleep as a trigger factor

Sleep was reported by 64.8% of respondents in this study as a trigger factor and was ranked as the third most often reported trigger factor. Insufficient sleep (57.9%) was reported more often than excessive sleep (9.4%) by respondents as a trigger factor. Literature reports sleep as a migraine trigger between 40% and 60% with the exception of the study by Fukui and colleagues (2008) in Brazil who reported 75.5%. The results of this study are slightly higher than those reported in literature. Table 5.14 gives a summary of studies reporting sleep as a migraine trigger factor.

Table 5.14 Summary of studies reporting sleep as a trigger factor

Country	**Description of sleep as trigger factor**	**%**	**Rank in study**	**References**
Brazil	sleep	75.5%	first	(Fukui, *et al*., 2008: 495)
US	too much/too little sleep	53.5%	second	(Andress-Rothrock, *et al*., 2010: 1368)
Italy	fatigue sleep deprivation excessive sleep	59.2% 45.8% 40.0%	third	(Baldacci, *et al*., 2013: 3)
US	sleep and disturbances	49.8%	fourth	(Kelman, 2007: 400)
India	sleep deprivation	44.4%	fourth	(Yadav, *et al*., 2010: 44)
Review study	sleep	43.0%	sixth	(Peroutka, 2014: 2)
China	sleep disturbances	40.1%	first	(Wang, *et al.*, 2013: 690)
Croatia	sleep disturbances	40.1%	fifth	(Zivadinov, *et al*., 2003: 339)

5.3.5.4 Food as a trigger factor

Food as a possible trigger was ranked fourth in this study with 64.2% of respondents being sensitive to various food factors. Table 5.15 gives a summary of the dietary factors identified in this study. Other food trigger factors listed by the respondents were

citrus (4 respondents), dairy products (3 respondents), sugar (2 respondents), starchy food, wheat, vinegar, biltong, nuts, avocado, almond essence, cinnamon, rich food and champagne.

Table 5.15 Summary of the percentage of respondents in relation to dietary trigger factors

Dietary factor	**% within trigger factors*** (n=159)	**% within food as a trigger factor**** (n=102)
Chocolate	27.7%	43.1%
Skipping meals	26.4%	41.2%
Caffeine	25.8%	40.2%
Cheese	17.6%	27.6%
Red wine	13.2%	20.6%
Other foods	8.8%	13.7%
Processed foods	8.2%	12.8%
Monosodium glutamate	5.7%	8.8%
Yeast	5.0%	7.8%
Artificial sweeteners	3.1%	4.9%

*This column gives the percentage of respondents within trigger factors reported
**This column gives the percentage of respondents within food as a trigger factor

Peroutka's systemic review listed fasting as the fourth most common, and alcohol as the tenth most common, trigger factor (Peroutka, 2014: 3). Fasting (46.3%) was third on Yadav and colleagues' list of trigger factors (Yadav, *et al*., 2010: 44). In Rocket and colleagues' (2012: 487) study on dietary factors, fasting or skipping meals (85.3%) were more common, being second to stress as trigger factors. Andress Rothrock, King and Rothrock reported that skipping meals (39%) was fourth on their list. Alcohol (20.5%) and food (18%) of which chocolate cheese and hot dogs were the main culprits. Caffeine as a trigger factor was low with only eight percent in Rockett and colleagues (2012: 1368) whereas in this study it was higher with 40.2%. Dietary factors (64%) and fasting (63.5%) were listed fourth and fifth on Fukui and co-authors list of triggers (Fukui, *et al*., 2008: 395). In Kelman's study, "not eating" (57.3%) was third as a trigger factor, with alcohol (37.8%) and food (26.9%) much lower down on the list (Kelman, 2007: 396). Eating habits (32.1%) and various food items (12.5%) were low on the list of Zivadinov and colleagues (2003: 339).

A literature review of 45 studies by Rockett and colleagues (2012: 485) to evaluate the published evidence of dietary triggers, found that fasting and skipping meals was the most frequent dietary trigger for migraine. In this study chocolate, skipping meals and caffeine were the most frequent dietary trigger factors reported by respondents. Studies tend to look at alcohol as opposed to red wine as a trigger factor and show that alcohol does have a significant impact on migraine as a trigger. Findings for cheese and red wine in this study are similar to those of Finocchi and Sivori (2012), cheese (30%), wine (20%). They reported multiple dietary triggers in 55% of subjects (Finocchi & Sivori, 2012: 485) which was lower than for this study.

Chocolate was the most reported dietary trigger by respondents in this study which does not reflect what was reported in literature. Lippi and colleagues (2014) did a short review on the ambiguous association of chocolate as a migraine trigger. They analysed 10 epidemiological surveys from 1984 to 2010 and found the frequency of migraine episodes attributed to chocolate to range from 0% to 20%. Three double-blind studies demonstrated that the likelihood of developing a migraine from ingesting chocolate to be the same as a placebo (Lippi, *et al.*, 2014: 216).

Caffeine consumption or caffeine withdrawal have been identified as migraine triggers. In Rockett and associates' literature review, the frequency of coffee as a trigger varied from 6.4% to 14.5% among migraineurs (Rockett, *et al*., 2012: 350). In this study caffeine (25.8%) was the third most common food trigger factor which was a much higher percentage than that reported in the literature.

In this study 3.1% of respondents reported artificial sweeteners as a trigger factor. Lipton and colleagues found that 8.2% of patients reported aspartame as a trigger for their headache (Lipton, *et al*., 1989: 90). A study by Schiffman and colleagues found aspartame less likely to cause migraine, whereas Koehler and Glaros in their study found aspartame to cause a significant increase in headache frequency in some migraineurs (Schiffman, *et al*., 1987: 1181; Koehler & Glaros, 1988: 10).

Literature shows variation in what percentage of respondents report a specific food substance as a trigger factor. Therefore, the findings of trigger factors are similar to some studies and different to others.

5.3.5.5 Excessive stimuli as a trigger factor

In this study, excessive stimuli were the fifth most often reported trigger factor and was reported by 60.4% of respondents. Excessive stimuli were subdivided into sub-categories and reported by respondents in descending order of response as follows: strong odours (30.8%), flashing lights (32.7%) and exercise (6.9%). Table 5.16 shows that in most studies as with this study, strong odours have an impact on migraine as a trigger factor. Excessive stimuli did, however, vary among the different studies.

Table 5.16 Summary of studies reporting excessive stimuli

Country	**Description of excessive stimuli as trigger factor**	**%**	**References**
Croatia	afferent stimuli physical activity	38.9% 29.4%	(Zivadinov, *et al*., 2003: 339)
US	perfume/odour light exercise	43.7% 38.1% 22.1%	(Kelman, 2007: 394)
Brazil	smell activities	35.5% 15.5%	(Fukui, *et al*., 2008: 496)
India	physical exhaustion/travelling	52.5%	(Yadav, *et al*., 2010: 44)
US	odours bright light loud noise	46.5% 7% 5%	(Andress-Rothrock, *et al*., 2010)
China	sunlight noise odour	32.7% 10.2% 9.9%	(Wang, *et al.,* 2013: 690)
Italy	light noise smells/perfume (odour)	25.8% 21.7% 18.3%	(Baldacci, *et al*., 2013: 3)
Review study	auditory visual olfactory	56% 38% 38%	(Peroutka, 2014)

5.3.5.6 Hormonal trigger factors

In this study the role of hormonal trigger factors was very low with only 8.2% of respondents indicated that hormonal factors played a role in triggering migraines. In most studies the menstrual cycle and fluctuating hormones are reported in greater numbers as trigger factors. There are a few studies such as the ones in China and India that report similar values to this study. Table 5.17 gives a summary of hormonal triggers in the literature.

Table 5.17 Summary of studies reporting hormonal triggers

Country	Description of hormonal trigger factors	%	Rank	References
US	hormone	65.1%	second	(Kelman, 2007: 394)
Italy	hormonal fluctuation	64.2%	second	(Baldacci, *et al*., 2013: 835)
Austria	menstruation	51.4%	third	(Wöber, *et al*., 2006: 191)
Croatia	menstrual cycle	49.4%	third	(Zivadinov, *et al.,* 2003: 339)
Review	hormonal	44%	fifth	(Peroutka, 2014: 2)
Brazil	hormonal	43.5	sixth	(Fukui, *et al.*, 2008: 494)
US	menstruation	26.5%	fifth	(Andress-Rothrock *et al*., 2010: 1368)
India	menstruation	12.8%	fifth	(Yadav, *et al.*, 2010: 44)
China	menstrual cycle	8.8%	last	(Wang, *et al.*, 2013: 690)

5.3.5.7 Smoking/smoke as a trigger factor

Twenty-two (13.8%) of the respondents reported smoking as a trigger factor of which six reported second hand smoke as the precipitant. In López-Mesonero and colleagues' (2009) study of 17 Spanish medical students, 12 thought smoking worsened migraine attacks, while 10 perceived smoking as a migraine trigger (López-Mesonero, *et al*., 2009: 101). Smoke as a trigger factor was reported tenth (35.7%) in Kelman's study and last (8.3%) in Baldacci and colleagues study (Kelman, 2007: 394; Baldacci, *et al.*, 2013: 835).

5.3.5.8 Other trigger factors

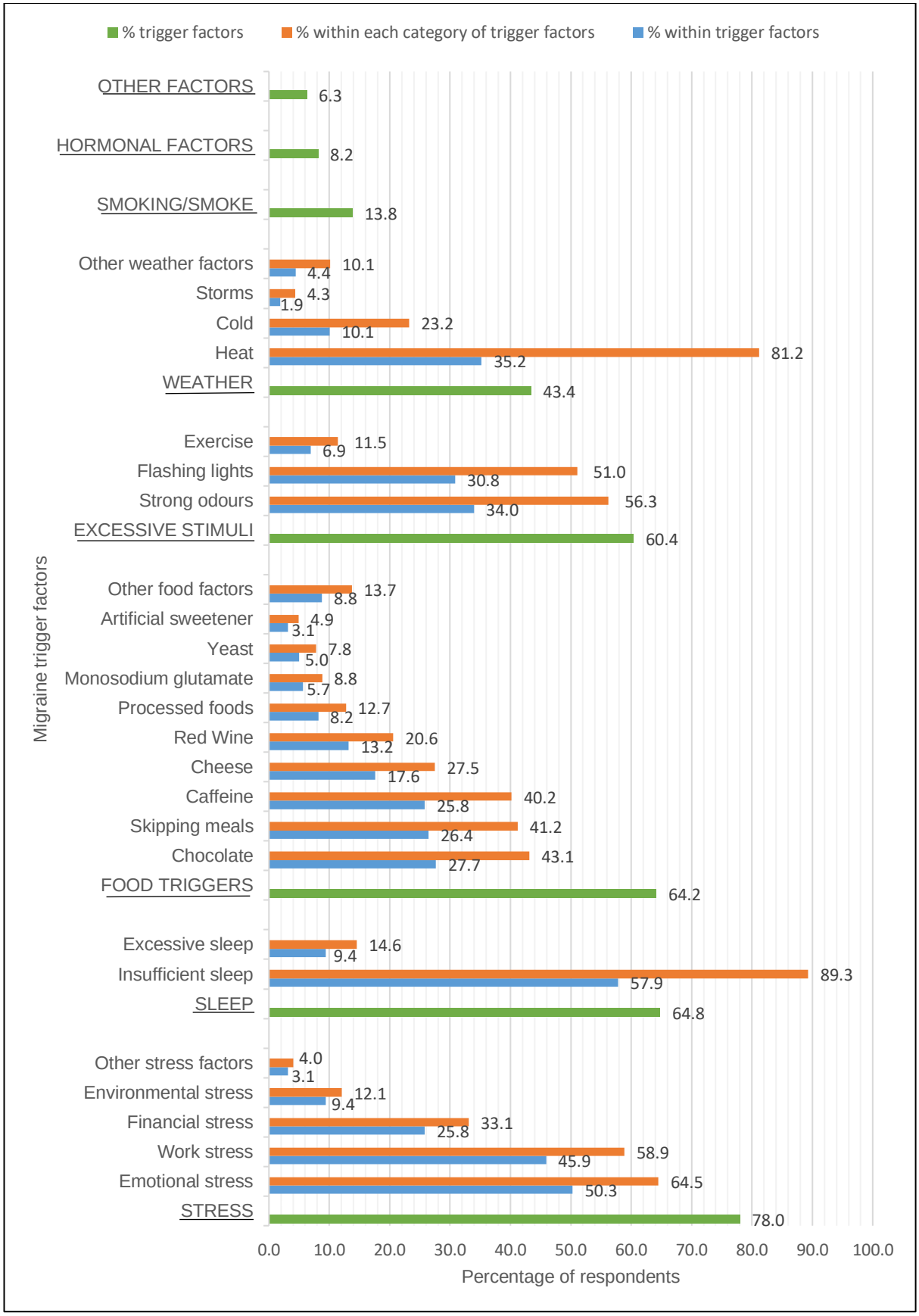
Ten respondents reported on other factors that triggered their migraine. Neck/back pain was reported by 2.5% of respondents. Other trigger factors reported were travelling long distances, flying, driving at night (oncoming car lights), low blood pressure, seasonal pollen and certain body sprays.

5.3.5.9 Conclusion

Figure 5.22 gives an overview of the percentage distribution of respondents with trigger factors and within each category of trigger factors. It can clearly be seen from Figure 5.22 that stress (78.0%) is the most often reported group of trigger factors followed by sleep as a trigger factor (64.8%), food as a trigger (64.2%) and excessive stimuli (60.4%) as a trigger factor. Insufficient sleep (57.9%) is the most often reported trigger factor followed in descending by, emotional stress (50.3%), work-based stress (45.9%) and heat (35.2%). The percentages reported for trigger factors depends on the type of study, the questions asked and the area in which the study took place.

5.3.6 Frequency distribution of trigger factors in relation to the presence of an aura

Table 5.17 illustrates the frequency distribution of trigger factors in relation to the presence of aura. It is clear from Table 5.18 that the majority of respondents (93.0%) indicated that they could identify trigger factors. In this study, there was a one-sided response to the ‘Presence of trigger factors’ as well as a one-sided response at each of the three levels of the ‘Presence of an aura’ which lead to the statistically non-significant result. Stated differently, the presence (or not) of an aura did not result in significantly different likelihoods of the presence of trigger factors (Chi-square =0.453, d.f.=2, p -value =0.797).



Capital letter words are the trigger factor categories
Lowercase words are the sub-categories within the trigger factor category

Figure 5.22 Percentage distribution of respondents in relation to trigger factors

Table 5.18 Frequency distribution of trigger factors in relation to the presence of an aura (n=157)

Presence of trigger factors	Presence of aura				
	No (n=20)	Sometimes (n=38)	Yes (n=99)	All respondents	
				Number	%r
No	10.0%	5.3%	7.1%	11	7.0%
Yes	90.0%	94.7%	92.9%	146	93.0%
All Respondents	100.0%	100.0%	100.0%	157	100.0%

A study by Hauge, Kirchmann and Olesen (2010: 346) stated that migraineurs who suffered from both migraine with and without aura reported more migraine trigger factors for their migraine with aura attacks as opposed to their migraine without aura attacks. In their study, 80% of patients with migraine reported at least one trigger factor and 67% indicated that at least one trigger often or always trigged an attack of migraine with aura. According to Zebenholzer and colleagues (2016) trigger factors are overestimated and/or underestimated in retrospective questionnaires (Zebenholzer, Frantal, Pablik, Lieba-Samal, Salhofer-Polanyi, Wöber-Bingöl & Wöber, 2016: 120). Similar to the findings of this study, the literature reports that those migraineurs who suffer from aura have more trigger factors.

In a study by Hauge, Kirchmann and Olesen (2011: 416) it was stated that the trigger factors such as hormones (62%), light (47%) and stress (42%) were reported to be responsible for triggering 50% or more of migraine with aura attacks. In this study stress as a trigger factor in the presence of aura was reported by 59.5% of respondents which was much higher than Hauges' study. The lowest trigger factor in the presence of aura were hormones (9.2%) in this study, which was significantly lower than that reported by Hauges' study (see Table 5.19). In this study the order of trigger factors from most reported to least reported did not vary when the presence of aura, visual aura and sensory aura was taken into account.

Table 5.19 Aura in the presence of various migraine trigger factors (n=173)

Trigger factors	Presence of aura (n=137)	Presence of visual aura (n=126)	Presence of sensory aura (n=98)	Total number of respondents (n=173)
Stress	59.5% (103)	56.6% (98)	41.6% (72)	72.8% (126)
Sleep	50.3% (87)	45.7% (79)	39.3% (68)	59.5% (103)
Food	48.6% (84)	45.7% (79)	37.6% (65)	59.0% (102)
Excessive stimuli	44.5% (77)	41.0% (71)	35.3% (61)	51.4% (89)
Weather	35.8% (62)	34.1% (59)	27.2% (47)	40.5% (70)
Smoke	10.4% (18)	9.8% (17)	8.7% (15)	13.3% (23)
Hormones	9.2% (16)	8.7% (15)	5.8% (10)	11.0% (19)

In Table 5.20 aura is separated into visual aura and sensory aura and shows the frequency distribution of trigger factors in relation to the presence of visual aura and sensory aura. The Chi-square test indicated that there was a statistical significant relationship between the presence of trigger factors and the presence of visual aura at the 5% level (Chi-square = 7.966, d.f. = 1, p-value = 0.005). Cramér's *V* showed a small practical significance at 0.218. There was no statistical significant relationship between the presence of trigger factors and the presence of sensory aura (Chi-square =0.34, d.f.=1, p-value = 0.560).

Table 5.20 Frequency distribution of trigger factors in relation to the presence of visual aura (n=126) and sensory aura (n=98)

Presence of trigger factors	Visual aura		Sensory aura		All respondents	
	Yes (n=126)	No (n-41)	Yes (n=98)	No (n=69)	%	Number (n=167)
No	4.0%	17.1%	8.2%	5.8%	7.2%	12
Yes	96.0%	82.9%	91.8%	94.2%	92.8%	155

5.3.7 Migraine symptoms

A large number of symptoms are associated with migraine. In this study a list of 20 symptoms were tabled for respondents to choose from. The most common migraine symptoms reported by respondents were sensitivity to light (82.3%), nausea (69.8%), sensitivity to sound (68.6%), neck pain (66.9%) and throbbing headache (65.1%). Figure 5.23 gives an overview the percentage of respondents in relation to the symptoms they experienced. Similar to this study, the National Headache Foundation of the US reports nausea as a common migraine symptom in 73% of patients

(Headaches.org, 2016: 4). Golden, Evans and Hu (2009: 96) reported that 60.4% of patients experienced nausea as a migraine symptom, with other studies reporting lower percentages for nausea, 43.7% (Reed, Fanning, Serrano, Buse & Lipton, 2015: 76) and 49.5% (Lipton, Buse, Saiers, Fanning, Serrano & Reed, 2013: 93-94). In this study, 58.6% of respondents reported nausea and vomiting as migraine symptoms. These results are similar to some literature studies such as the study of elderly French migraineurs who reported nausea and/or vomiting in 56.7% of attacks and vomiting was reported by 57.6% in another study (Tzourio, *et al*., 2003; Golden, *et al*., 2009: 96).

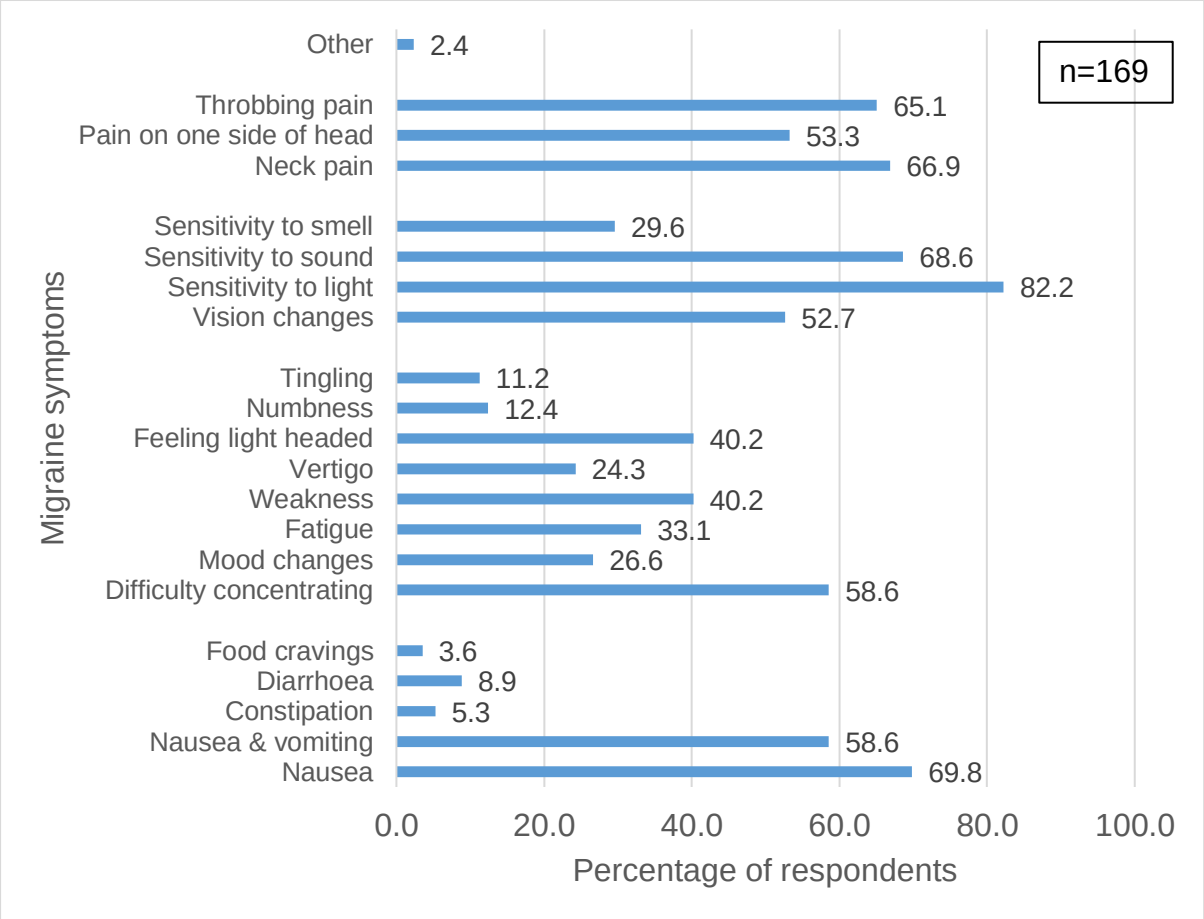


Figure 5.23 Percentage distribution of respondents in relation to migraine symptoms

Difficulty with concentration was reported by 58.6% of respondents and mood changes by 26.6% of respondents in this study. Behavioural or personality changes (63.0%), sensory symptoms such as tingling and numbness (39.7%) and speech or language symptoms (24.7%) were reported by patients in Schürks and colleagues' study (2011: 865). Vision changes were reported by 52.7% of respondents in this study, which is higher than those reported in other studies. Lipton and colleagues (2001) reported that

44% of patients had blurred vision as a symptom of migraine (Lipton, *et al*., 2001: 650). In Schürks and colleagues' (2011: 865) study, 26.5% of female migraineurs reported double vision, and 50.9% reported other visual changes.

The results for sensitivity to light (82.2%), sensitivity to sound (68.6%) and sensitivity to smell (29.6%) were similar to some studies and differed from others. Higher percentages for sensitivity to light were reported by Kelman and Tanis (2006: 549) (93.9%) and Schürks and colleagues (2011: 865) (93.0%). Similar percentages were reported by Mulleners and colleagues (2001: 24) (84.8%), Lipton and colleagues (2001: 650) (85%) and the National Headache Foundation reported that 80% reported light sensitivity (Headaches.org, 2016: 4). Higher percentages were reported for phonophobia by Kelman and Tanis, (2006: 549) (91.4%) and Schürks and colleagues (2011: 865) (86.1%), while Golden and colleagues (2009: 96) (60.1%) reported lower percentages. Higher percentages were reported for osmophobia by Baldacci and colleagues (2014: 45) (58.0%) and similar percentages by Kelman and Tanis, (2006: 549) (28.0%).

Pain was reported as a common symptom. The types of pain experienced by respondents were as follows: neck pain (66.9%), throbbing pain (pulsating) (65.1%) and pain on one side of head (unilateral) (53.3%). Similar results for neck pain were reported by Lampl and colleagues (2015: 1) (66.4%) and Florencio and colleagues (2014: 1203) (69.0%). A study of elderly migraineurs in France, reported unilateral pain (42.1%) and pulsating pain (41.7%) as the type of pain experienced during a migraine attack, which is lower than reported in this study (Tzourio, *et al.*, 2003: 239). In Nachit-Ouinekh and colleagues study (2004: 120) 72.2% of migraineurs experienced unilateral pain while 69.5% experienced pulsating pain as the type of migraine pain, which was similar for unilateral pain but higher for throbbing pain than this study. Similar percentages for neck pain to this study were reported in the literature.

The number of migraine symptoms reported were analysed. The findings were that respondents reported experiencing one to 17 symptoms, with seven symptoms being the most frequently number (25 respondents) reported. Figure 5.24 gives an overview of the percentage distribution of respondents in relation to the number of migraine

symptoms experienced. The average number of symptoms reported was 8.1 (mode=7.0 and standard deviation=3.3). Those respondents who reported less than four symptoms do not necessarily meet the requirements as classified by the ICHD-3 (see Section 2.5 in Chapter two on migraine classification).

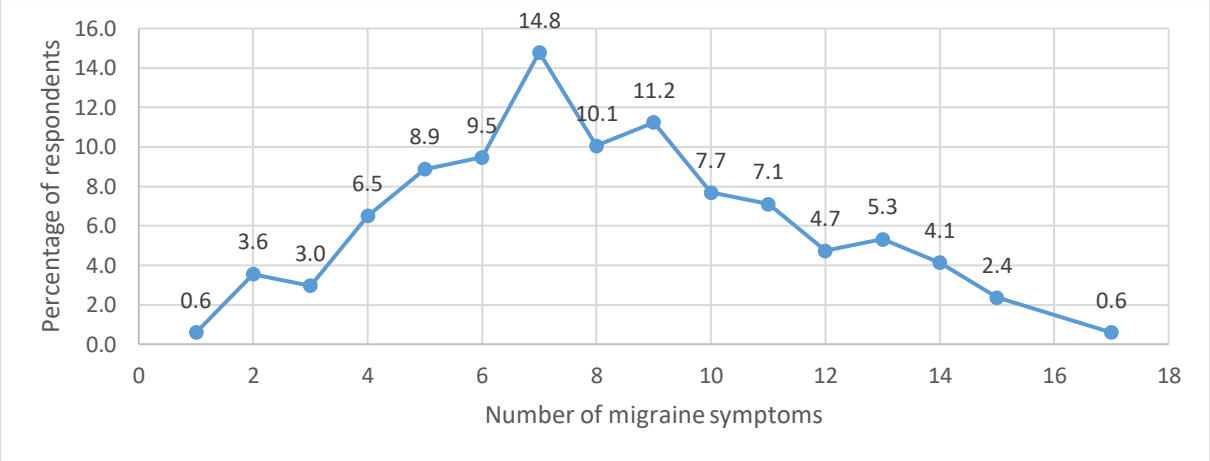


Figure 5.24 Percentage distribution of respondents in relation to the number of migraine symptoms experienced

5.3.8 Frequency distribution of migraine symptoms in relation to the presence of aura

In Table 5.21 the frequency distribution of migraine symptoms in relation to the presence of aura are illustrated. The percentages in the table are the percentages for symptoms within “Experience an aura”, “Experience an aura sometimes” and “no aura” for each column. The frequencies are displayed in brackets and the percentages are *column percentages.* As can be seen in Table 5.19, respondents who suffered from aura were more likely to experience symptoms such as sensitivity to light (81.8%), throbbing pain (70.7%), sensitivity to sound (69.7%) and neck pain (68.7%). Those respondents who only “sometimes” experienced an aura were more likely to experience symptoms such as sensitivity to light (84.2%), nausea (76.3%), neck pain (73.7%) and sensitivity to light (71.1%). Those respondents who did not experience an aura were more likely symptoms such as to experience nausea (85.0%), sensitivity to light (80.0%), pain on one side of the head (70.0%), sensitivity to sound (65.0%) and neck pain (65.0%). There was only a slight variation in the most frequently reported symptoms experienced by respondents who experience an aura, sometimes experience an aura and did not experience an aura, however, the order of frequency

did differ. Nausea and vomiting, sensitivity to light and sound and throbbing one-sided pain are the symptoms that are used to help diagnosis that a patient suffers from migraine (see Section 2.5).

Table 5.21 Frequency distribution of migraine symptoms in relation to the presence of aura

Symptoms	**Presence of aura**			Total (n=157)
	Experience an aura (n=99)	Experience an aura sometimes (n=38)	No aura (n=20)	
Sensitivity to light	81.8% (81)	84.2% (32)	80.0% (16)	129
Throbbing pain	70.7% (70)	60.5% (23)	55.0% (11)	104
Sensitivity to sound	69.7% (69)	71.1% (27)	65.0% (13)	109
Neck pain	68.7% (68)	73.7% (28)	65.0% (13)	109
Nausea	63.6% (63)	76.3% (29)	85.0% (17)	109
Difficulty concentrating	63.6% (63)	50.0% (19)	45.0% (9)	91
Nausea and vomiting	56.6% (56)	52.6% (20)	50.0% (10)	86
Vision changes	54.5% (54)	68.4% (26)	35.0% (7)	87
Feeling light headed	45.5% (45)	36.8% (14)	25.0% (5)	64
Pain on one side head	43.4% (43)	68.4% (26)	70.0% (14)	83
Weakness	43.4% (43)	39.5% (15)	30.0% (6)	64
Fatigue	36.4% (36)	31.6% (12)	30.0% (6)	54
Sensitivity to smell	30.3% (30)	42.1% (16)	15.0% (3)	49
Mood changes	27.3% (27)	26.3% (10)	25.0% (5)	42
Vertigo	27.3% (27)	26.3% (10)	20.0% (4)	41
Numbness	16.2% (16)	10.5% (4)	5.0% (1)	21
Tingling	14.1% (14)	5.3% (2)	15.0% (3)	19
Diarrhoea	11.1% (11)	2.6% (1)	15.0% (3)	15
Food craving	4.0% (4)	5.3% (2)	5.0% (1)	7
Constipation	2.0% (2)	13.2% (5)	5.0% (1)	8

Those respondents who experienced aura were more likely to report throbbing pain (second on their list of symptoms reported) than those who did not experience an aura (fifth on their list of symptoms). Respondents who did not experience an aura where more likely to report nausea (first on their list of symptoms reported) as a symptom than those who did experience an aura (fifth on their list of symptoms). Sensitivity to light was the most commonly reported symptom for respondents who experienced aura (81.8%) and sometimes experienced an aura (84.2%) and second for those who did not experience an aura (80.0%). These findings show that independent of whether you experience an aura or not sensitivity to light is experienced by most migraineurs.

5.3.9 Comorbid conditions

Fifty-nine percent of respondents in this study indicated that they suffered from comorbid conditions. The most frequently reported comorbid condition was anxiety (36.3%), followed by irritable bowel syndrome (28.4%), hypertension (28.4%) and depression (25.5%). Figure 5.25 illustrates the comorbid conditions and percentage respondents that suffered from each condition. The literature states that migraineurs have a 2- to 5-fold greater odds ratio of a major depressive disorder and a 2- to 6-fold ratio of an anxiety disorder (Chai, *et al.*, 2012: 8). A study in Taiwan by Lau and co-authors (2014) reported that the incidence of irritable bowel syndrome was 1.9-fold higher in the migraine cohort than the control group particularly in the young population (Lau, *et al*., 2014: 1198).

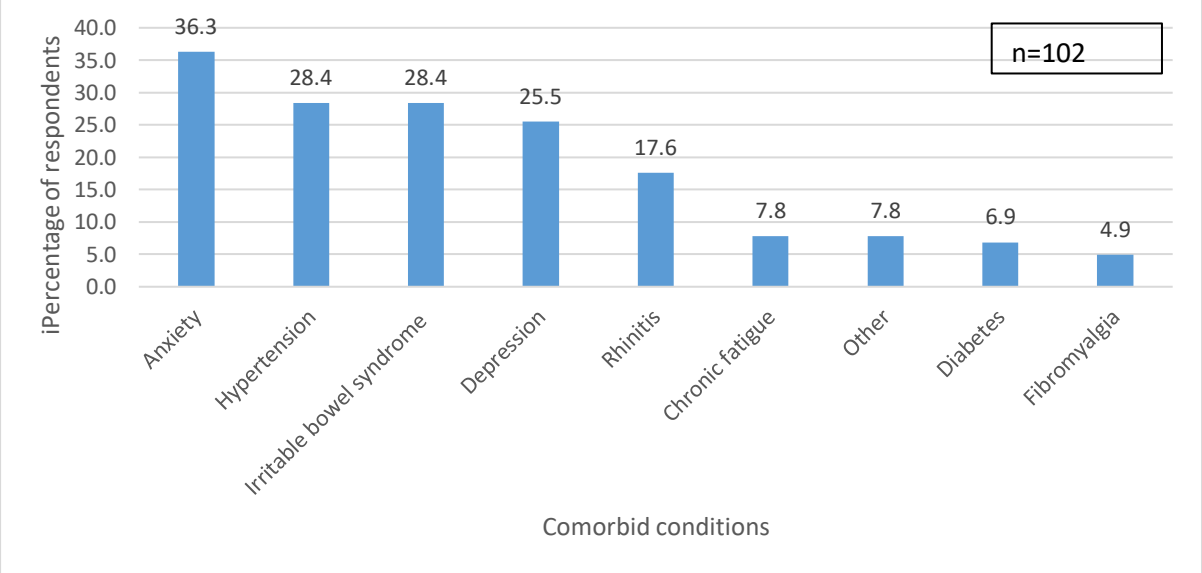


Figure 5.25 Percentage distribution of respondents in relation to comorbid conditions

5.3.10 Abortive medication

Most of the respondents (169) in this study indicated what type of abortive medication they used to treat their migraine attacks. Respondents tend to use more than one type of medication to abort their migraine attacks. If one medication did not work, they would then take another until they had aborted the migraine attack. There were those who would start with a combination analgesic and then move to a migraine kit and those

who would start with a migraine kit and then move to an injection from a doctor. Figure 5.26 gives an overview of the percentage distribution of respondents in relation to the type of medication used to abort a migraine attack. The largest percentage of respondents used single ingredient analgesics (46.5%) followed by migraine kits (39.6%) and combination analgesics (36.5%). Six of the nine combination analgesics used by the respondents contained codeine phosphate.

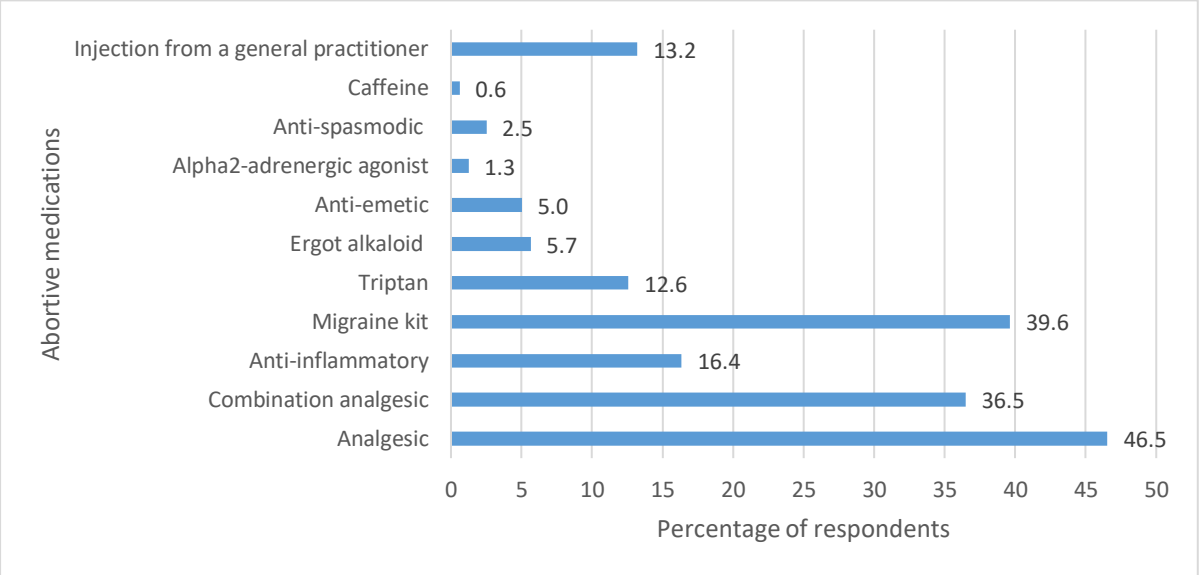


Figure 5.26 Percentage distribution of respondents in relation to the abortive medications that they used

Migraine specific medications such as triptans were used by 12.6% and ergot alkaloids by 5.6%, indicating that only a few respondents were using medication specific to migraine. Eighty percent of the respondents who used a triptan to abort their migraine used rizatriptan. In South Africa, five triptans are available with sumatriptan being the only triptan with a generic available. According to Truter (2015: 447) rizatriptan was the most frequently prescribed triptan in South Africa in her study. Rizatriptan has been shown in clinical trials to be superior or as effective as other oral migraine specific agents in the acute treatment of migraine and has been shown to have more consistent long term efficacy across multiple migraine attacks (Láinez, 2006: 247). Thirteen percent of respondents indicated that they needed to go to a doctor for an injection to help abort a migraine attack. Opioid analgesics may be relied on to relieve severe and chronic pain (Rossiter, 2013: 402).

Patients may attempt to treat themselves with OTC medications, which may be effective in some individuals but in other individuals may lead to the development of

medication overuse or rebound headaches (Unger, 2006: 374). The severity of migraine attacks and their response to treatment may vary from one attack to another. Patients may require only one drug for one attack and several for more severe attacks (Goadsby, *et al*., 2002: 261). Migraineurs rely heavily on OTC medication to which they have easy access rather than having access to migraine-specific therapies that are highly effective in reducing the frequency, intensity, and duration of their headaches (Unger, 2006: 376). There were over 100 combination analgesic available from retail pharmacies in South Africa in 1993 (Truter & Kotze, 1996: 1394). The same trend as reported in literature are seen in this study as the majority of respondents used OTC medication. Triptans are expensive and require a prescription in South Africa. Table 5.22 gives an overview of the cost of triptans in South Africa showing that even generic triptans are expensive. The average price of a "migraine kit" is R18.40 which is more affordable than a triptan. In the US those migraineurs less likely to use triptans included males, African Americans, older adults, and the uninsured (Chu, *et al*., 2012: 213).

Table 5.22 Single dose price of triptans in South Africa (19 April 2016)

Trade name	**Active Ingredient**	**Strength**	**Single dose Price**
Originators			
Naramig®	Naratriptan	2.5 mg tablets	R 59.06
Zomig®	Zolmitriptan	2.5 mg tablets Rapimelts	R 71.53 R 52.14
Relpax®	Eletriptan	100 mg 50 mg	R 85.23 R 63.00
Maxalt®	Rizatriptan	5 mg/10 mg tablets 10 mg wafers	R 73.53
Imigran®	Sumatriptan	50 mg 100 mg Nasal spray Injection	R112.13 R 79.12 R304.90 R627.42
Generic			
Accord Sumatriptan® Migrex® Triptan®	Sumatriptan	50 mg 100 mg 50 mg 100 mg 50 mg 100 mg	R 43.17 R 52.56 R 47.77 R 57.33 R 40.75 R 49.29

(Source: - Database of Medicine Prices, 2016)

5.3.11 Frequency distribution of abortive medication in relation to the presence of aura

The frequency distribution of abortive medication in relation to the presence of aura is illustrated in Table 5.23. Those respondents who did not experience an aura were more likely to use migraine specific medication (38.9%) and migraine kits (33.3%) to abort their migraine attacks. Respondents who experienced an aura were more likely to use migraine kits (29.1%) to abort their migraine attacks, although there was not a large difference in the type of medication used. The results for those respondents who used a migraine kit within aura were as follows: no aura (33.3%), aura sometimes (29.4%) and aura (29.1%). This indicated that there was no real difference between the number of respondents with or without aura who used a migraine kit to abort a migraine attack. Statistical analysis of the results from the migraine questionnaire did not show any significant relationship between those respondents who did or did not experience an aura and the type of medication that they used to abort a migraine (Chi-square = 6.227, d.f. = 6, p-value = 0.398).

Table 5.23 Frequency distribution of abortive medication in relation to the presence of aura (n=138)

Abortive Medication	**Presence of aura**			
	No aura (n=18)	Aura sometimes (n=34)	Aura (n=8)	Total (n=138)
Analgesic	22.2% (4)	41.2% (14)	27.9% (24)	30.4% (42)
Migraine kit	33.3% (6)	29.4% (10)	29.1% (25)	29.7% (41)
Triptans/ Ergots/ Tranquilisers	38.9% (7)	14.7% (5)	25.6% (22)	24.6% (34)
Injection from a general practitioner	5.6% (1)	14.7% (5)	17.4% (15)	15.2% (21)

Aura was divided into visual aura and sensory aura. The frequency distribution of abortive medication in relation to the presence of visual aura and sensory aura was analysed and is illustrated in Table 5.24. There was a slightly higher percentage of respondents who experienced sensory aura (32.2%) who used analgesics to abort

their migraine than those who experienced from visual aura (30.7%). There was a slightly higher percentage of respondents who experienced visual aura (17.5%) who needed to visit a general practitioner to abort their migraine than those who experienced from sensory aura (16.1%). The type of medication used by respondents who experienced visual aura and sensory aura was very similar (see percentages in the “Yes” column for visual and sensory aura). There was no statistical significant relationship between those respondents who experienced either visual or sensory aura and the type of medication used to abort a migraine attack (visual aura: Chi-square = 6.162, d.f. = 3, p-value = 0.104; sensory aura: Chi-square = 1.115, d.f. = 3, p-value = 0.773).

Table 5.24 Frequency distribution of abortive medication in relation to the presence of visual and sensory aura (n=153)

Abortive medication	Visual Aura		Sensory Aura		Total
	Yes	No	Yes	No	
Analgesic	30.7% (35)	35.9% (14)	32.2% (28)	31.8% (21)	32.0% (49)
Migraine kit	30.7% (35)	30.8% (12)	29.9% (26)	31.8% (21)	30.7% (47)
Triptans/ Ergots/ Tranquilisers	21.1% (24)	30.8% (12)	21.8% (19)	25.8% (17)	23.5% (36)
Injection from a general practitioner	17.5% (20)	2.6% (10)	16.1% (14)	10.6% (7)	13.7% (21)
Total	100.0% (n=114)	100.0% (n=39)	100.0% (n=87)	100.0% (n=66)	100.0% (n=153)

5.3.12 Frequency distribution of abortive medication in relation to the number of migraine symptoms

The total number of migraine symptoms experienced by respondents were divided into three categories, namely 1 to 5 symptoms, 6 to 10 symptoms and 11 or more symptoms. Table 5.25 illustrates the frequency distribution of abortive medication in relation to the number of migraine symptoms experienced by respondents. Those

respondents who reported one to five symptoms were more likely to use analgesics (45.2%) and migraine kits (35.5%), than migraine specific medication (19.4%) and an injection from a general practitioner (0.0%) to abort their migraine attacks. Respondents who experienced 11 or more symptoms were more likely to use a migraine kit (35.1%) to abort a migraine attack. The type of medication used to abort a migraine attack did vary greatly for those respondents who experienced six to 10 symptoms. The more symptoms experienced by respondents the more migraine specific was the medication that they used. There was a statically significant relationship, at the 10% level, between abortive medication used and the number of migraine symptoms reported by respondent (Chi-square = 11.175, d.f. = 6, p-value = 0.083).

Table 5.25 Frequency distribution of abortive medication in relation to the number of migraine symptoms (n=149)

Abortive Medication	**Number of Symptoms**			**Total** (n=149)
	1 – 5 (n=31)	6 – 10 (n=81)	11+ (n=37)	
Analgesic	45.2% (14)	32.1% (26)	18.9% (7)	31.5% (47)
Migraine kit	35.5% (11)	25.9% (21)	35.1% (13)	30.2% (45)
Triptans/ Ergots/ Tranquilisers	19.4% (6)	23.5% (19)	29.7% (11)	24.2% (36)
Injection from a general practitioner	0.0% (0)	18.5% (15)	16.2% (6)	14.1% (21)
Total	100.0% (31)	100.0% (81)	100.0% (37)	100.0% (149)

5.3.13 Frequency distribution of abortive medication in relation to the presence of trigger factors

Respondents who experienced trigger factors reported that they used migraine specific medication or visited their doctor for an injection to abort a migraine attack. While those who did not have trigger factors used migraine kits (75.0%) and analgesics (25.0%) to abort their migraine attacks. This showed that those respondents with trigger factors were more likely to seek further medical intervention

to help control their migraine attacks (see table 5.26). The frequencies are displayed in brackets and the percentages are *column percentages.* According to the Chi-square test there was a statistical relationship between abortive medication and the presence of trigger factors (Chi-square = 8.775, d.f. = 3, p-value = 0.032). Cramér's *V* (0.244) shows that this relationship was of small practical significance.

Table 5.26 Frequency distribution of abortive medication in relation to the presence of trigger factors (n=147)

Abortive Medication	**Presence of trigger factors**		Total (n=147)
	No (n=8)	Yes (n=139)	
Analgesic	25.0% (2)	31.7% (44)	31.3% (46)
Migraine kit	75.0% (6)	28.1% (39)	30.6% (45)
Triptans/ Ergots/ Tranquilisers	0.0% (0)	25.2% (35)	23.8% (35)
Injection from a general practitioner	0.0% (0)	15.1% (21)	14.3% (21)
Total	100.0% (8)	100.0% 139)	100.0% (147)

5.3.14 Frequency distribution of abortive medication in relation to the presence of aura and trigger factors

Table 5.27 illustrates the frequency distribution of abortive medication in relation to the presence of aura only for the subgroup of respondents (n=131) who reported trigger factors. The frequencies are displayed in brackets and the percentages are *column percentages*, that is they represent the percentage of respondents within each of the "Presence of aura" levels that used the different abortive medicines. In the presence of both trigger factors and aura (that is the "Yes" column), there were only slight differences in the percentages of the type of abortive medication used to abort a migraine, with injection from a general practitioner the least likely to be used (18.3%). Respondents who had trigger factors and only sometimes experience an aura were more likely to use analgesics (42.4%) to abort their migraine attacks. Those respondents who had trigger factors and did not experience an aura were more likely

to use migraine specific medication (43.8%) to abort their migraine attacks. A Chi-square test was performed to test whether the relationship between “Presence of aura” and “Abortive medication used” was statistically significant, that is whether the type of medication used was dependent on the presence/absence of an aura. The test yielded a non-significant result (Chi-square = 6.499, df = 6, p = 0.370). It can therefore be concluded that although some trends had been observed, it could have occurred only by chance and should therefore be treated cautiously.

Table 5.27 Frequency distribution of abortive medication in relation to aura (only for those who reported trigger factors) (n=131)

Abortive medication	**Presence of aura**			
	Yes (n=82)	Sometimes (n=33)	No (n=16)	Total (n=131)
Analgesic	28.0% (23)	42.4% (14)	25.0% (4)	31.3% (41)
Migraine kit	26.8% (22)	27.3% (9)	25.0% (4)	26.7% (35)
Triptans/ Ergots/ Tranquilisers	26.8% (22)	15.2% (5)	43.8% (7)	26.0% (34)
Injection from a general practitioner	18.3% (15)	15.2% (5)	6.3% (1)	16.0% (21)
Total	100.0% (82)	100.0% (33)	100.0% (18)	100.0% (131)

5.3.15 Preventative medication

Only 12.7% of respondents indicated that they were taking a migraine preventative medication of whom 11.6% reported on their medications. Similar results were reported in the literature. A study in the US that reported a result of 12.4% of migraineurs taking a migraine preventative medication (Diamond, Bigal, Silberstein, Loder, Reed & Lipton, 2007: 355). However Ramadan, Silberstein and Freitag (2000: 1) reported that an estimated six percent of men and 15% to 17% of women in the US had migraine, but only three to five percent of them received prophylactic migraine treatment. A cross-sectional study by Kol and colleagues (2008) reported that that 55% of patients with two or more attacks per month wanted to use prophylaxis, while only eight percent actually used this treatment (Kol, Dekker, Knuistingh Neven,

Assendelft & Blom, 2008: 98). A study in the Netherlands (2002) reported that 12% of migraineurs in their study had initiated prophylactic migraine therapy (Rahimtoola, *et al.*, 2003: 293).

Figure 5.27 illustrates the percentage distribution of respondents in relation to what type of medication they used to prevent their migraines. Sixty percent used only one medication, 30.0% used two medications and 10.0% used three medications to help to prevent a migraine attack. The tricyclic antidepressant amitriptyline (65.0%) was the most commonly used drug either on its own (30.0%) of in combination with other drugs (35.0%). This was followed by the anti-epileptic drug topiramate (40.0%) either on its own (10.0%) of in combination with other drugs (30.0%).

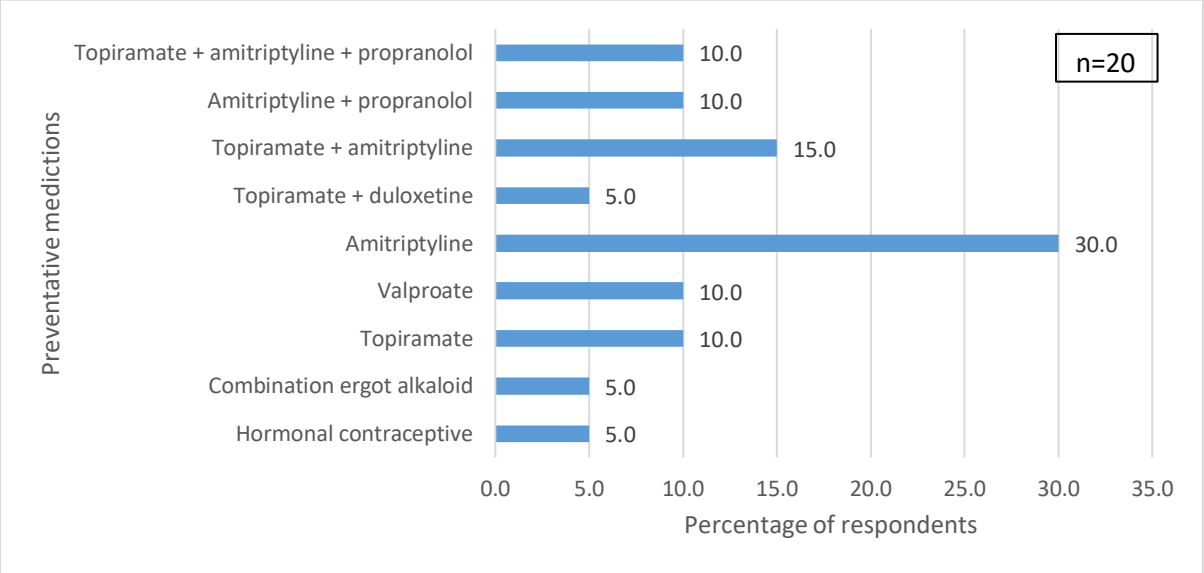


Figure 5.27 Preventative drugs and the percentage respondent

The European Federation of Neurological Societies' (2009) guidelines on migraine prophylactic treatment state that the first choice of drugs are – beta-blockers (propranolol and metoprolol), flunarizine, valproic acid, and topiramate, and drugs of second choice amitriptyline, naproxen, butterbur, and bisoprolol (Evers, Áfra, Frese, Goadsby, Linde, May & Sándor, 2009: 968).

5.3.16 Reason why medication was discontinued

Thirty-five percent of respondents indicated what type of medication they had used that did not work to treat their migraine and gave the reasons as to why they had

stopped the medication. Respondents had tried a number of medications from single ingredient analgesics to triptans to abort their migraine attacks and medications that should prevent a migraine attack. Some respondents indicated that they had discontinued more than one medication. Table 5.28 illustrates the type of medication that was tried and the reason for discontinuing the medication. The most common reason for discontinuing a specific medication was due to the medication not aborting or preventing their migraine attacks. A few of the "other" medications were: clonidine, beta-blocker and injection from a general practitioner.

Table 5.28 Medication tried and reason for discontinuing

Drug class	**Number of respondents**	**Reason for discontinuing medication**			
		Did not work	Side effects	Other	No reason
Analgesics	34	30	4	2	
Ergot alkaloid	13	6	4	1	2
Migraine kit	11	6	4		1
Triptans	5	3		1	1
Tricyclic antidepressants	6	4	3		
Calcium channel blockers	3		1	1	1
Flunarizine	3	1	1	1	
Other	7	5	3	1	

5.3.17 Other medical conditions

Other medical conditions were reported by 32.9% of respondents of whom 43.9% reported more than one condition. The types of conditions reported were diverse with cardiovascular conditions being reported by 47.4% of respondents. This was followed in decreasing order by: physiological conditions (29.8%), hyperlipidaemia (15.8%) and asthma, diabetes and menopause related symptoms (8.8%) respectively.

5.3.18 Complementary and alternative medication

Respondents were asked if they had tried alternative medication to help manage their migraines. Only 18.5% of respondents indicated that they used alternative medication to treat their migraines. However, 48.0% of respondents indicated alternative medications or practices used to treat their migraine attacks. The discrepancy could be due in part to supplements being listed even though they were not specifically taken for migraines. Of those who indicated that they used alternative medication, 41.0% used herbal medicines, 56.6% vitamin and/or mineral supplements, with 32.5% using mind-body practices (behavioural treatments) and 56.6% manipulative and body-based practices (manual therapies).

Figure 5.28 illustrates the percentage distribution of respondents in relation to each alternative medicine used. The vitamins and minerals most used by respondents were magnesium (54.9%) and vitamin B_2 and B_6 (41.2%, respectively).

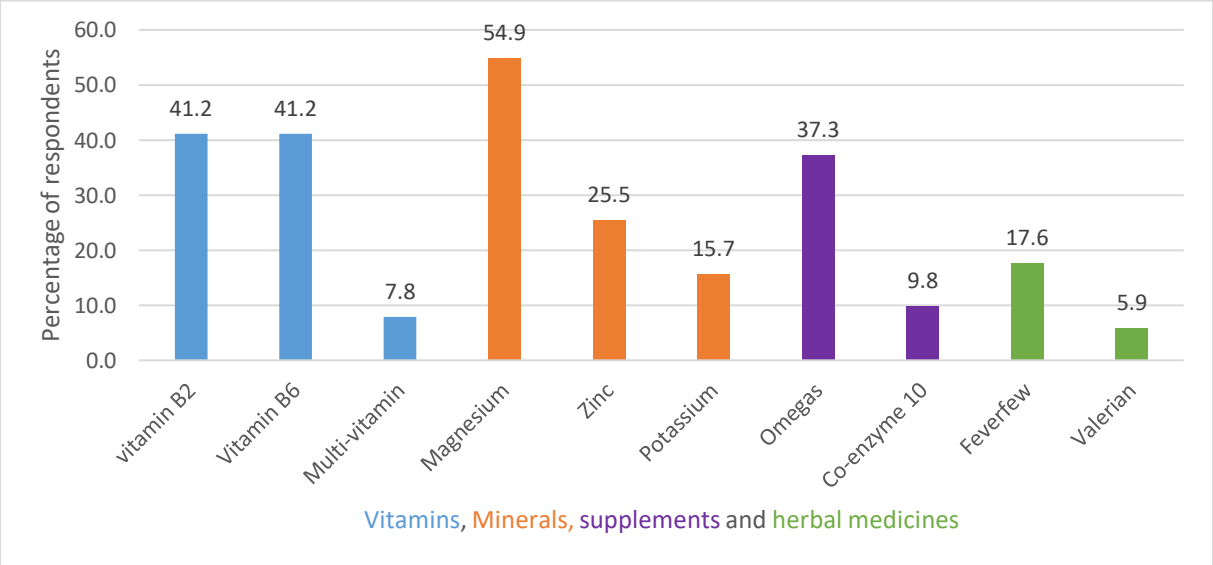


Figure 5.28 Percentage distribution of respondents in relation to vitamin, mineral and herbal medicines used

A review of vitamin B_2 evidence between 1994 and 2014 reported that migraine symptoms were probably reduced when treated with high doses 400 mg of vitamin B_2 (Sadeghi, *et al.* 2014). A study by Demirkaya and colleagues showed that oral magnesium was an effective and well tolerated drug in the prophylaxis of migraine (Demirkaya, *et al.* 2001: 179). In this study, 17.6% of respondents used feverfew to

help treat their migraines. Meschino (n.d.: 1) reported that clinical studies showed that a feverfew supplement reduced migraine attacks by 50% in chronic migraine sufferers**.** Literature supports the use of alternative medications to treat migraine.

Figure 5.29 gives an overview of the percentage of respondents in relation to each behavioural treatment and manual therapy used. Respondents tended to use more manual therapies than behavioural treatments. Holroyd and Drew (2006: 204) reported that behavioural migraine management was clearly effective, with headache activity being reduced by 50% or more for some patients. However, one-third to one-half of behavioural treatment patients do not achieve such success. A visit to a chiropractor (51.8%), physiotherapist (42.9%) and massage therapist (41.1%) were the practices most frequently used by respondents in this study. Chaibi and colleagues (2011: 132), reported that current randomised control trials suggest that massage therapy, physiotherapy, relaxation and chiropractic spinal manipulative therapy might be equally efficient as propranolol and topiramate in the prophylactic management of migraine.

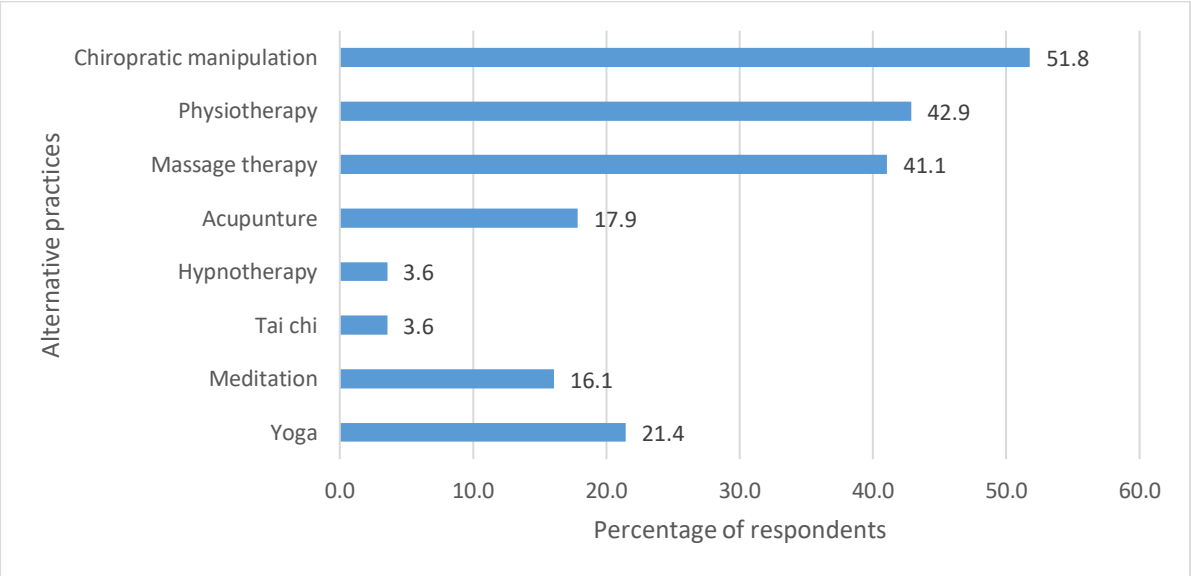


Figure 5.29 Percentage distribution of respondents in relation to behavioural treatments and manual therapies used

Of those who had tried alternative medication (n=83) to treat their migraine, 25.3% reported on what assisted in the treatment of their migraine and 10.8% on what did not assist in the treatment of their migraine. The most successful alternative medications reported to work were in decreasing order as follows: massage therapy

(23.8%), chiropractic manipulation (19.0%), yoga (19.0%), physiotherapy (14.3%) and meditation (14.3%). Acupuncture, omegas, vitamins and magnesium were reported by 9.9% respectively, with only 4.8% reporting that valerian worked. Each alternative medication was reported by one respondent respectively not to work. As with pharmaceutical medications there would be those respondents that benefit from alternative medications and those who do not benefit.

5.3.19 Description of a typical migraine attack

Respondents were asked to describe a typical migraine attack. One page was given in the questionnaire for this response. The type of responses varied from very short to very detailed. Nearly all (94.8%) respondents completed this question of which 93.1% completed the question in English. Most respondents (94.4%) gave a description of the type of pain or mentioned the *pain* they experienced during a migraine attack. *Nausea and/or vomiting* was reported by 75.2% of respondents. *Aura*, whether visual or sensory, were reported by 46.0% of respondents with 42.2% of respondents reporting that they had *light sensitivity* during a migraine attack. Only 6.8% mentioned *trigger factors*, while 36.0% reported on the *medication* used to abort a migraine attack. Insufficient or excessive *sleep* has been reported to trigger migraines, while sleeping in a dark room can abort a migraine attack. Waking up with a migraine was reported by 11.2% of respondents and 39.1% of respondents reported that laying down or sleeping in a dark room helped to resolve their migraine attack.

5.3.19.1 Aura

Examples of descriptions of a visual migraine aura were reported. The four responses below explain the progression of a visual aura similar in some ways to Airy's descriptions of his aura "*a teichopsia starting in the left paracentral area and expanding into the left hemifield, eventually obscuring most of the left field of vision"* (Tfelt-Hansen & Koehler, 2011: 756).

> *"It mainly starts visually. I have trouble seeing as my vision goes light. Like looking into a bright light. Then I start seeing chevron signs."*

"It will start with zig-zag lines in the corner of my eyes. This gradually grows until I have complete blurred vision."

"small round flashes of light - getting worse. I cannot see anything later on."

"I will see an aura like you get when looking into direct sunlight, which is centre vision. This will spread to my peripherals; I will be able to focus only on which is centre vision."

The following respondents were explaining the visual aura symptoms that they experience:

"an aura of flashing lights and vision spots."

"Sometimes I will just get the flashing lights which I see from the sides and the I just know it's coming."

"It starts with of with silver sparks in front of my eyes."

Illusionary splitting shows objects or people that appear to be split or displaced into two or more parts along fracture lines. Below is a respondent's description of their aura:

"I will start noticing that I can only see half a person's face. Half my vision is very strange zig-zag lines flickering…"

"The aura will last about half an hour or longer and is coloured and jiggered like a stain glass window."

As can be seen from these descriptions, visual auras encompass a wide variety of visual symptoms from different patterns to different colours to different fields of vision.

5.3.19.1 Pain

Respondents had varying descriptions of the type of pain and its effect on how they felt about the pain. The following are examples of pain as reported by respondents:

> *“an irritating pain on one side of the head Then the pain increases and it feels like someone is hitting you with a hammer over and over again."*

> *"feels like someone hitting head with hammer eyes want to pop out."*

> *"the pain is almost unbearable, starts with very mild throbbing and then escalates to severe throbbing. It’s as if I can hear my heart beats in head and my head feels heavy."*

> *"my head feels like someone is playing drums. It almost feels as if my head is too heavy for my neck and throbbing pain in lower part of my head. There is no other pain that can be compared to a migraine attack as some people tend to think that you're over reacting."*

Throbbing, beating and hammering were common descriptions of migraine pain reported by respondents in this study:

> *"The pain feels like something wants to break out of my head."*

> *"Pain so much that you want to screw your head off."*

The pain experienced tended to be unbearable as can be seen by the descriptions of wanting to get away from the pain.

5.3.19.3 Trigger factors

Not many respondents reported on their trigger factors (6.8%). The following are a few examples of the trigger factors described by respondents:

"My migraines usually get triggered by stress, strong smells or on very hot days."

"I find my migraines are triggered sometimes by: stress, strong smells- air freshener, perfumes etc. Previously cheese was a problem."

"I found that migraines occur when I did not get enough sleep plus I ate something wrong or it's very hot that day."

From these descriptions of trigger factors it can be seen that there are a number of factors that are capable of triggering a migraine attack.

5.3.19.4 Medication

The descriptions on medication use by respondents, showed that for some there was quick relief ("*a couple of hours"*), while for others several different medications had to be used before the migraine was aborted. The following are a few examples of respondents' descriptions of medication used:

"Sometimes pain tablets will relieve the throbbing. If I am to nauseous to take tablets, or have excessive vomiting, I will go to the doctor for an Injection."

"Get into bed and take a migraine mix. After about two hours I will then take 3-4 Adcodol® and that puts me to sleep."

"I will take 2x normal headache tablets and if it doesn't clear up within two hours I have to take a migraine kit or go to the dr. for an injection."

"I take Maxalt® and lie down and usually within a couple of hours the pain is gone."

It would appear from these descriptions of medication used that migraine-specific medication (rizatriptan) had better results than starting with pain medication (analgesics). However, vomiting was problematic as a person would not be able to take oral medication and thus required a different formulation.

5.3.19.5 Conclusion

The respondents' ability to describe a migraine attack varied from only reporting on the pain associated with a migraine attack to explaining all the phases of a migraine attack. Educating respondents on migraine and migraine-specific-medication could go a long way in reducing the length and number of migraines experienced.

5.3.20 Summary of major findings

The major findings of both the pharmacist survey and the migraine patient questionnaire are summarised below.

The major findings from the *Pharmacist survey* were as follows:

- On average, pharmacists reported that 22 patients consulted them per month about migraine of which 72.2% were female. The average age of these patients was 33.4 years.
- Most patients (80.0%) used their pharmacy for OTC medication/pharmacist-initiated therapy.
- An average of 30 migraine cocktails/kits were sold per month in pharmacies with an average price of R18.40 (standard deviation=R6.42; mode=R15.00; median=R17.00 and interquartile range=R5.00).
- Medications with the highest possibility of being included in a migraine cocktail/kit were: an anti-inflammatory (85.7%), an anti-emetic (85.7%), followed by a combination analgesic (57.1%) which all contained codeine phosphate.

The major findings from the *Migraine patient survey* were as follows:

The majority of the respondents were female (89.3%). More respondents in the age group 30 to 39 years (31.0%) responded than those in the age group 50 to 60 years (18.5%). The largest ethnic group was White respondents (81.5%).

Age of onset in the age range of 11 to 20 was reported by 43.0% of respondents of whom 84.5% were female respondents. No respondents reported migraine onset after 50 years of age. A chi-square test was performed, which indicated a significant relationship between gender and age of migraine onset at the 10% level (Chi-square = 10.742; d.f = 5; p-value =0.057). Cremer's *V* showed a small practical significance at 0.261. Migraine was diagnosed by a general practitioner in 59.3% of respondents. Only 6.4% of respondents reported that injury or illness was the cause of their migraines.

One to three migraines per month was experienced by 72.5% of respondents with one to 12 migraines being experienced per year by 60.4% of respondents. Migraine was experienced on one to three days per month by 67.3% of respondents and on one to 12 days per year by 55.0% of respondents. There was a small group of females (6.9%) who experienced migraine on 11 to 30 days of the month.

A small percentage of respondents (8.2%, all female) had migraine attacks lasting longer than 72 hours. Fifty percent of respondents' migraines resolved within 24 hours, 60.0% within 36 hours, 76.7% within 48 hours and 91.8% within 72 hours.

Severe pain (upwards of eight on the pain intensity scale) was experienced by 60.5% of respondents. Sixty-one percent of respondents who suffered from medium intensity pain and 65.4% who suffered from high intensity pain were diagnosed by their general practitioners. The mean pain intensity for male respondents (7.94; SD = 1.305) was slightly higher than for female respondents (7.67; SD = 1.782). The chi-square test indicated that there was a statistical significant relationship between who diagnosed respondents' migraine and the pain intensity at the 10% level (Chi-square =14.076, d.f.=8, p-value = 0.080). Cramér's *V* showed a small practical significance at 0.203.

A positive family history of migraine was reported by 52.3% of respondents with some reporting more than one family member. More respondents reported female family members with migraine, with 47.3% of respondents having mothers who also suffered from migraine.

Experiencing an aura before a migraine attack was reported by 43.9% of respondents and an aura only sometimes by 22.5% of respondents. Visual auras were experienced by 92.0% of respondents who experienced aura and sensory auras were experienced by 71.5% of respondents, with 62.8% of respondents experiencing both visual and sensory auras. Blurred vision (71.5%) was the most commonly experienced type aura followed by vertigo (31.4%).

Trigger factors were experienced by 89.0% of respondents. The most commonly reported factor was stress (78.0%) followed in decreasing order as follows, sleep (64.8), food triggers (64.2%), excessive stimuli (60.4%), weather (43.4%), smoke/smoking (13.8%) and hormonal factors (8.2%). Insufficient sleep was reported by 57.9% of respondents and emotional stress by 50.3% of respondents.

The most common migraine symptoms reported by respondents were sensitivity to light (82.3%), nausea (69.8%), sound (68.6%), neck pain (66.9%) and throbbing headache (65.1%). The average number of symptoms reported was eight symptoms.

The largest percentage of respondents used single ingredient analgesics (46.5%) followed by migraine kits (39.6%) and combination analgesics (36.5%). Six of the nine combination analgesics used by the respondents contained codeine phosphate. Migraine specific medications such as triptans were used by 12.6% and ergot alkaloids by 5.6%, indicating that only a few respondents were using medication specific to migraine. Eighty percent of the respondents who used a triptan to abort their migraine used rizatriptan. Preventative medication was used by 11.6% of respondents.

The presence (or not) of an aura did not result in significantly different likelihoods of the presence of trigger factors. The Chi-square test indicated that there was a statistical significant relationship between the presence of trigger factors and the presence of visual aura at the 5% level (Chi-square = 7.966, d.f. = 1, p-value = 0.05).

Cramér's *V* showed a small practical significance at 0.218. There was no statistical significant relationship between the presence of trigger factors and the presence of sensory aura.

There was a statically significant relationship, at the 10% level, between abortive medication used and the number of migraine symptoms reported by respondent (Chi-square = 11.175, d.f. = 6, p-value = 0.083). According to the Chi-square test there was a statistical relationship between abortive medication and the presence of trigger factors (Chi-square = 8.775, d.f. = 3, p-value = 0.032). Cramér's *V* (0.244) shows that this relationship was of small practical significance. There was no significant relationship between those respondents who did or did not experience an aura and the type of medication that they used to abort a migraine.

A Chi-square test was performed to test whether the relationship between "Presence of aura" and "Abortive medication used" was statistically significant (for those respondents who had trigger factors), that is, whether the type of medication used was dependent on the presence/absence of an aura. The test yielded a non-significant result (Chi-square = 6.499, df = 6, p = 0.370). It can therefore be concluded that although some trends have been observed, it may have occurred only by chance and should therefore be treated cautiously. These findings indicated that there was no significant relationship between the experiencing of aura or trigger factors and the type of medication used to abort a migraine attack.

Chapter 6

Conclusions and recommendations

6.1 Study overview

Migraine is a neurological disease, defined as a common disabling primary headache disorder, often accompanied by symptoms such as nausea, vomiting, photophobia, phonophobia and osmophobia. Certain criteria need to be met for a headache to be classified as a migraine (ICHD-3, 2013: 644). Women are three times more likely to suffer from migraine than men (Lipton, *et al.*, 2001: 6). Migraine prevalence is highest during the economically productive years (25 to 35 years), increasing from age 15 years, peaking between the late 30's to early 40's and declining thereafter (Lipton, *et al.*, 2001: 4-6).

Migraine pathophysiology has evolved from the vascular theory of Harold Wolff to a neurological disorder. The exact sequence of events that trigger a migraine are still not fully explained (Ravishankar, 2010: 30). There is a genetic component to migraine. Clinical and genetic studies have shown that migraine is a multifactorial disorder with complex interaction between multiple predisposing genetic and modulating non genetic factors (Gupta, *et al.*, 2007: 76). There are four clinical phases of migraine which have been identified, namely, premonitory symptoms, the aura, the headache and the resolution phase (ICHD-3, 2013: 644). Migraineurs have triggers which are precipitating factors that can increase the probability of an attack occurring (Lipton, *et al.*, 2014: 1662). For some migraineurs, the migraine headache phase is preceded by a transient disturbance in neurological function (an aura). An aura could be visual or sensory in nature. Visual auras are the most common type, taking the form of zig-zag lines, bright coloured lights that flicker and change shape and are often surrounded by an area of dimmed or absent vision. Sensory auras could be factors such as numbness of the face, arm or leg, vertigo or speech impairments. Auras usually last 20 to 30 minutes, but can last up to an hour (Schmidt & Willis, 2007: 144). Migraine treatment involves treating acute migraine attacks when they occur (abortive treatment) and developing preventative strategies for reducing frequency and severity of migraine attacks (prophylactic treatment) (Sheikh & Mathew, 2012: 19).

Due to the frequency and incapacitating nature of migraine attacks it has a major impact on personal, social and work life (Siliberstein, 2012:1-2). In the Global Burden of Disease Survey 2010, migraine was ranked as the third most prevalent disorder

and the seventh highest specific cause of disability worldwide (Steiner, Stovner & Birbeck, 2013: 289). The World Health Organization estimates the worldwide prevalence of migraine to be 10% and lifetime prevalence to be 14% (WHO, 2011). The adjusted prevalence of migraine is highest in North America, followed by South and Central America, Europe, Asia and Africa (Chawla, 2015: 10). This low percentage for Africa could be in part due to the fact that there are only a few studies that have been carried out in Africa.

A large number of global studies have been conducted on all aspects of migraine. There are, however, limited studies in South Africa on migraine, with most studies investigating migraine treatment and not auras and trigger factors. This study was therefore conducted with the aim of analysing the relationship between migraine triggers, aura and treatment. The research objectives outlined in Section 1.4 specify the main objectives of both questionnaire-based surveys. The methodology employed for the fulfilment of the study objectives included the undertaking of a literature review and the administration of questionnaire surveys.

The questionnaires surveys were self-administrated and conducted through distribution of questionnaires to pharmacists and migraine patients. The analysis of the pharmacist questionnaire included the type of medication used and information on migraine cocktails/kits sold to migraineurs by pharmacists to treat an acute migraine attack. The analysis of the migraine patient questionnaire included specific information on migraine triggers, auras and treatment as reported by migraine patients which was used to achieve the stated research objectives. The stated research objectives were achieved after conclusion of the empirical analysis. The major findings of the study are summarised in Section 6.2.

6.2 Summary of major findings

The study consisted of two questionnaire-based surveys. The major findings of the pharmacist questionnaire and the patient questionnaire will be discussed separately. The summary will include a synopsis of the results of the analyses discussed in Chapters 5.

6.2.1 Major findings of the pharmacist survey

A total of 18 *pharmacist questionnaires* were analysed. On average, pharmacists reported that 22 (SD=15.3) patients consulted them per month about migraine. The average age of these patients were 33.4 (SD=6.0) years, with most patients being female (72.2%). Most migraine patients (80.0%) came into the pharmacy for OTC medication/pharmacist-initiated therapy. On average, only 19.7% of patients came to the pharmacy with prescriptions for their migraine. Pharmacists indicated that most prescriptions (58.9%) were from general practitioners, with 23.5% patients having prescriptions from specialists.

Fifteen of the 18 pharmacies reported that they sold migraine kits. An average of 30 (SD=21.3) migraine cocktails/kits were reported to be sold by pharmacists per month. Fourteen pharmacists were willing to indicate what medications were included in their migraine cocktails/kits. Medications with the highest possibility of being included in a migraine cocktail/kit were: an anti-inflammatory (85.7%), an anti-emetic (85.7%), followed by a combination analgesic (57.1%). The price of a migraine kit varied from R8.00 to R30.00 (average price: R18.40; standard deviation=R6.42; mode=R15.00; median=R17.00 and interquartile range=R5.00).

6.2.2 Major findings of the migraine patient survey

A total of 173 *Migraine questionnaires for patients* were received and analysed. The majority of respondents were female (89.3%) with the largest group of respondents being in their third decade of life (31.0%). Most of the respondents reported being White (81.5%).

The onset of migraine was reported by 43.0% of respondents to be between the ages of 11 to 20 years, of whom 84.5% were female. Most respondents reported the onset of their migraine to be before the age of 30 years (82.7%). No respondents reported onset of migraine after the age of 50 years. A general practitioner diagnosed migraine in 59.3% of migraineurs. There was a high percentage (20.3%) of a self-diagnosed

migraine. Only 6.4% of respondents reported that injury or illness was the cause of their migraines.

Most of the respondents (72.5%) experienced one to three migraines per month. A small percentage (4.0%) of respondents, all female, experienced between 11 and 30 migraines per month. One to 12 migraines per year were experienced by 60.4% of respondents. Nearly 70.0% of respondents experienced a migraine on one to three days per month. A small group of female respondents (6.9%) reported they experienced a migraine on 11 to 30 days per month. A migraine on 24 days or less per year was reported by 73.7% of respondents. There was a small group of respondents (5.5%) who experience a migraine on more than 80 days per year.

Migraines lasting less than four hours were reported by 15.9% of respondents. A small percentage of respondents (8.2%, all female) had migraine attacks lasting longer than 72 hours. Fifty percent of respondents' migraines resolved within 24 hours, 60.0% within 36 hours, 76.5% within 48 hours and 91.8% within 72 hours.

Severe pain, (upwards of eight on the pain intensity scale) was experienced by 60.5% of respondents. The mean pain intensity for male respondents (7.94; SD = 1.305) was slightly higher than for female respondents (7.67; SD = 1.782). Sixty-one percent of respondents who suffered from medium intensity pain (6 to 8) and 65.4% who suffered from high intensity pain (9 to extreme) were diagnosed by their general practitioners. Respondents who were diagnosed by a specialist experienced medium or high intensity pain. The Chi-square test indicated that there was a statistically significant relationship between who diagnosed respondents' migraine and the pain intensity at the 10% level. (Chi-square =14.076, d.f.=8, p-value = 0.080). Cramér's *V* showed a small practical significance (0.203).

Just more than half (52.3%) of respondents had a positive family history of migraine. More respondents had female family members with migraine, with 47.3% of respondents having mothers who also suffered from migraine. The number of family members with migraine per respondent were as follows: 71% one family member, 15.1% two family members, 11.8% three family members and 2.2% had four family

members. This is consistent with clinical and genetic studies which show that migraine has a genetic component.

Experiencing an aura before a migraine attack was reported by 43.9% of respondents and 22.5% of respondents reported that they only “sometimes” experiencing an aura. Visual auras were experienced by 92.0% of respondents who experienced an aura and sensory auras were experienced by 71.5% of respondents, with 62.8% of respondents experiencing both visual and sensory auras. Blurred vision (71.5%) was the most frequently experienced type of aura experienced followed by vertigo (31.4%). More respondents reported experiencing auras in this study compared to literature findings which report that 30% to 40% of migraineurs experience auras, however, as with literature more respondents reported visual auras than sensory auras. The higher percentages in this study could be a reflection of the respondents limited understanding of what an aura is.

Almost all of the respondents (89.0%) reported trigger factors. As expected stress (78.0%) was the most common trigger factor, with 50.3% experiencing emotional stress. Sleep as a trigger factor was experienced by 64.8% of respondents with insufficient sleep (57.9%) more likely to be a trigger factor than excessive sleep (9.4%). Food triggered migraine in 64.2% of respondents with chocolate (27.7%), skipping meals (26.4%), caffeine (25.8%) and cheese (17.6%) being the most commonly reported. Excessive stimuli as a trigger factor were reported by 60.4% of respondents: strong odours (35.2%) and flashing lights (30.8%) being more likely to trigger a migraine than exercise (6.9%). Weather can trigger migraines with 43.4% of respondents reporting changes in weather as trigger factors. More respondents reported heat (35.2%) than cold (10.1%) as a weather trigger factors. Smoking was reported by 13.8% and hormonal changes by 8.2% of respondents. These findings indicate the extent of trigger factors as experienced by respondents.

There was a one-sided response to both aura and trigger factors in this study. Experiencing an aura or not experience an aura did not result in a significantly different likelihood of you experiencing trigger factors (Chi-square =0.453, d.f.=2, p -value =0.797). When aura was divided into visual and sensory aura, the Chi-square test indicated that there was a statistically significant relationship between the presence of

trigger factors and the presence of visual aura at the 5% level (Chi-square = 7.966, d.f. = 1, p-value = 0.005). Cramér's *V* showed a small practical significance at 0.218. There was no statistically significant relationship between the presence of trigger factors and the presence of sensory aura (Chi-square =0.34, d.f.=1, p-value = 0.56). In this study the order of trigger factors experienced as reported did not vary when the presence of aura, visual aura and sensory aura was taken into account.

The most common migraine symptoms reported by respondents were sensitivity to light (82.3%), nausea (69.8%), sound (68.6%), neck pain (66.9%) and throbbing headache (65.1%). The type of pain experienced by respondents were as follows: neck pain (66.9%), throbbing pain (pulsating) (65.1%) and pain on one side of the head (unilateral) (53.3%). The number of symptoms experienced by respondents varied from one to 17, with seven symptoms being the most frequently number of symptoms reported by respondents (25). The most commonly reported symptoms are those that meet the ICHD-3 criteria for a headache to be classified as a migraine. There was a statically significant relationship, at the 10% level, between abortive medication used and the number of migraine symptoms reported by respondent (Chi-square = 11.175, d.f. = 6, p-value = 0.083).

Respondents tend to use more than one type of medication to abort their migraine attacks. The largest percentage of respondents used single ingredient analgesics (46.5%) followed by migraine kits (39.6%) and combination analgesics (36.5%) to abort an acute attack of migraine. Migraine specific medications such as triptans were used by 12.6% and ergot alkaloids by 5.6%, indicating that only a few respondents were using medication specific to migraine. Eighty percent of the respondents who used a triptan to abort their migraine used rizatriptan. Thirteen percent of respondents indicated that they needed to go to a doctor for an injection to help abort a migraine attack. These findings are in keeping with the 80% of patients that the pharmacist reported used OTC medication to treat their migraines. Over-the-counter medication are more accessible than migraine specific medication such as triptans.

Those respondents who did not experience an aura were more likely to use migraine specific medication (38.9%) and migraine kits (33.3%) to abort their migraine attacks. Respondents who only sometimes experienced an aura were more likely to use

analgesics to abort their migraine attacks. Respondents who experienced an aura were more likely to use migraine kits (29.1%), however, there was not much difference in the type of medication that they used. There was no significant relationship between those respondents who did or did not experience an aura and the type of medication that they used to abort a migraine (Chi-square = 6.227, d.f. = 6, p-value = 0.398). When aura was divided into visual aura and sensory aura there was still no statistical significant relationship between those respondents who experienced either visual or sensory aura and the type of medication used to abort a migraine attack (visual aura: Chi-square = 6.162, d.f. = 3, p-value = 0.104; sensory aura Chi-square = 1.115, d.f. = 3, p-value = 0.773). The type of medication used by respondents who experienced visual aura and sensory aura was very similar.

Respondents who experienced trigger factors reported that they used migraine specific medication or visited their doctor for an injection to abort a migraine attack. While those who did not have trigger factors used migraine kits (75.0%) and analgesics (25.0%) to abort their migraine attacks. This showed that those respondents with trigger factors were more likely to seek further medical intervention to help control their migraine attacks. According to the Chi-square test there was a statistical relationship between abortive medication and the presence of trigger factors (Chi-square = 8.775, d.f. = 3, p-value = 0.032). Cramér's *V* showed a small practical significance at 0.244.

There were some trends observed in the type of abortive medication used and the presence or absence of an aura in the presence of trigger factors. In the presence of both trigger factors and auras, there were only slight differences in the percentages of the type of abortive medication used to abort a migraine, with injection from a general practitioner the least likely to be used (18.3%). Respondents who had trigger factors and only sometimes experience an aura were more likely to use analgesics (42.4%) to abort their migraine attacks. Those respondents who had trigger factors and did not experience an aura were more likely to use migraine specific medication (43.8%) to abort their migraine attacks. A Chi-square yielded a non-significant result (Chi-square = 6.499, df = 6, p = 0.370) for there being a relationship between "presence of aura" and "abortive medication used". Therefore the medication used was not dependent on the presence/absence of an aura. It can therefore be concluded that although some

trends have been observed, it may have occurred only by chance and should therefore be treated cautiously.

Only 12.7% of respondents indicated that they were taking a migraine preventative medication. Sixty percent used only one drug, 30% used two drugs and 10% used three drugs to help to prevent a migraine attack. As with literature this study reported a low percentage for use of preventative medication.

Complementary and alternative medications or practices were used to treat migraine in 48.0% of respondents. The type of medications or treatments used were as follows: 41% used herbal medicines, 56.6% vitamin and/or mineral supplements, with 32.5% using mind-body practices (behavioural treatments) and 56.6% manipulative and body-based practices (manual therapies). A visit to a chiropractor (51.8%), physiotherapist (42.9%) and massage therapist (41.1%) were the practices used in descending order by respondents. There are those migraineurs who do not want to use pharmaceutical medication and thus make use of alternative means to treat their migraine. Literature, as does this studies reports positive results for these treatments and practices.

6.3 Recommendations

Based on the major findings of the study, certain recommendations regarding further studies investigating migraine with specific reference to triggers, auras and migraine treatment in South Africa can be made.

6.3.2 Recommendations regarding further research

The findings of this study indicate that there is a need for further research into various aspects of migraine. Migraine is a highly individualistic disorder in that what is experienced (trigger factors, auras and symptoms) by one person and what medication works for them is not the same for the next person. The more information available regarding trigger factors, auras and treatments used, the better the

understanding of migraine. In South Africa, we have a unique gene pool that could give valuable insight into migraine as it has a genetic component.

More than half of the respondents reported a family history of migraine, with many reporting more than one relative with migraine. A higher percentage of respondents reported experiencing an aura than is reported in the literature. As migraine has a genetic component, especially migraine with aura, studies need to be conducted in other parts of South Africa to determine if similar, results to this study for experiencing an aura, would be reported. Further studies into the relationship between trigger factors and visual aura need to be carried out to determine if the same result of a statistical relationship at the 5% level would be reported.

About 80% of respondents treated their migraine with OTC medication. Studies need to be conducted in other cities to see if more affluent cities would report the same results or if more respondents would be using migraine specific medication. Migraine is associated with a high degree of disability and affects people in their economic productive years. More effective treatment of migraine could reduce the personnel, social and economic burden of migraine. A better understanding of medication used, could lead to recommendations for more effective suggestions as to what medication would be the best option to treat migraine.

There was a statistical relationship between abortive medication and the presence of trigger factors. Some trends were observed between the presence of aura and abortive medication used. There was no statistical relationship between auras and abortive medication in those that did have trigger factors. The trends observed could have occurred only by chance and should therefore be treated cautiously. Further studies therefore need to be conducted to determine if these trends were due to chance. If these trends were not due to chance they could be used to help in deciding on what medication would be the most effective to use.

There were a few respondents who did not appear to understand or had a limited understanding of the terms “aura” and “trigger factors”. The poor response from certain ethnic groups could be in part due not recognising that they did suffer from migraine. Education regarding migraine and appropriate support groups need to be established.

A high percentage of respondents reported aura and trigger factors. Educating respondents to recognise trigger factors so that they can manage or avoid their trigger factors could reduce the incidence of migraine attacks. Pain follows aura in a migraine attack, therefore if a respondent understands what an aura is they can treat their migraine early and thereby reduce the disability associated with a migraine attack.

A person who suspects that they suffer from migraine or those who are newly diagnosed should be encouraged to keep a migraine diary. In this way a record can be established as to what trigger factors they experience, if they experience an aura and the type of aura experienced, and what medication they have used which has been effective in treating their migraine and was ineffective. This information can then be used to ensure that the person is receiving the best advice and treatment for their migraine.

The conducting of a questionnaire-based survey could be used to determine whether the incidence of migraine in South Africa differs between racial or cultural groups as the demographics of the country are reflected in the participants.

6.3.3 Concluding statement

Globally there is a large amount of information available regarding migraine. Given the prevalence and burden reported, it is important to ensure that research is undertaken to allow for a better understanding of migraine in South Africa. Migraine is a complex medical condition associated with a high degree of disability which affects people of all ages. In this study, there appears to be a statistical relationship between visual auras and trigger factors and between abortive medication and trigger factors. There was, however, no statistical relationship between aura and abortive medication in the presence of trigger factors. Further studies need to be conducted to substantiate these findings. Each migraineur's experience of migraine is different. Identifying relationships between what triggers a migraine and/or what auras are experienced and/or the type of medication used to treat a migraine, could lead to better management of migraine. Migraine needs to be diagnosed correctly with the proper

care and preventative measures put in place to reduce the burden of migraine and improve the quality of life of the migraineur.

South Africa has diverse cultures and belief systems which could influence the understanding and treatment of migraine. Traditional healers, distrust of medical care providers and accessibility to adequate treatment has a large impact on the knowledge of migraine in South Africa and Africa in general. Few African migraineurs use specific medications with the majority opting for traditional and herbal therapies. Studies need to be carried out to determine if there are variations in trigger factors reported, auras experienced and the type of medication used by the various ethnic groups.

"*If migraine patients have a common and legitimate second complaint besides their migraines, it is that they have not been listened to by physicians. Looked at, investigated, drugged, charged, but not listened to.*"

Oliver Sacks

(Source: - A-Z Quotes, 2016)

References

Aamodt, A.H., Stovner, L.J., Langhammer, A., Hagen, K. & Zwart, J.A., 2007. Is Headache Related to Asthma, Hay Fever, and Chronic Bronchitis? The Head-HUNT Study. *Headache*, 47(2), pp.204–212.

Abu-Salameh, I., Plakht, Y. & Ifergane, G., 2010. Migraine exacerbation during Ramadan fasting. The *Journal of Headache and Pain*, 11(6), pp.513–517.

Adam, E.I., Gore, S.M. & Price, W.H., 1978. Double blind trial of clonidine in the treatment of migraine in a general practice. *The Journal of the Royal College of General Practitioners*, 28(195), pp.587–590.

Addis, L., Chiang, T., Clarke, T., Hardison, H., Kugler, S., Mandelbaum, D.E., Novotny, E., Wolf, S., Strug, L.J. & Pal, D.K., 2014. Evidence for linkage of migraine in Rolandic epilepsy to known 1q23 FHM2 and novel 17q22 genetic loci. *Genes, Brain and Behavior*, 13(3), pp.333–340.

Adelman, J.U. & Lewit, E.J., 2001. Comparative aspects of triptans in treating migraine. *Clinical Cornerstone*, 4(3), pp.53–64.

Adoukonou, T., Houinato, D., Kankouan, J., Makoutode, M., Paraiso, M., Tehindrazanarivelo, A., Viader, F. & Preux, P.M., 2009. Migraine among University students in Cotonou (Benin). *Headache*, 49(6), pp.887–893.

Aggarwal, M., Puri, V. & Puri, S., 2012. Serotonin and CGRP in migraine. *Annals of Neurosciences*, 19(2), pp.88–94.

Agosti, R., Duke, R.K., Chrubasik, J.E. & Chrubasik, S., 2006. Effectiveness of Petasites hybridus preparations in the prophylaxis of migraine: A systematic review. *Phytomedicine*, 13(9–10), pp.743–746.

Agostoni, E. & Aliprandi, A., 2006. The complications of migraine with aura. *Neurological Sciences*, 27(2), pp.s91–s95.

Aguggia, M., 2012. Allodynia and migraine. *Neurological Sciences*, 33(1), pp.s12–s14.

Aiba, S., Tatsumoto, M., Saisu, A., Iwanami, H., Chiba, K., Senoo, T. & Hirata, K., 2010. Prevalence of typical migraine aura without headache in Japanese ophthalmology clinics. *Cephalalgia*, 30(8), pp.962–967.

Ailani, J., 2014. Migraine and patent foramen ovale. *Current Neurology and Neuroscience Reports*, 14(2), pp.1–5.

Akdal, G., Baykan, B., Ertas, M., ZarifoĞlu, M., Karli, N., Saip, S. & Siva, A., 2015. Population-based study of vestibular symptoms in migraineurs. *Acta Oto-laryngologica*, 135(5), pp.435–439.

Akdal, G., Özge, A. & Ergör, G., 2015. Vestibular symptoms are more frequent in migraine than in tension type headache patients. *Journal of the Neurological Sciences*, 357(1), pp.295–296.

Akerman, S. & Goadsby, P.J., 2007. Dopamine and migraine: Biology and clinical implications. *Cephalalgia*, 27(11), pp.1308–1314.

Al-Hashel, J.Y., Ahmed, S.F., Alroughani, R. & Goadsby, P.J., 2014. Migraine among medical students in Kuwait University. *The Journal of Headache and Pain*, 15(1), pp.1-6.

Almas, M., Tepper, S., Landy, S. & Ramos, E., 2013. Eletriptan provides consistent migraine relief: results of a within-patient multiple-dose study. *The Journal of Headache and Pain*, 14(1), pp.1.

Alonso-Navarro, H. & Jiménez-Jiménez, F., 2009. Sensory “pseudoperipheral” migraine aura. *Journal of Neurology*, 256(8), pp.1349–1350.

Alstadhaug, K., 2009. Migraine and the hypothalamus. *Cephalalgia*, 29(8), pp.809–817.

Alstadhaug, K.B., 2014. Histamine in migraine and brain. *Headache*, 54(2), pp.246–259.

Alzoubi, K.H., Mhaidat, N., Azzam, S. Al, Khader, Y., Salem, S., Issaifan, H. & Haddadin, R., 2009. Prevalence of migraine and tension-type headache among adults in Jordan. The *Journal of Headache and Pain*, 10(4), pp.265–270.

Ambrosetto, P., Nicolini, F., Zoli, M., Cirillo, L., Feraco, P. & Bacci, A., 2014. Ophthalmoplegic migraine: From questions to answers. *Cephalalgia*, 34(11), pp.914–919.

Andreatta, M., Puschmann, A. K., Sommer, C., Weyers, P., Pauli, P. & Muhlberger, A., 2012. Altered processing of emotional stimuli in migraine: An event-related potential study. *Cephalalgia*, 32(15), pp.1101–1108.

Andress-Rothrock, D., King, W. & Rothrock, J., 2010. An analysis of migraine triggers in a clinic-based population. *Headache*, 50(8), pp.1366–1370.

Anon, 2011. “A Snapshot of the Impact of Migraine on Australians” Headache Australia and Allergan Survey August 2011, (August). Available at: http://headacheaustralia.org.au/wpcontent/uploads/2015/06/Headache_Australia_Survey_-_Summary_Sept_2011.pdf [Accessed 15 July 2016].

Arulmani, U., MaassenVanDenBrink, A., Villalón, C.M. & Saxena, P.R., 2004. Calcitonin gene-related peptide and its role in migraine pathophysiology. *European Journal of Pharmacology*, 500(1), pp.315–330.

Asghar, M.S., Hansen, A.E., Amin, F.M., Van Der Geest, R.J., Koning, P. Van Der, Larsson, H.B.W., Olesen, J. & Ashina, M., 2011. Evidence for a vascular factor in migraine. *Annals of Neurology*, 69(4), pp.635–645.

Ashcroft, D.M. & Millson, D., 2004. Naratriptan for the treatment of acute migraine: Meta-analysis of randomised controlled trials. *Pharmacoepidemiology and Drug Safety*, 13(2), pp.73–82.

Ashina, S., Bendtsen, L. & Ashina, M., 2013. Pathophysiology of migraine and tension-type headache. *Techniques in Regional Anesthesia and Pain Management*, 16(1), pp.14–18.

Ashina, S., Bendtsen, L., Lyngberg, A.C., Lipton, R.B., Hajiyeva, N. & Jensen, R., 2015. Prevalence of neck pain in migraine and tension-type headache: A population study. *Cephalalgia*, 35(3), pp.211–219.

Ashina, S. & Portenoy, R.K., 2012. Intravenous treatment of migraine. *Techniques in Regional Anesthesia and Pain Management*, 16(1), pp.25–29.

Asuni, C., Manchia, M., Deidda, A., Stochino, M.E., Cherchi, A. & Del Zompo, M., 2010. Mixture analysis of age at onset in migraine without aura: Evidence for three subgroups. *Headache*, 50(8), pp.1313–1319.

Aurora, S.K., 2004. Pathophysiology of migraine and cluster headaches. *Seminars in Pain Medicine*, 2(2), pp.62–71.

Aurora, S.K., Kori, S.H., Barrodale, P., McDonald, S. A & Haseley, D., 2006. Gastric stasis in migraine: more than just a paroxysmal abnormality during a migraine attack. *Headache*, 46(1), pp.57–63.

Ayzenberg, I., Katsarava, Z., Sborowski, A., Obermann, M., Chernysh, M., Osipova, V., Tabeeva, G. & Steiner, T.J., 2015. Headache yesterday in Russia: its prevalence and impact, and their application in estimating the national burden attributable to headache disorders. *The Journal of Headache and Pain*, 16(1), pp.1-6.

A-Z Quotes. (2016). *Joan Didion Quote*. [online] Available at: http://www.azquotes.com/quote/1159209?ref=migraine [Accessed 15 July 2016].

A-Z Quotes. (2016). *Oliver Sacks Quote*. [online] Available at: http://www.azquotes.com/quote/827347 [Accessed 15 July 2016].

Baldacci, F., Lucchesi, C., Ulivi, M., Cafalli, M., Vedovello, M., Vergallo, A., Prete, E. Del, Nuti, A., Bonuccelli, U. & Gori, S., 2014. Clinical features associated with ictal osmophobia in migraine. *Neurological Sciences*, 36(1), pp.43–46.

Baldacci, F., Vedovello, M., Ulivi, M., Vergallo, A., Poletti, M., Borelli, P., Nuti, A. & Bonuccelli, U., 2013. How aware are migraineurs of their triggers? *Headache*, 53(5), pp.834–837.

Bánk, J. & Márton, S., 2000. Hungarian migraine epidemiology. *Headache*, 40(2), pp.164–169.

Baron, E.P. & Tepper, S.J., 2010. Revisiting the role of ergots in the treatment of migraine and headache. *Headache*, 50(8), pp.1353–1361.

Barry, A.E., Chaney, B., Piazza-Gardner, A.K. & Chavarria, E.A., 2014. Validity and reliability reporting practices in the field of health education and behavior: A review of seven journals. *Health Education and Behavior*. 41(1), pp.12–18.

Becker, W.J., 2013. The premonitory phase of migraine and migraine management. *Cephalalgia*, 33(13), pp.1117–1121.

Becker, W.J., 2011. Weather and migraine: can so many patients be wrong? *Cephalalgia*, 31(4), pp.387–390.

Bell, C.F., Foley, K.A., Barlas, S., Solomon, G. & Hu, X.H., 2006. Time to pain freedom and onset of pain relief with rizatriptan 10 mg and prescription usual-care oral medications in the acute treatment of migraine headaches: A multicenter, prospective, open-label, two-attack, crossover study. *Clinical Therapeutics*, 28(6), pp.872–880.

Benoit, D.P., 2009. An introduction to migraine pathophysiology. *Techniques in Regional Anesthesia and Pain Management*, 13(1), pp.5–8.

Bernstein, C. & Burstein, R., 2012. Sensitization of the trigeminovascular pathway: Perspective and implications to migraine pathophysiology. *Journal of Clinical Neurology (Korea)*, 8(2), pp.89–99.

Bhattacherjee, A., 2012. *Social Science Research: principles, methods, and practices*. In USF Tampa Bay Open Access Textbooks Collection. Available at: http://scholarcommons.usf.edu/cgi/viewcontent.cgi?article=1002&context=oa_textbooks [Accessed 9 March 2014].

Bigal, M.E., Bordini, C.A., Antoniazzi, A.L. & Speciali, J.G., 2003. The triptan formulations: A critical evaluation. *Arquivos de Neuro-Psiquiatria*, 61(2 A), pp.313–320.

Bigal, M.E. & Krymchantowski, A. V, 2006. Migraine triggered by sucralose--a case report. *Headache*, 46(3), pp.515–517.

Bigal, M.E., Liberman, J.N. & Lipton, R.B., 2006. Obesity and migraine: A population study. *Neurology*, 66(4), pp.545–550.

Bigal, M.E. & Lipton, R.B., 2008. Concepts and mechanisms of migraine chronification. *Headache*, 48(1), pp.7–15.

Bigal, M.E. & Lipton, R.B., 2006. Migraine at all ages. *Current Pain and Headache Reports*, 10(3), pp.207–213.

Bigal, M.E., Lipton, R.B. & Stewart, W.F., 2004. The epidemiology and impact of migraine. *Current Neurology and Neuroscience Reports*, 4(2), pp.98–104.

Bigal, M.E., Serrano, D., Reed, M. & Lipton, R.B., 2008. Chronic migraine in the population: Burden, diagnosis, and satisfaction with treatment. *Neurology*, 71(8), pp.559–566.

Bigal, M.E. & Tepper, S.J., 2003. Ergotamine and dihydroergotamine: a review. *Current Pain and Headache Reports*, 7(1), pp.55–62.

Blau, J.N., 2005. Water deprivation: A new migraine precipitant. *Headache*, 45(6), pp.757–759.

Bloudek, L.M., Stokes, M., Buse, D.C., Wilcox, T.K., Lipton, R.B., Goadsby, P.J., Varon, S.F., Blumenfeld, A.M., Katsarava, Z., Pascual, J. & Lanteri-Minet, M., 2012. Cost of healthcare for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS). *The Journal of Headache and Pain*, *13*(5), pp.361-378.

Blumenfeld, A.M., Varon, S.F., Wilcox, T.K., Buse, D.C., Kawata, A.K., Manack, A., Goadsby, P.J. & Lipton, R.B., 2011. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia*, 31(3), pp.301–315.

Bohár, Z., Fejes-Szabó, A., Tar, L., Varga, H., Tajti, J., Párdutz, Á. & Vécsei, L., 2013. Evaluation of c-Fos immunoreactivity in the rat brainstem nuclei relevant in migraine pathogenesis after electrical stimulation of the trigeminal ganglion. *Neurological Sciences*, 34(9), pp.1597–1604.

Bolay, H., 2013. En'lightning' the impact of atmospheric conditions in headache. *Cephalalgia*, 33(6), pp.362–364.

Bolay, H. & Rapoport, A., 2011. Does low atmospheric pressure independently trigger migraine? *Headache*, 51(9), pp.1426–1430.

Bond, D.S., Roth, J., Nash, J.M. & Wing, R.R., 2011. Migraine and obesity: Epidemiology, possible mechanisms and the potential role of weight loss treatment. *Obesity Reviews*, 12(501), pp.e362–e371.

Brandes, J.L., Saper, J.R., Diamond, M., Couch, J.R., Lewis, D.W., Schmitt, J., Neto, W., Schwabe, S. & Jacobs, D., 2004. Topiramate for migraine prevention: a randomized controlled trial. *Jama*, 291(8), pp.965–973.

Brink, H., van der Walt, C. & van Rensberg, G., 2006. *Fundamentals of Research Methodology for Health Care Professionals*. In Cape Town: Juta and Company LTD: pp.1-226.

Brink, P.J. & Wood, M.L., 1998. *Advanced Design in Nursing Research*. In London: SAGE: pp.1-413.

Burch, R.C., Rist, P.M., Winter, A.C., Buring, J.E., Pradhan, A.D., Loder, E.W. & Kurth, T., 2012. Migraine and risk of incident diabetes in women: A prospective study. *Cephalalgia*, 32(13), pp.991–997.

Burstein, R., Cutrer, M.F. & Yarnitsky, D., 2000. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain*, 123, pp.1703–1709.

Buse, D.C., Loder, E.W., Gorman, J. A., Stewart, W.F., Reed, M.L., Fanning, K.M., Serrano, D. & Lipton, R.B., 2013. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine prevalence and prevention (AMPP) study. *Headache*, 53(8), pp.1278–1299.

Buse, D.C., Pearlman, S.H., Reed, M.L., Serrano, D., Ng-Mak, D.S. & Lipton, R.B., 2012. Opioid use and dependence among persons with migraine: Results of the ampp study. *Headache*, 52, pp.18–36.

Cady, R.C., Ryan, R., Jhingran, P., O'Quinn, S. & Pait, D.G., 1998. Sumatriptan Injection Reduces Productivity Loss During a Migraine Attack: Results of a Double-blind, Placebo-Controlled Trial. *Archive of Internal Medicine*, 158(9), pp.1013–1018.

Cady, R.K., Farmer, K., Dexter, J.K. & Hall, J., 2012. The Bowel and Migraine: Update on Celiac Disease and Irritable Bowel Syndrome. *Current Pain and Headache Reports*, 16(3), pp.278–286.

Cady, R.K., Schreiber, C.P. & Farmer, K.U., 2004. Understanding the patient with migraine: The evolution from episodic headache to chronic neurologic disease. A proposed classification of patients with headache. *Headache*, 44(5), pp.426–435.

Calandre, E.P., Garcia-Leiva, J.M., Rico-Villademoros, F., Vilchez, J.S. & Rodriguez-Lopez, C.M., 2010. Pregabalin in the treatment of chronic migraine: an open-label study. *Clinical Neuropharmacology*, 33(1), pp.35–39.

Calhoun, A.H., Ford, S., Millen, C., Finkel, A.G., Truong, Y. & Nie, Y., 2010. The prevalence of neck pain in migraine. *Headache*, 50(8), pp.1273–1277.

Calhoun, A.H., Ford, S., Pruitt, A.P. & Fisher, K.G., 2011. The point prevalence of dizziness or vertigo in migraine - And factors that influence presentation. *Headache*, 51(9), pp.1388–1392.

Carod-Artal, F.J., Ezpeleta, D., Martín-Barriga, M.L. & Guerrero, A.L., 2011. Triggers, symptoms, and treatment in two populations of migraneurs in Brazil and Spain. A cross-cultural study. *Journal of the Neurological Sciences*, 304(1-2), pp.25–28.

Carmona, S. & Bruera, O., 2009. Prophylatic treatment of migraine and migraine clinical variants with topiramate: an update. *Therapeutics and Clinical Risk Management*, 5(3), pp.661–669.

Cassidy, E.M., Tomkins, E., Dinan, T., Hardiman, O. & O'Keane, V., 2003. Central 5-HT receptor hypersensitivity in migraine without aura. *Cephalalgia*, 23(1), pp.29–34.

Casucci, G. & Cevoli, S., 2013. Controversies in migraine treatment: Opioids should be avoided. *Neurological Sciences*, 34(S1), pp.125–129.

Casucci, G., Villani, V., Cologno, D. & D'Onofrio, F., 2012. Migraine and metabolism. *Neurological Sciences*, 33(S1), pp.81–85.

Cervellin, G. & Lippi, G., 2015. Abdominal migraine in the differential diagnosis of acute abdominal pain. *The American Journal of Emergency Medicine*, pp.2014–2016.

Cevoli, S., D'Amico, D., Martelletti, P., Valguarnera, F., Del Bene, E., De Simone, R., Sarchielli, P., Narbone, M.C., Testa, L., Genco, S. & Bussone, G., 2009. Underdiagnosis and undertreatment of migraine in Italy: a survey of patients attending for the first time 10 headache centres. *Cephalalgia*, *29*(12), pp.1285-1293.

Cha, Y.-H., Lee, H., Santell, L.S. & Baloh, R.W., 2009. Association of benign recurrent vertigo and migraine in 208 patients. *Cephalalgia*, 29(5), pp.550–555.

Cha, Y.-H., Millett, D., Kane, M., Jen, J. & Baloh, R., 2007. Adult-onset hemiplegic migraine with cortical enhancement and oedema. *Cephalalgia*, 27(10), pp.1166–1170.

Cha, Y.M. & Baloh, R.W.M., 2007. Migraine-associated vertigo. *Journal of Clinical Neurology*, 3(3), pp.121–126.

Chai, N.C., Rosenberg, J.D. & Lee Peterlin, B., 2012. The epidemiology and comorbidities of migraine and tension-type headache. *Techniques in Regional Anesthesia and Pain Management*, 16(1), pp.4–13.

Chaibi, A., Tuchin, P.J. & Russell, M.B., 2011. Manual therapies for migraine: a systematic review. *The Journal of Headache and Pain*, 12(2), pp.127–133.

Chang, F.Y. & Lu, C.L., 2013. Irritable bowel syndrome and migraine: Bystanders or partners? *Journal of Neurogastroenterology and Motility*, 19(3), pp.301–311.

Chang, M. & Rapoport, A.M., 2009. Acute treatment of migraine headache. *Techniques in Regional Anesthesia and Pain Management*, 13(1), pp.9–15.

Charles, A., 2013. The evolution of a migraine attack - A review of recent evidence. *Headache*, 53(2), pp.413–419.

Chawla, J., 2015. Migraine Headache. *Medscape Reference*. Available at: http://emedicine.medscape.com/article/1142556-overview#showall [Accessed 10 February 2015]

Chen, Y.C., Tang, C.H., Ng, K. & Wang, S.J., 2012. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. The *Journal of Headache and Pain*, 13(4), pp.311–319.

Chillemi, S., 2013. Weather-Related Migraines. *NeurologyNow*, 9(3), p.12-15.

Chitsaz, A., Najafi, M.R., Zangeneh, F.A., Norouzi, R. & Salari, M., 2012. Pizotifen in migraine prevention: A comparison with sodium valproate. *Neurology Asia*, 17(4), pp.319–324.

Chu, M.K., Buse, D.C., Bigal, M.E., Serrano, D. & Lipton, R.B., 2012. Factors associated with triptan use in episodic migraine: Results from the American migraine prevalence and prevention study. *Headache*, 52(2), pp.213–223.

Clarke, T., Baskurt, Z., Strug, L.J. & Pal, D.K., 2009. Evidence of shared genetic risk factors for migraine and rolandic epilepsy. *Epilepsia*, 50(11), pp.2428–2433.

Clow, K. & James, K., 2014. *Essentials of Marketing Research: Putting Research into Practice*. In Thousand Oaks: Sage Publications Ltd: pp. 322–357.

Cole, J.A., Rothman, K.J., Cabral, H.J., Zhang, Y. & Farraye, F.A., 2006. Migraine, fibromyalgia, and depression among people with IBS: A prevalence study. *BMC Gastroenterology*, 6(1), pp.1-6.

Colman, I., Brown, M.D., Innes, G.D., Grafstein, E., Roberts, T.E. & Rowe, B.H., 2004. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ (Clinical Research ed.)*, 329(7479), pp.1369–1373.

Cologno, D., Torelli, P., Cademartiri, C. & Manzoni, G.C., 2000. A prospective study of migraine with aura attacks in a headache clinic population. *Cephalalgia*, 20(10), pp.925–930.

Colton, D. & Covert, R.W., 2007. *Designing and Constructing Instrument for Social Research and Evaluation*. In San Francisco: Jossey-Bass: pp 1-394.

Cooke, L.J. & Becker, W.J., 2010. Migraine prevalence, treatment and impact: the canadian women and migraine study. *The Canadian Journal of Neurological Sciences*, 37(5), pp.580–587.

Cooke, L.J., Rose, M.S. & Becker, W.J., 2000. Chinook winds and migraine headache. *Neurology*, 54(2), pp.302–302.

Coppola, M., Yealy, D.M. & Leibold, R.A., 1995. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Annals of Emergency Medicine*, 26(5), pp.541–546.

Costa, C., Tozzi, A., Rainero, I., Cupini, L.M., Calabresi, P., Ayata, C. & Sarchielli, P., 2013. Cortical spreading depression as a target for anti-migraine agents. *The Journal of Headache and Pain*, 14(1), p.62.

Couch, J.R., 2011. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache*, 51(1), pp.33–51.

Cutrer, F.M. & Charles, A., 2008. The Neurogenic Basis of Migraine. *Headache :The Journal of Head and Face Pain*, 48(9), pp.1411–1414.

D'Andrea, G., Granella, F., Perini, F., Farruggio, A., Leone, M. & Bussone, G., 2006. Platelet levels of dopamine are increased in migraine and cluster headache. *Headache*, 46(4), pp.585–591.

D'Souza, P.J., Lumley, M.A., Kraft, C.A. & Dooley, J.A., 2008. Relaxation training and written emotional disclosure for tension or migraine headaches: a randomized, controlled trial. *Annals of Behavioral Medicine*, *36*(1), pp.21-32.

Da Cas, R., Nigro, A., Terrazzino, S., Sances, G., Viana, M., Tassorelli, C., Nappi, G., Cargnin, S., Pisterna, A., Traversa, G. & Genazzani, A.A., 2015. Triptan use in Italy: Insights from administrative databases. *Cephalalgia*, 35(7), pp.619–626.

Da Silva, A.N. & Tepper, S.J., 2012. Acute treatment of migraines. *CNS Drugs*, 26(10), pp.823–839.

Dahlöf, C. & Linde, M., 2001. One-year prevalence of migraine in Sweden: A population-based study in adults. *Cephalalgia*, 21(6), pp.664–671.

Dahlöf, C. & Maassen VanDenBrink, A., 2012. Dihydroergotamine, ergotamine, methysergide and sumatriptan - basic science in relation to migraine treatment. *Headache*, 52(4), pp.707–714.

Dahlöf, C.G.H., Rapoport, A.M., Sheftell, F.D. & Lines, C.R., 1999. Rizatriptan in the treatment of migraine. *Clinical Therapeutics*, 21(11), pp.1823–1836.

Dalkara, T. & Kiliç, K., 2013. How does fasting trigger migraine? A hypothesis. *Current Pain and Headache Reports*, 17(10), pp.1–7.

Danese, E., Montagnana, M. & Lippi, G., 2014. Platelets and migraine. *Thrombosis Research*, *134*(1), pp.17-22.

Daniel, B.T., 2014. *Migraine*. In AuthorHouse. Available at: http://www.amazon.com/Migraine-Britt-Talley-Daniel-MD/dp/1449069622 ebook 13 Chapters [Accessed 5 May 2015].

Database of Medicine Prices, 19 April 2016. South African Medicine Price Registry. http://www.mpr.gov.za/ [Accessed 5 May 2016].

Davey, G., Sedgwick, P., Maier, W., Visick, G., Strachan, D.P. & Anderson, H.R., 2002. Association between migraine and asthma: matched case-control study. *The British Journal of General Practice*, 52(482), pp.723–727.

Dekker, F., Neven, A.K., Andriesse, B., Kernick, D., Reis, R., Ferrari, M.D. & Assendelft, W.J.J., 2012. Prophylactic treatment of migraine; the patient's view, a qualitative study. *BMC Family Practice*, 13(1), pp.1–9.

Deleu, D., Khan, M.A., Humaidan, H., Al Mantheri, Z. & Al Hashami, S., 2001. Prevalence and clinical characteristics of headache in medical students in Oman. *Headache*, 41(8), pp.798–804.

Demaagd, G., 2008. The pharmacological management of migraine, part 1: overview and abortive therapy. *P & T : A Peer-reviewed Journal for Formulary Management*, 33(7), pp.404–416

Demaagd, G., 2008. The pharmacological management of migraine, part 2: preventative therapy. *P & T : A Peer-reviewed Journal for Formulary Management*, 33(8), pp.480–487.

Demarquay, G., Royet, J.P., Giraud, P., Chazot, G., Valade, D. & Ryvlin, P., 2006. Rating of olfactory judgements in migraine patients. *Cephalalgia*, 26(9), pp.1123–1130.

Demirkaya, S., Dora, B., Topcuoglu, M.A., Ulas, U.H. & Vural, O., 2000. A comparative study of magnesium, flunarizine and amitriptyline in the prophylaxis of migraine. The *Journal of Headache and Pain*, 1(3), pp.179–186.

Dent, W., Spiss, H.K., Helbok, R., Matuja, W.B.P., Scheunemann, S. & Schmutzhard, E., 2004. Prevalence of migraine in a rural area in South Tanzania: A door-to-door survey. *Cephalalgia*, 24(11), pp.960–966.

Derry, C., Derry, S. & Moore, R., 2012a. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. *Cochrane Database Review*, (2), pp.1–89.

Derry, C., Derry, S. & Moore, R., 2012b. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database Review*, (2), pp.1–320.

Derry, S. & Moore, R.A., 2013. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *The Cochrane Database of Systematic Reviews*, (4), pp.1–58.

Derry, S., Rabbie, R. & Moore, R., 2013. Diclofenac with or without an antiemetic for acute migraine headaches in adults (Review). *The Cochrane Database of Systematic Reviews*, (4), pp.1–43.

Diamond, S., 2007. Evolution of migraine drugs. *Drug Development Research*, 68(6), pp.270–275.

Diamond, S., Bigal, M.E., Silberstein, S., Loder, E., Reed, M. & Lipton, R.B., 2007. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: Results from the American migraine prevalence and prevention study. *Headache*, 47(3), pp.355–363.

Diamond, S. & Franklin, M., 2005. *Headache Through The Ages*. In New York: Professional Communications, Inc: pp 1-134.

Diener, H.-C., Dodick, D.W., Turkel, C.C., Demos, G., Degryse, R.E., Earl, N.L. & Brin, M.F., 2014. Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. *European Journal of Neurology*, 21(6), pp.851–859.

Diener, H.C., Holle, D. & Dodick, D., 2011. Treatment of chronic migraine. *Current Pain and Headache Reports*, 15(1), pp.64–69.

Diener, H.C., Küper, M. & Kurth, T., 2008. Migraine-associated risks and comorbidity. *Journal of Neurology*, 255(9), pp.1290–1301.

Diener, H.C., Matias-Guiu, J., Hartung, E., Pfaffenrath, V., Ludin, H.P., Nappi, G. & De Beukelaar, F., 2002. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia*, 22(3), pp.209–221.

Dodick, D.W., Lipton, R.B., Goadsby, P.J., Tfelt-Hansen, P., Ferrari, M.D., Diener, H.C., Almas, M., Albert, K.S. & Parsons, B., 2008. Predictors of migraine headache recurrence: A pooled analysis from the eletriptan database. *Headache*, 48(2), pp.184–193.

Doganay, H., Akcali, D., Goktaş, T., Çaglar, K., Erbas, D., Saydam, C. & Bolay, H., 2009. African dust-laden atmospheric conditions activate the trigeminovascular system. *Cephalalgia*, 29, pp.1059–1068.

Dong, Z., Di, H., Dai, W., Liang, J., Pan, M., Zhang, M., Zhou, Z., Li, Z., Liu, R. & Yu, S., 2012. Application of ICHD-II Criteria in a Headache Clinic of China. *PLoS ONE*, 7(12), pp.1–6.

Donnet, A., Daniel, C., Milandre, L., Berbis, J. & Auquier, P., 2012. Migraine with aura in patients over 50 years of age: The Marseille's registry. *Journal of Neurology*, 259, pp.1868–1873.

Dowson, A., Bundy, M., Salt, R. & Kilminster, S., 2007. Patient preference for triptan formulations: A prospective study with zolmitriptan. *Headache*, 47(8), pp.1144–1151.

Dulli, D.A., 1999. Naratriptan: An Alternative for Migraine. *The Annals of Pharmacotherapy*, 33, pp.407–445.

Dussor, G., Yan, J., Xie, J.Y., Ossipov, M.H., Dodick, D.W. & Porreca, F., 2014. Targeting TRP Channels For Novel Migraine Therapeutics. *ACS Chemical Neuroscience*, 5(11), pp.1085–1096.

Dzoljic, E., Sipetic, S., Vlajinac, H., Marinkovic, J., Brzakovic, B., Pokrajac, M. & Kostic, V., 2002. Prevalence of menstrually related migraine and nonmigraine primary headache in female students of Belgrade University. *Headache*, 42(3), pp.185–193.

Dzoljic, E., Vlajinac, H., Sipetic, S., Marinkovic, J., Grbatinic, I. & Kostic, V., 2014. A survey of female students with migraine: what is the influence of family history and lifestyle? *The International Journal of Neuroscience*, 124(2), pp.82–87.

Eikermann-Haerter, K. & Ayata, C., 2010. Cortical spreading depression and migraine. *Current Neurology and Neuroscience Reports*, 10(3), pp.167–173.

Eken, C., 2015. Critical reappraisal of intravenous metoclopramide in migraine attack: a systematic review and meta-analysis. *The American Journal of Emergency Medicine*, 33(3), pp.331–337.

Elo, S. & Kyngäs, H., 2008. The qualitative content analysis process. *Journal of Advanced Nursing*, 62(1), pp.107–115.

Engstrøm, M., Hagen, K., Bjørk, M. & Sand, T., 2013. Answer to comment on “sleep quality, arousal and pain thresholds in migraineurs: a blinded controlled polysomnographic study”. *The Journal of Headache and Pain*, 14(12), pp.1–10.

Eriksen, M.K., Thomsen, L.L., Andersen, I., Nazim, F. & Olesen, J., 2004. Clinical characteristics of 362 patients with familial migraine with aura. *Cephalalgia*, 24(7), pp.564–575.

Eriksen, M.K., Thomsen, L.L. & Olesen, J., 2006. Implications of clinical subtypes of migraine with aura. *Headache*, 46(2), pp.286–297.

Eriksen, M.K., Thomsen, L.L. & Olesen, J., 2005. The Visual Aura Rating Scale (VARS) for migraine aura diagnosis. *Cephalalgia*, 25(10), pp.801–810.

Eriksen, M.K., Thomsen, L.L. & Russell, M.B., 2004. Prognosis of migraine with aura. *Cephalalgia*, 24(1), pp.18–22.

Ertas, M., Baykan, B., Kocasoy Orhan, E., Zarifoglu, M., Karli, N., Saip, S., Onal, A.E. & Siva, A., 2012. One-year prevalence and the impact of migraine and tension-type headache in Turkey: A nationwide home-based study in adults. The *Journal of Headache and Pain*, 13(2), pp.147–157.

Evans, R.W. & Aurora, S.K., 2012. Migraine with persistent visual aura. *Headache*, 52(3), pp.494–501.

Evans, R.W., Finkel, A.G. & Mokri, B., 2002. Triggering migraine in a 20-year-old athletic male. *Headache*, 42(7), pp.690–692.

Evans, R.W. & Grosberg, B.M., 2008. Retinal migraine: migraine associated with monocular visual symptoms. *Headache*, 48(1), pp.142–145.

Evans, R.W., Seifert, T. & Mathew, N.T., 2005. Are triptans effective and safe when taken during the aura phase of migraine? *Headache*, 45(5), pp.601–603.

Evans, R.W. & Whyte, C., 2013. Cyclic vomiting syndrome and abdominal migraine in adults and children. *Headache*, 53(6), pp.984–993.

Evers, S., 2008. Treatment of migraine with prophylactic drugs. *Expert Opinion on Pharmacotherapy*, 9(15), pp.2565–2573.

Evers, S., Áfra, J., Frese, A., Goadsby, P.J., Linde, M., May, A. & Sándor, P.S., 2009. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. *European Journal of Neurology*, 16(9), pp.968–981.

Fernández-de-las-Peñas, C., Hernández-Barrera, V., Carrasco-Garrido, P., Alonso-Blanco, C., Palacios-Ceña, D., Jiménez-Sánchez, S. & Jiménez-García, R., 2010. Population-based study of migraine in Spanish adults: Relation to socio-demographic factors, lifestyle and co-morbidity with other conditions. The *Journal of Headache and Pain*, 11(2), pp.97–104.

Fernández-de-las-Peñas, C., Palacios-Ceña, D., Salom-Moreno, J., López-de-Andres, A., Hernández-Barrera, V., Jiménez-Trujillo, I., Jiménez-García, R., Gallardo-Pino, C., García-Gómez-de-las-Heras, M.S. & Carrasco-Garrido, P., 2014. Has the Prevalence of Migraine Changed over the Last Decade (2003–2012)? A Spanish Population-Based Survey. *PLoS ONE*, 9(10), p.e110530 pp.1-8.

Ferrante, T., Manzoni, G.C., Russo, M., Taga, A., Camarda, C., Veronesi, L., Pasquarella, C., Sansebastiano, G. & Torelli, P., 2014. The PACE study: past-year prevalence of tension-type headache and its subtypes in Parma's adult general population. *Neurological Sciences*, 32(5), pp.358–365.

Ferrari, M.D., Goadsby, P.J., Roon, K.I. & Lipton, R.B., 2002. Triptans (Serotonin, 5-HT1B/1D Agonists) in Migraine: Detailed Results and Methods of A Meta-Analysis of 53 Trials. *Cephalalgia*, *22*(8), pp.633–658.

Finocchi, C. & Sivori, G., 2012. Food as trigger and aggravating factor of migraine. *Neurological Sciences*, *33*(1), pp.77-80.

Finocchi, C. & Viani, E., 2013. Opioids can be useful in the treatment of headache. *Neurological sciences*, 34(1), pp.119–124.

Florencio, L.L., Chaves, T.C., Carvalho, G.F., Gonçalves, M.C., Casimiro, E.C.B., Dach, F., Bigal, M.E. & Bevilaqua-Grossi, D., 2014. Neck pain disability is related to the frequency of migraine attacks: A cross-sectional study. *Headache*, 54(7), pp.1203–1210.

Frediani, F., Cominelli, F. & Sgarzi, M., 2001. Anticonvulsant drugs in migraine prophylaxis. *The Journal of Headache and Pain*, 2(1), pp.s121–s124.

Freedom, T. & Evans, R.W., 2013. Headache and sleep. *Headache*, 53(8), pp.1358–1366.

Friedman, B.W., Esses, D., Solorzano, C., Dua, N., Greenwald, P., Radulescu, R., Chang, E., Hochberg, M., Campbell, C., Aghera, A. & Valentin, T., 2008. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. *Annals of Emergency Medicine*, *52*(4), pp.399-406.

Friedman, D.I. & De Ver Dye, T., 2009. Migraine and the environment. *Headache*, 49(6), pp.941–952.

Fukui, P.T., Gonçalves, T.R.T., Strabelli, C.G., Lucchino, N.M.F., Matos, F.C., dos Santos, J.P.M., Zukerman, E., Zukerman-Guendler, V., Mercante, J.P., Masruha, M.R., Vieira, D.S. & Peres, M.F.P., 2008. Trigger factors in migraine patients. *Arquivos de Neuro-Psiquiatria*, *66*(3A), pp.494-499.

Furman, J.M., Marcus, D.A. & Balaban, C.D., 2013. Vestibular migraine: Clinical aspects and pathophysiology. *The Lancet Neurology*, 12(7), pp.706–715.

Gallagher, R.M. & Mueller, L., 2003. Managing intractable migraine with naratriptan. *Headache*, 43(9), pp.991–993.

Gantenbein, A.R., Afra, J., Jenni, W. & Sándor, P.S., 2012. Complementary and alternative treatments for migraine. *Techniques in Regional Anesthesia and Pain Management*, 16(1), pp.76–81.

Garcia-Leiva, J.M., Calandre, E.P. & Rico-Villademoros, F., 2008. An open-label trial of pregabalin effectiveness and tolerability in the prophylactic treatment of chronic migraine. *European Neuropsychopharmacology*, 18(S4), p.S570.

García-Martín, E., Martínez, C., Serrador, M., Alonso-Navarro, H., Navacerrada, F., Agúndez, J.A. & Jiménez-Jiménez, F.J., 2010. Alcohol dehydrogenase 2 genotype and risk for migraine. *Headache*, 50(1), pp.85–91.

Gasparini, C.F., Sutherland, H.G. & Griffiths, L.R., 2013. Studies on the pathophysiology and genetic basis of migraine. *Current Genomics*, 14(5), pp.300–315.

Gaul, C., Diener, H.-C. & Danesch, U., 2015. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. *The Journal of Headache and Pain*, 16(32), pp.1–8.

Gelfand, A.A. & Goadsby, P.J., 2012. A Neurologist's Guide to Acute Migraine Therapy in the Emergency Room. *The Neurohospitalist*, 2(2), pp.51–59.

Giannini, G., Zanigni, S., Grimaldi, D., Melotti, R., Pierangeli, G., Cortelli, P. & Cevoli, S., 2013. Cephalalgiaphobia as a feature of high-frequency migraine: a pilot study. *The Journal of Headache and Pain*, 14(1), pp.1–6.

Giffin, N.J., Ruggiero, L., Lipton, R.B., Silberstein, S.D., Tvedskov, J.F., Olesen, J., Altman, J., Goadsby, P.J. & Macrae, A., 2003. Premonitory symptoms in migraine: an electronic diary study. *Neurology*, 60(6), pp.935–940.

Gilman, S., 2010. *Oxford American Handbook of Neurology*. In New York: Oxford University Press: pp.1-462.

Gilmore, B. & Michael, M., 2011. Treatment of acute migraine headache. *American Family Physician*, 83(3), pp.271–280.

Goadsby, P.J., 2007. Recent advances in understanding migraine mechanisms, molecules and therapeutics. *Trends in Molecular Medicine*, 13(1), pp.39–44.

Goadsby, P.J., Lipton, R.B. & Ferrari, M.D., 2002. Migraine current understanding and treatment. *The New England Journal of Medicine*, 346(4), pp.257–270.

Goadsby, P.J., Schoenen, J., Ferrari, M.D., Silberstein, S.D. & Dodick, D., 2006. Towards a definition of intractable headache for use in clinical practice and trials. *Cephalalgia*, 26(9), pp.1168–1170.

Göbel, C.H., Göbel, A. & Göbel, H., 2013. "Compulsive plague! pain without end!" How Richard Wagner played out his migraine in the opera Siegfried. *BMJ*, 347, pp.f6952 1-4.

Göbel, H., Heinze, A., Heinze-Kuhn, K. & Lindner, V., 2001. Efficacy and tolerability of rizatriptan 10 mg in migraine: experience with 70 527 patient episodes. *Headache*, 41(3), pp.264–270.

Golden, W., Evans, J.K. & Hu, H., 2009. Migraine strikes study: Factors in patients' decision to treat early. The *Journal of Headache and Pain*, 10(2), pp.93–99.

Granella, F., Sances, G., Allais, G., Nappi, R.E., Tirelli, A., Benedetto, C., Brundu, B., Facchinetti, F. & Nappi, G., 2004. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. *Cephalalgia*, 24(9), pp.707–716.

Grosberg, B.M., Solomon, S. & Lipton, R.B., 2005. Retinal migraine. *Current Pain and Headache Reports*, 9(4), pp.268–271.

Guidetti, D., Rota, E., Morelli, N. & Immovilli, P., 2014. Migraine and Stroke: "Vascular" Comorbidity. *Frontiers in Neurology*, 5(October), pp.1–11.

Guidotti, M., Mauri, M., Barrilà, C., Guidotti, F. & Belloni, C., 2007. Frovatriptan vs. transdermal oestrogens or naproxen sodium for the prophylaxis of menstrual migraine. *The Journal of Headache and Pain*, 8(5), pp.283–288.

Guldiken, B., Guldiken, S., Taskiran, B., Koc, G., Turgut, N., Kabayel, L. & Tugrul, A., 2009. Migraine in Metabolic Syndrome. *The Neurologist*, 15(2), pp.55–58.

Gupta, S., Mehrotra, S., Villalón, C.M., Perusquía, M., Saxena, P.R. & MaassenVanDenBrink, A., 2007. Potential role of female sex hormones in the pathophysiology of migraine. *Pharmacology & Therapeutics*, 113(2), pp.321–340.

Gupta, S., Nahas, S.J. & Peterlin, B.L., 2011. Chemical mediators of migraine: Preclinical and clinical observations. *Headache*, 51(6), pp.1029–1045.

Haan, J. & Ferrari, M.D., 2011. Picasso's migraine: Illusory cubist splitting or illusion? *Cephalalgia*, 31(9), pp.1057–1060.

Hadjikhani, N., del Rio, M.S., Wu, O., Schwartz, D., Bakker, D., Fischl, B., Kwong, K.K., Cutrer, F.M., Rosen, B.R., Tootell, R.B. & Sorensen, A.G., 2001. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proceedings of the National Academy of Sciences*, *98*(8), pp.4687-4692.

Haimanot, R.T., 2003. Burden of headache in Africa. The *Journal of Headache and Pain*, 4(1), pp.s47–s54.

Hamel, E., 2007. Serotonin and migraine: Biology and clinical implications. *Cephalalgia*, 27(11), pp.1295–1300.

Hansen, J.M., Goadsby, P.J. & Charles, A. C., 2016. Variability of clinical features in attacks of migraine with aura. *Cephalalgia*, 36(3), pp.1–9.

Harris, S.P., 2005. Chiropractic management of a patient with migraine headache. *Journal of Chiropractic Medicine*, 4(1), pp.25–31.

Hauge, A.W., Kirchmann, M. & Olesen, J., 2011. Characterization of consistent triggers of migraine with aura. *Cephalalgia*, 31(4), pp.416–438.

Hauge, A.W., Kirchmann, M. & Olesen, J., 2010. Trigger factors in migraine with aura. *Cephalalgia*, 30(3), pp.346–353.

Hazard, E., Munakata, J., Bigal, M.E., Rupnow, M.F.T. & Lipton, R.B., 2009. The burden of migraine in the United States: current and emerging perspectives on disease management and economic analysis. *Value in health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 12(1), pp.55–64.

He, Y., Li, Y. & Nie, Z., 2015. Typical aura without headache: a case report and review of the literature. *Journal of Medical Case Reports*, 9(40), pp.1–5.

Headache Australia. (2016). *Home - Headache Australia*. [online] Available at: http://headacheaustralia.org.au [Accessed 12 July 2016].

Headache Classification Committee of the International Headache Society (IHS), 2013. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*, 33(9), pp.629–808.

Headaches.org. (2016). [online] Available at: http://www.headaches.org/wp-content/uploads/2015/05/Your-Migraine-Your-Symptoms_What-You-Need-To-Know-No-Marks.pdf?7a7d37 [Accessed 30 July 2016].

Hedborg, K., Anderberg, U.M. & Muhr, C., 2011. Stress in migraine: personality-dependent vulnerability, life events, and gender are of significance. *Upsala journal of medical sciences*, 116(3), pp.187–199.

Hedborg, K. & Muhr, C., 2012. The influence of multimodal behavioral treatment on the consumption of acute migraine drugs: a randomized, controlled study. *Cephalalgia*, 32(4), pp.297–307.

van Hemert, S., Breedveld, A.C., Rovers, J.M.P., Vermeiden, J.P.W., Witteman, B.J.M., Smits, M.G. & de Roos, N.M., 2014. Migraine Associated with Gastrointestinal Disorders: Review of the Literature and Clinical Implications. *Frontiers in Neurology*, 5, p. 241. pp.1–7.

Henry, P., Michel, P., Brochet, B., Dartigues, J.F., Tison, S. & Salamon, R., 1992. A nationwide survey of migraine in France: Prevalence and clinical features in adults. *Cephalalgia*, 12(4), pp.229–237.

Hering-Hanit, R., Friedman, Z., Schlesinger, I. & Ellis, M., 2001. Evidence for activation of the coagulation system in migraine with aura. *Cephalalgia*, 21(2), pp.137–139.

Heywood, J., Bomhof, M.A.M., Pradalier, A., Thaventhiran, L., Winter, P. & Hassani, H., 2000. Tolerability and efficacy of naratriptan tablets in the acute treatment of migraine attacks for 1 year. *Cephalalgia*, 20(5), pp.470–474.

Heywood, J., Colgan, T. & Coffey, C., 1998. Prevalence of headache and migraine in an Australian city. *Journal of Clinical Neuroscience*, 5(4), pp.485–490.

Hoffmann, J. & Goadsby, P.J., 2014. Emerging targets in migraine. *CNS Drugs*, 28(1), pp.11–17.

Hoffmann, J., Lo, H., Neeb, L., Martus, P. & Reuter, U., 2011. Weather sensitivity in migraineurs. *Journal of Neurology*, 258(4), pp.596–602.

Hoffmann, J., Schirra, T., Lo, H., Neeb, L., Reuter, U. & Martus, P., 2014. The influence of weather on migraine – are migraine attacks predictable ? *Annals of Clinical and Translational Neurology*, 2(1), pp.22–28.

Holroyd, K.A., Cottrell, C.K., O'Donnell, F.J., Cordingley, G.E., Drew, J.B., Carlson, B.W. & Himawan, L., 2010. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. *BMJ (Clinical Research ed.)*, 341, p.c4871.

Holroyd, K.A. & Drew, J.B., 2006. Behavioral Approaches to the Treatment of Migraine. Seminars in Neurology, 1(212), pp.199–207.

Houinato, D., Adoukonou, T., Ntsiba, F., Adjien, C., Avode, D.G. & Preux, P.M., 2010. Prevalence of migraine in a rural community in south Benin. *Cephalalgia*, 30(1), pp.62–67.

Houtveen, J.H. & Sorbi, M.J., 2013. Prodromal functioning of migraine patients relative to their interictal state - an ecological momentary assessment study. *PLoS ONE*, 8(8), p.e72827 1-10.

Hsu, L.C., Wang, S.J. & Fuh, J.L., 2011. Prevalence and impact of migrainous vertigo in mid-life women: a community-based study. *Cephalalgia*, *31*(1), pp.77-83.

Hu, Y., Guan, X., Fan, L. & Jin, L., 2013. Triptans in prevention of menstrual migraine: a systematic review with meta-analysis. *The Journal of Headache and Pain*, *14*(1), pp.1-9.

Huang, Y., Cai, X., Song, X., Tang, H., Huang, Y., Xie, S. & Hu, Y., 2013. Steroids for preventing recurrence of acute severe migraine headaches: A meta-analysis. *European Journal of Neurology*, 20(8), pp.1184–1190.

Humphrey, P.P.A., 2008. The discovery and development of the triptans, a major therapeutic breakthrough. *Headache*, 48(5), pp.685–687.

Ibiloglu, A.O. & Caykoylu, A., 2011. The comorbidity of migraine in bipolar disorder. *Journal of Mood Disorders*, 1(1), pp.25–33.

Ibrahimi, K., Couturier, E.G.M. & MaassenVanDenBrink, A., 2014. Migraine and perimenopause. *Maturitas*, 78(4), pp.277–280.

Ifergane, G., Buskila, D., Simiseshvely, N., Zeev, K. & Cohen, H., 2006. Prevalence of fibromyalgia syndrome in migraine patients. *Cephalalgia*, 26(4), pp.451–456.

Ihs-headache.org. (2016). *International Headache Society*. [online] Available at: http://www.ihs-headache.org/ichd-guidelines [Accessed 12 July 2016].

Irimia, P., Palma, J.-A., Fernandez-Torron, R. & Martinez-Vila, E., 2011. Refractory migraine in a headache clinic population. *BMC Neurology*, 11(1), p.94 1-6.

Izzati-Zade, K.F., 2008. The role of serotonin in the pathogenesis and clinical presentations of migraine attacks. *Neuroscience and Behavioral Physiology*, 38(5), pp.501–505.

Jackson, J.L., Cogbill, E., Santana-Davila, R., Eldredge, C., Collier, W., Gradall, A., Sehgal, N. & Kuester, J., 2015. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. *PLoS ONE*, 10(7), pp.1–60.

Jahromi, S.R., Abolhasani, M., Meysamie, A. & Togha, M., 2013. The effect of body fat mass and fat free mass on migraine headache. *Iranian Journal of Neurology*, 12(1), pp.23–27.

Jiménez-Sánchez, S., Fernández-de-las-Peñas, C., Jiménez-García, R., Hernández-Barrera, V., Alonso-Blanco, C., Palacios-Ceña, D. & Carrasco-Garrido, P., 2013. Prevalence of migraine headaches in the Romany population in Spain sociodemographic factors, lifestyle and co-morbidity. *Journal of Transcultural Nursing*, *24*(1), pp.6-13.

Johnston, M.M. & Rapoport, A.M., 2010. Triptans for the management of migraine. *Drugs*, 70(12), pp.1505–1518.

Jones, J.M., 2015. Refractory Migraine in a “Just World.” *Headache*, 55(1), pp.183–185.

Jones, J., Pack, S. & Chun, E., 1996. Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *The American Journal of Emergency Medicine*, 14(3), pp.262–264.

Jonker, J. & Pennink, B., 2010. *The Essence of Research Methodology*. In Heildelberg. Springer; pp.1-171.

Jürgens, T., Berger, K., Straube, A. & Khil, L., 2015. Migraine with aura is associated with impaired colour vision: Results from the cross-sectional German DMKG headache study. *Cephalalgia*, 35(6), pp.508–515.

Jürgens, T.P., Schulte, L.H. & May, A., 2014. Migraine trait symptoms in migraine with and without aura. *Neurology*, 82(16), pp.1416–1424.

Kalita, J., Bhoi, S.K. & Misra, U.K., 2013. Amitriptyline vs divalproate in migraine prophylaxis: A randomized controlled trial. *Acta Neurologica Scandinavica*, 128(1), pp.65–72.

Kaniecki, R.G., 2009. Basilar-type migraine. *Current Pain and Headache Reports*, 13(3), pp.217–220.

Kato, Y., Hayashi, T., Kobayashi, T. & Tanahashi, N., 2013. Migraine prevalence in patients with atrial septal defect. *The Journal of Headache and Pain*, 14(1), p.63 1-4.

Katsarava, Z., Buse, D.C., Manack, A.N. & Lipton, R.B., 2012. Defining the differences between episodic migraine and chronic migraine. *Current Pain and Headache Reports*, 16(1), pp.86–92.

Kelley, N.E. & Tepper, D.E., 2012. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications. *Headache*, 52(3), pp.467–482.

Kelman, L., 2004a. Osmophobia and taste abnormality in migraineurs: A tertiary care study. *Headache*, 44(10), pp.1019–1023.

Kelman, L., 2004b. The aura: a tertiary care study of 952 migraine patients. *Cephalalgia*, 24(9), pp.728–734.

Kelman, L., 2004c. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache*, 44(9), pp.865–872.

Kelman, L., 2006. The postdrome of the acute migraine attack. *Cephalalgia*, 26(2), pp.214–220.

Kelman, L., 2007. The triggers or precipitants of the acute migraine attack. *Cephalalgia*, 27(5), pp.394–402.

Kelman, L. & Tanis, D., 2006. The relationship between migraine pain and other associated symptoms. *Cephalalgia*, 26(5), pp.548–553.

Kibler, J.L., Rhudy, J.L., Penzien, D.B., Rains, J.C., Meeks, G.R., Bennett, W. & Dollar, K.M., 2005. Hormones, menstrual distress, and migraine across the phases of the menstrual cycle. *Headache*, 45(9), pp.1181–1189.

Kim, B.-K., Chung, Y.K., Kim, J.-M., Lee, K.-S. & Chu, M.K., 2013. Prevalence, clinical characteristics and disability of migraine and probable migraine: a nationwide population-based survey in Korea. *Cephalalgia*, 33(13), pp.1106–1116.

Kimoto, K., Aiba, S., Takashima, R., Suzuki, K., Takekawa, H., Watanabe, Y., Tatsumoto, M. & Hirata, K., 2011. Influence of barometric pressure in patients with migraine headache. *Internal Medicine (Tokyo, Japan)*, 50(18), pp.1923–1928.

Kirthi, V., Derry, S. & Moore, R.A., 2013. Aspirin with or without an antiemetic for acute migraine headaches in adults. *The Cochrane Database of Systematic Reviews*, (4), pp.1–75.

Koehler, P.J. & Islet, H., 2002. The early use of ergotamine in migraine. Edward Woakes' report of 1868, its theoretical and practical background and its international reception. *Cephalalgia*, 22(1), pp.686–691.

Koehler, S.M. & Glaros, A., 1988. The effect of aspartame on migraine headache. *Headache*, *28*(1), pp.10-14.

Kol, C.M.C., Dekker, F., Knuistingh Neven, A., Assendelft, W.J.J. & Blom, J.W., 2008. Acceptance or rejection of prophylactic medicine in patients with migraine: A cross-sectional study. *British Journal of General Practice*, 58(547), pp.98–101.

Koppen, H. & van Veldhoven, P.L., 2013. Migraineurs with exercise-triggered attacks have a distinct migraine. *The Journal of Headache and Pain*, 14(1), pp.1–4.

Köseoglu, E., Naçar, M., Talaslioglu, A., & Çetinkaya, F., 2003. Epidemiological and clinical characteristics of migraine and tension type headache in 1146 females in Kayseri, Turkey. *Cephalalgia*, 23(5), pp.381–388.

Kothari, C.R., 2004. *Research Methodology Methods and Techniques*. In New Delhi: New Age International Publishers: pp.1-418.

Krymchantowski, A.V. & da Cunha Jevoux, C., 2014. Wine and headache. *Headache*, 54(6), pp.967–975.

Krymchantowski, A.V., Silva, M.T., Barbosa, J.S. & Alves, L.A., 2002. Amitriptyline versus amitriptyline combined with fluoxetine in the preventative treatment of transformed migraine: A double-blind study. *Headache*, 42(6), pp.510–514.

Küçükşen, S., Genç, E., Yılmaz, H., Sallı, A., Gezer, İ.A., Karahan, A.Y., Salbaş, E., Cingöz, H.T., Nas, Ö. & Uğurlu, H., 2013. The prevalence of fibromyalgia and its relation with headache characteristics in episodic migraine. *Clinical Rheumatology*, 32(7), pp.983–990.

Kulkarni, G., Rao, G., Gururaj, G., Subbakrishna, D., Steiner, T. & Stovner, L., 2014. EHMTI-0333. The prevalence and burden of migraine in india: results of a population-based study in Karnataka state. *The Journal of Headache and Pain*, 15(S1), p.B18.

Kumar, R., 2014. *Research Methodology a step-by-step guide for beginners*. K. Metzler, ed. In London: Sage Publications Ltd: pp.1-500.

Kutlu, A., Yaluğ, I., Mülayim, S., Temel Obuz, Ö. & Selekler, M., 2010. Trigger factors for migraine. *Archives of Neuropsychiatry*, 47(1), pp.58–64.

Kwak, C., Vuong, K.D. & Jankovic, J., 2003. Migraine headache in patients with Tourette syndrome. *Archives of Neurology*, 60(11), pp.1595–1598.

Labour.gov.za. (2016). *Basic Guide to Sick Leave — Department of Labour*. [online] Available at: http://www.labour.gov.za/DOL/legislation/acts/basic-guides/basic-guide-to-sick-leave/ [Accessed 13 July 2016].

Láinez, M.J.A., 2006. Rizatriptan in the treatment of migraine. *Neuropsychiatric Disease and Treatment*, 2(3), pp.247–259.

Lal, V. & Singla, M., 2010. Migraine comorbidities-a discussion. *Journal of The Association of Physicians of India*, 58(Supplement), pp.18–20.

Lampl, C., Buzath, A., Baumhackl, U. & Klingler, D., 2003. One-year prevalence of migraine in Austria: A nation-wide survey. *Cephalalgia*, 23(4), pp.280–286.

Lampl, C., Rudolph, M., Deligianni, C.I. & Mitsikostas, D.D., 2015. Neck pain in episodic migraine: premonitory symptom or part of the attack? *The Journal of Headache and Pain*, 16(80), pp.1–5.

Landy, S.H., Runken, M.C., Bell, C.F., Higbie, R.L. & Haskins, L.S., 2012. Examining the interrelationship of migraine onset, duration, and time to treatment. *Headache*, 52(3), pp.363–373.

Landy, S.H., Tepper, S.J., Schweizer, E., Almas, M. & Ramos, E., 2014. Outcome for headache and pain-free nonresponders to treatment of the first attack: a pooled post-hoc analysis of four randomized trials of eletriptan 40 mg. *Cephalalgia*, 34(5), pp.376–381.

Lane, R. & Davies, P., 2006. *Migraine (Neurological Disease and Therapy)*. In New York: Taylor & Francis: pp.1-368.

Lane, R. & Davies, P., 2010. Ophthalmoplegic migraine: The case for reclassification. *Cephalalgia*, 30(6), pp.655–661.

Latsko, M., Silberstein, S. & Rosen, N., 2011. Frovatriptan as preemptive treatment for fasting-induced migraine. *Headache*, 51(3), pp.369–374.

Lau, C.I., Lin, C.C., Chen, W.H., Wang, H.C. & Kao, C.H., 2014. Association between migraine and irritable bowel syndrome: A population-based retrospective cohort study. *European Journal of Neurology*, 21, pp.1198–1204.

Laurell, K., Artto, V., Bendtsen, L., Hagen, K., Häggström, J., Linde, M., Söderström, L., Tronvik, E., Wessman, M., Zwart, J.A. & Kallela, M., 2015. Premonitory symptoms in migraine: A cross-sectional study in 2714 persons. *Cephalalgia*, pp.1–9.

Lavados, P.M. & Tenhamm, E., 2001. Consulting behaviour in migraine and tension-type headache sufferers: A population survey in Santiago, Chile. *Cephalalgia*, 21(7), pp.733–737.

Law, S., Derry, S. & Moore, R. A., 2013. Naproxen with or without an antiemetic for acute migraine headaches in adults. *The Cochrane Database of Systematic Reviews*, 1(4), pp.1–50.

Leedy, P.D. & Ormrod, J.E., 2010. Chapter 1-3. In *Practical Research Planning and Design*. New Jersey: Merrill: pp.1–65.

Lemos, C., Alonso, I., Barros, J., Sequeiros, J., Pereira-Monteiro, J., Mendonça, D. & Sousa, A., 2012. Assessing risk factors for migraine: differences in gender transmission. *PloS one*, 7(11), pp.1–6.

Lempert, T. & Neuhauser, H., 2009. Epidemiology of vertigo, migraine and vestibular migraine. *Journal of Neurology*, 256(3), pp.333–338.

Leo, A. P., 1944. Spreading depression of activity in the cerebral cortex. *Journal of Physiology*, 7, pp.359–390.

Leonardi, M., 2015. Burden of migraine: what should we say more? *Neurological Sciences*, 36(S1), pp.1–3.

Leonardi, M., Raggi, A., Bussone, G. & D'Amico, D., 2010. Health-related quality of life, disability and severity of disease in patients with migraine attending to a specialty headache center. *Headache*, 50(10), pp.1576–1586.

Leonardi, M., Steiner, T.J., Scher, A.T. & Lipton, R.B., 2005. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *The Journal of Headache and Pain*, 6(6), pp.429–440.

Lepcha, A., Amalanathan, S., Augustine, A.M., Tyagi, A.K. & Balraj, A., 2013. Flunarizine in the prophylaxis of migrainous vertigo: a randomized controlled trial. *European Archives of Oto-Rhino-Laryngology*, 271, pp.2931–2936.

Levin, M.M. & Ward, T.N.M., 2004. Ophthalmoplegic migraine. *Current Pain and Headache Reports*, 8, pp.306–309.

Levy, D., Burstein, R. & Strassman, A.M., 2005. Calcitonin gene-related peptide does not excite or sensitize meningeal nociceptors: Implications for the pathophysiology of migraine. *Annals of Neurology*, 58(5), pp.698–705.

Li, Y., Zheng, H., Witt, C.M., Roll, S., Yu, S., Yan, J., Sun, G., Zhao, L., Huang, W. & Chang, X., 2012. Acupuncture for migraine prophylaxis: a randomized controlled trial. *Canadian Medical Association Journal*, 184(4), pp.401–410.

Limmroth, V. & Michel, M.C., 2001. The prevention of migraine: a critical review with special emphasis on β-adrenoceptor blockers. *British Journal of Clinical Pharmacology*, 52(3), pp.237–243.

Linde, K. & Rossnagel, K., 2012. Propranolol for migraine prophylaxis (Review) Propranolol for migraine prophylaxis. *The Cochrane Library*, (2), pp.1-119.

Linde, K., Streng, A., Jürgens, S., Hoppe, A., Brinkhaus, B., Witt, C., Wagenpfeil, S., Pfaffenrath, V., Hammes, M.G. & Weidenhammer, W., 2005. Acupuncture for patients with migraine: a randomized controlled trial. *Jama*, 293(17), pp.2118–2125.

Linde, M., Mulleners, W., Chronicle, E. & McCrory, D., 2013. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *The Cochrane Database of Systematic Reviews*, 6(6), pp.1–52.

Linde, M., Mulleners, W., Chronicle, E. & McCrory, D., 2014. Topiramate for the prophylaxis of episodic migraine in adults (Review). *Cochrane Database of Systematic Reviews*, (6), pp.1–110.

Linde, M., Mulleners, W.M., Chronicle, E.P. & McCrory, D.C., 2016. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults (Review). *Cochrane Database of Systematic Reviews*, (6), pp.1–52.

Lippi, G., Mattiuzzi, C. & Cervellin, G., 2014. Chocolate and migraine : the history of an ambiguous association. *Acta Biomed*, 85(3), pp.216–221.

Lipton, R.B. & Bigal, M.E., 2005. Migraine: epidemiology, impact, and risk factors for progression. *Headache*, 45 (S1), pp.s3–s13.

Lipton, R.B. & Bigal, M.E., 2007. Ten lessons on the epidemiology of migraine. *Headache*, 47(1), pp.2–9.

Lipton, R.B., Bigal, M.E., Diamond, M., Freitag, F., Reed, M.L. & Stewart, W.F., 2007. Migraine prevalence , disease burden , and the need for preventive therapy Herein we describe the epidemiology of migraine. *Neurology*, 68(5), pp.343–359.

Lipton, R.B., Buse, D.C., Saiers, J., Fanning, K.M., Serrano, D. & Reed, M.L., 2013. Frequency and burden of headache-related nausea: Results from the american migraine prevalence and prevention (AMPP) study. *Headache*, 53(1), pp.93–103.

Lipton, R.B., Gobel, H., Einhaupl, K.M., Wilks, K. & Mauskop, A., 2004. Petasites Hybridus Root (Butterbur) is an Effective Preventive Treatment for Migraine. *Neurology. The Official Journal of the American Academy of Neurology*, 63(12), pp.2240–2244.

Lipton, R.B., Newman, L.C., Cohen, J.S. & Solomon, S., 1989. Aspartame as a dietary trigger of headache. *Headache*, 29(2), pp.90–92.

Lipton, R.B., Pavlović, J.M., Haut, S.R., Grosberg, B.M. & Buse, D.C., 2014. Methodological issues in studying trigger factors and premonitory features of migraine. *Headache*, 54(10), pp.1661–1669.

Lipton, R.B. & Silberstein, S.D., 1994. Why study the comorbidity of migraine? *Neurology*, 44(10S7), pp.S4–S5.

Lipton, R.B., Silberstein, S., Dodick, D., Cady, R., Freitag, F., Mathew, N., Biondi, D.M., Ascher, S., Olson, W.H. & Hulihan, J., 2011. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. *Cephalalgia*, *31*(1), pp.18-30.

Lipton, R.B., Stewart, W.F., Diamond, S., Diamond, M.L. & Reed, M., 2001. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache*, 41(7), pp.646–657.

Lipton, R.B., Stewart, W.F. & Scher, A.I., 2001. Epidemiology and economic impact of migraine. *Current Medical Research and Opinion*, 17(S1), pp.s4–s12.

Loder, E., 2005. Fixed drug combinations for the acute treatment of migraine: Place in therapy. *CNS Drugs*, 19(9), pp.769–784.

Loder, E., Burch, R. & Rizzoli, P., 2012. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache*, 52(6), pp.930–945.

Loder, E., Rizzoli, P. & Golub, J., 2007. Hormonal management of migraine associated with menses and the menopause: A clinical review: CME. *Headache*, 47(2), pp.329–340.

Loder, S., Sheikh, H.U. & Loder, E., 2015. The Prevalence, Burden, and Treatment of Severe, Frequent, and Migraine Headaches in US Minority Populations: Statistics From National Survey Studies. *Headache*, 55(2), pp.214–228.

Lodi, R., Iotti, S., Cortelli, P., Pierangeli, G., Cevoli, S., Clementi, V., Soriani, S., Montagna, P. & Barbiroli, B., 2001. Deficient energy metabolism is associated with low free magnesium in the brains of patients with migraine and cluster headache. *Brain Research Bulletin*, 54(4), pp.437–441.

López-Mesonero, L., Márquez, S., Parra, P., Gámez-Leyva, G., Muñoz, P. & Pascual, J., 2009. Smoking as a precipitating factor for migraine: A survey in medical students. The *Journal of Headache and Pain*, 10(2), pp.101–103.

Lovati, C., Giani, L., Castoldi, D., Mariotti D'Alessandro, C., DeAngeli, F., Capiluppi, E., D'Amico, D. & Mariani, C., 2015. Osmophobia in allodynic migraineurs: cause or consequence of central sensitization? *Neurological Sciences*, 36(1), pp.145–147.

Lucas, C., Géraud, G., Valade, D., Chautard, M.H. & Lantéri-Minet, M., 2006. Recognition and therapeutic management of migraine in 2004, in France: Results of FRAMIG 3, a French nationwide population-based survey. *Headache*, 46(5), pp.715–725.

Lucchetti, G. & Peres, M.F.P., 2011. The prevalence of migraine and probable migraine in a Brazilian favela: Results of a community survey. *Headache*, 51(6), pp.971–979.

Luciani, R., Carter, D., Mannix, L., Hemphill, M., Diamond, M. & Cady, R., 2000. Prevention of migraine during prodrome with naratriptan. *Cephalalgia*, 20(2), pp.122–126.

Lyngberg, A.C., Rasmussen, B.K., Jørgensen, T. & Jensen, R., 2005. Has the prevalence of migraine and tension-type headache changed over a 12-year period? A Danish population survey. *European Journal of Epidemiology*, 20(3), pp.243–249.

MacGregor, E.A., Brandes, J. & Eikermann, A., 2003. Migraine prevalence and treatment patterns: The global Migraine And Zolmitriptan Evaluation survey. *Headache*, 43(1), pp.19–26.

MacGregor, E.A., Pawsey, S.P., Campbell, J.C. & Hu, X., 2010. Safety and tolerability of frovatriptan in the acute treatment of migraine and prevention of menstrual migraine: Results of a new analysis of data from five previously published studies. *Gender Medicine*, 7(2), pp.88–108.

MacGregor, E.A., Victor, T.W., Hu, X., Xiang, Q., Puenpatom, R. A., Chen, W. & Campbell, J.C., 2010. Characteristics of menstrual vs nonmenstrual migraine: A post hoc, within-woman analysis of the usual-care phase of a nonrandomized menstrual migraine clinical trial. *Headache*, 50(4), pp.528–538.

Mäki, K., Vahtera, J., Virtanen, M., Elovainio, M., Keltikangas-Järvinen, L. & Kivimäki, M., 2008. Work stress and new-onset migraine in a female employee population. *Cephalalgia*, 28(1), pp.18–25.

Maleki, N., Becerra, L., Nutile, L., Pendse, G., Brawn, J., Bigal, M., Burstein, R. & Borsook, D., 2011. Migraine attacks the Basal Ganglia. *Molecular Pain*, 7(1), pp.1-11.

Maleki, N., Linnman, C., Brawn, J., Burstein, R., Becerra, L. & Borsook, D., 2012. Her versus his migraine: multiple sex differences in brain function and structure. *Brain*, 135, pp.2546–2559.

Manack, A.N., Buse, D.C. & Lipton, R.B., 2011. Chronic migraine: Epidemiology and disease burden. *Current Pain and Headache Reports*, 15(1), pp.70–78.

Mancia, G., Rosei, E.A., Ambrosioni, E., Avino, F., Carolei, A., Dacco, M., Di Giacomo, G., Ferri, C., Grazioli, I., Melzi, G. & Nappi, G., 2011. Hypertension and migraine comorbidity: prevalence and risk of cerebrovascular events: evidence from a large, multicenter, cross-sectional survey in Italy (MIRACLES study). *Journal of Hypertension*, *29*(2), pp.309-318.

Maniyar, F.H., Sprenger, T., Schankin, C. & Goadsby, P.J., 2013. Imaging the premonitory phase of migraine-new insights into generation of the migraine attack. The *Journal of Headache and Pain*, 14(S1), p.P112.

Maniyar, F.H., Sprenger, T., Schankin, C. & Goadsby, P.J., 2014. The origin of nausea in migraine-a PET study. *The Journal of Headache and Pain*, 15(84), pp.1–6.

Marcus, D.A., Bernstein, C. & Rudy, T.E., 2005. Fibromyalgia and headache: an epidemiological study supporting migraine as part of the fibromyalgia syndrome. *Clinical Rheumatology*, 24(6), pp.595–601.

Marcus, D.A. & Bhowmick, A., 2013. Fibromyalgia comorbidity in a community sample of adults with migraine. *Clinical Rheumatology*, 32(10), pp.1553–1556.

Marmura, M.J., Silberstein, S.D. & Schwedt, T.J., 2015. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. *Headache*, 55(1), pp.3–20.

Martelletti, P., Katsarava, Z., Lampl, C., Magis, D., Bendtsen, L., Negro, A., Russell, M.B., Mitsikostas, D.D. & Jensen, R.H., 2014. Refractory chronic migraine : A Consensus Statement on clinical definition from the European Headache Federation. *The Journal of Headache and Pain*, 15(47), pp.1–6.

Martin, G. V, Houle, T., Nicholson, R., Peterlin, A. & Martin, V.T., 2013. Lightning and its association with the frequency of headache in migraineurs: An observational cohort study. *Cephalalgia*, 33(6), pp.375–383.

Martin, P.R., 2010. Behavioral management of migraine headache triggers: Learning to cope with triggers. *Current Pain and Headache Reports,* 14(3), pp 221-227*.*

Martin, V.T., 2014. Migraine and the menopausal transition. *Neurological Sciences*, 35(S1), pp.65–69.

Martin, V.T., Fanning, K.M., Serrano, D., Buse, D.C., Reed, M.L., Bernstein, J. A. & Lipton, R.B., 2014. Chronic rhinitis and its association with headache frequency and disability in persons with migraine: Results of the American Migraine Prevalence and Prevention (AMPP) Study. *Cephalalgia*, 34(5), pp.336–348.

Martin, V.T. & Lipton, R.B., 2008. Epidemiology and biology of menstrual migraine: Research submission. *Headache*, 48(3), pp.124–131.

Martin, V.T., Taylor, F., Gebhardt, B., Tomaszewski, M., Ellison, J.S., Martin, G. V, Levin, L., Al-Shaikh, E., Nicolas, J. & Bernstein, J.A., 2011. Allergy and immunotherapy: are they related to migraine headache? *Headache*, 51(1), pp.8–20.

Martins, I.P. & Gouveia, R.G., 2007. More on water and migraine. *Cephalalgia*, 27(4), pp.372–374.

Marugán, J.M., Fernández-Castaño, M.T., Del Carmen Torres, M. & Del Carmen De Fuentes, M., 2008. The functional recurrent abdominal pain (RAP) in children may be the precursor of adult migraine. *Cephalalgia*, 28(5), pp.571–572.

Masruha, M.R., Lin, J., De Souza Vieira, D.S., Minett, T.S.C., Cipolla-Neto, J., Zukerman, E., Vilanova, L.C.P. & Peres, M.F.P., 2010. Urinary 6-sulphatoxymelatonin levels are depressed in chronic migraine and several comorbidities. *Headache*, 50(3), pp.413–419.

Mathew, N.T., 1999. Migraine and hypertension. *Cephalalgia*, 19(25), pp.17–19.

Mathew, N.T., 2011. Pathophysiology of chronic migraine and mode of action of preventive medications. *Headache*, 51(S2), pp.84–92.

Mathew, N.T., Kailasam, J. & Meadors, L., 2004. Early treatment of migraine with rizatriptan: a placebo-controlled study. *Headache*, 44(7), pp.669–673.

Mathew, N.T., Kailasam, J. & Seifert, T., 2004. Clinical recognition of allodynia in migraine. *Neurology*, 63(5), pp.848–852.

Mathew, N.T., Rapoport, A., Saper, J., Magnus, L., Klapper, J., Ramadan, N., Stacey, B. & Tepper, S., 2001. Efficacy of gabapentin in migraine prophylaxis. *Headache*, 41(2), pp.119–128.

Matías-Guiu, J., Porta-Etessam, J., Mateos, V., Díaz-Insa, S., Lopez-Gil, A. & Fernández, C., 2011. One-year prevalence of migraine in Spain: a nationwide population-based survey. *Cephalalgia*, 31(4), pp.463–470.

Mattsson, P., 2007. Migraine headache and obesity in women aged 40-74 years: A population-based study. *Cephalalgia*, 27(8), pp.877–880.

Mbewe, E., Zairemthiama, P., Paul, R., Birbeck, G.L. & Steiner, T.J., 2015. The burden of primary headache disorders in Zambia: national estimates from a population-based door-to-door survey. *The Journal of Headache and Pain*, 16(1), p.1-8.

Mbewe, E., Zairemthiama, P., Yeh, H.-H., Paul, R., Birbeck, G.L. & Steiner, T.J., 2015. The epidemiology of primary headache disorders in Zambia: a population-based door-to-door survey. *The Journal of Headache and Pain*, 16(1), p.30 1-9.

McCormack, P.L. & Keating, G.M., 2006. Eletriptan: A review of its use in the acute treatment of migraine. *Drugs*, 66(9), pp.1129–1149.

Menon, B. & Kinnera, N., 2013. Prevalence and characteristics of migraine in medical students and its impact on their daily activities. *Annals of Indian Academy of Neurology*, 16(2), pp.221–225.

Merikangas, K.R., 2013. Contributions of epidemiology to our understanding of migraine. *Headache*, 53(2), pp.230–246.

Merikangas, K.R., Whitaker, A E., Isler, H. & Angst, J., 1994. The Zurich Study: XXIII. Epidemiology of headache syndromes in the Zurich cohort study of young adults. *European Archives of Psychiatry and Clinical Neuroscience*, 244(3), pp.145–152.

Meschino, J.P., Natural Supplements for Migraine Prevention : Butterbur and Feverfew. pp.1–8.
Available at: http://www.dynamicchiropractic.com/mpacms/dc/article.php?id=54885 [Accessed 2 Aug 2015].

Misakian, A.L., Langer, R.D., Bensenor, I.M., Cook, N.R., Manson, J.E., Buring, J.E. & Rexrode, K.M., 2003. Postmenopausal hormone therapy and migraine headache. *Journal of Women's Health (2002)*, 12(10), pp.1027–1036.

Mitchell, P., Wang, J.J., Currie, J., Cumming, R.G. & Smith, W., 1998. Prevalence and vascular associations with migraine in older Australians. *Australian and New Zealand Journal of Medicine*, 28(5), pp.627–632.

Modi, S. & Lowder, D.M., 2006. Medications for migraine prophylaxis. *American Family Physician*, 73(1), pp.72–78.

Moini, J., 2009. *Fundemaental Pharmacology for Pharmacy Technicians*. In New York: Delmar Cengage Learning: pp.1-594.

Mollaoğlu, M., 2013. Trigger factors in migraine patients. *Journal of Health Psychology*, 18(7), pp.984–994.

Monteith, T.S. & Goadsby, P.J., 2011. Acute migraine therapy: New drugs and new approaches. *Current Treatment Options in Neurology*, 13, pp.1–14.

Morgan, I., Eguia, F., Gelaye, B., Peterlin, B.L., Tadesse, M.G., Lemma, S., Berhane, Y. & Williams, M. A, 2015. Sleep disturbances and quality of life in Sub-Saharan African migraineurs. *The Journal of Headache and Pain*, 16(1), pp.12–19.

Morillo, L.E., Alarcon, F., Aranaga, N., Aulet, S., Chapman, E., Conterno, L., Estevez, E., Garcia-Pedroza, F., Garrido, J. & Macias-Islas, M., 2005. Prevalence of migraine in Latin America. *Headache*, 45(2), pp.106–117.

Moschiano, F., D'Amico, D., Allais, G., Rigamonti, A., Melzi, P., Schieroni, F. & Bussone, G., 2005. Early triptan intervention in migraine: an overview. *Neurological Sciences*, *26*(2), pp.s108-s110.

Mouton, J. & Marais, H., 1990. *Basic Concepts in the methodology of the social sciences*. Johann Mouton, ed. In Pretoria: Human Sciences Research Council Press: pp.1-269.

Mulak, A. & Paradowski, L., 2004. [Migraine and irritable bowel syndrome]. *Neurologia i neurochirurgia polska*, 39(4 S1), pp.55–60 Abstract.

Mulleners, W.M., Aurora, S.K., Chronicle, E.P., Stewart, R., Gopal, S. & Koehler, P.J., 2001. Self-reported photophobic symptoms in migraineurs and controls are reliable and predict diagnostic category accurately. *Headache*, 41(1), pp.31–39.

Mulleners, W.M. & Chronicle, E.P., 2008. Anticonvulsants in migraine prophylaxis: A Cochrane review. *Cephalalgia*, 28(6), pp.585–597.

Munakata, J., Hazard, E., Serrano, D., Klingman, D., Rupnow, M.F.T., Tierce, J., Reed, M. & Lipton, R.B., 2009. Economic burden of transformed migraine: Results from the american migraine prevalence and prevention (AMPP) study. *Headache*, 49(4), pp.498–508.

Murtaza, M., Kisat, M., Daniel, H. & Sonawalla, A.B., 2009. Classification and clinical features of headache disorders in Pakistan: a retrospective review of clinical data. *PloS one*, 4(6), p.e5827.

Nachit-Ouinekh, F., Chrysostome, V., Henry, P., Sourgen, C., Dartigues, J.F. & El Hasnaoui, A, 2005. Variability of reported headache symptoms and diagnosis of migraine at 12 months. *Cephalalgia*, 25(2), pp.117–123.

Nadelson, C., 2006. Sport and exercise-induced migraines. *Current Sports Medicine Reports*, 5(1), pp.29–33.

Nestoriuc, Y. & Martin, A., 2007. Efficacy of biofeedback for migraine: A meta-analysis. *Pain*, 128, pp.111–127.

Newman, L.C. & Yugrakh, M.S., 2014. Menstrual migraine: treatment options. *Neurological Sciences*, 35(S1), pp.57–60.

Ng-Mak, D.S., Fitzgerald, K.A., Norquist, J.M., Banderas, B.F., Nelsen, L.M., Evans, C.J., Healy, C.G., Ho, T.W. & Bigal, M., 2011. Key concepts of migraine postdrome: A qualitative study to develop a post-migraine questionnaire. *Headache*, 51, pp.105–117.

Nicholson, R.A., Buse, D.C., Andrasik, F. & Lipton, R.B., 2011. Nonpharmacologic treatments for migraine and tension-type headache: How to choose and when to use. *Current Treatment Options in Neurology*, 13(1), pp.28–40.

Nicholson, R., Nash, J. & Andrasik, F., 2005. A self-administered behavioral intervention using tailored messages for migraine. *Headache*, 45(9), pp.1124–1139.
Pascual, J., 2002. Clinical Benefits of Early Triptan Therapy for Migraine. *Headache*, 42(S1), pp.10–17.

Nicholson, R.A., Rooney, M., Vo, K., Laughlin, E.O., Gordon, M., Rooney, M., Vo, D. & Louis, S., 2006. Migraine Care Among Different Ethnicities. *Headche*, 46(5), pp.754–765.

O'Brien, B., Goeree, R. & Streiner, D., 1994. Prevalence of migraine headache in Canada: a population-based survey. *International Journal of Epidemiology*, 23(5), pp.1020–1026.

Oedegaard, K.J., Angst, J., Neckelmann, D. & Fasmer, O.B., 2005. Migraine aura without headache compared to migraine with aura in patients with affective disorders. *The Journal of Headache and Pain*, 6(5), pp.378–386.

Oedegaard, K.J., Greenwood, T.A., Johansson, S., Jacobsen, K.K., Halmoy, A., Fasmer, O.B., Akiskal, H.S., Haavik, J. & Kelsoe, J.R., 2010. A genome-wide association study of bipolar disorder and comorbid migraine. *Genes, Brain and Behavior*, 9(7), pp.673–680.

Olesen, J., Burstein, R., Ashina, M. & Tfelt-Hansen, P., 2009. Origin of pain in migraine: evidence for peripheral sensitisation. *The Lancet Neurology*, 8(7), pp.679–690.

Ortiz, A., Cervantes, P., Zlotnik, G., Van De Velde, C., Slaney, C., Garnham, J., Turecki, G., O'Donovan, C. & Alda, M., 2010. Cross-prevalence of migraine and bipolar disorder. *Bipolar Disorders*, 12(4), pp.397–403.

Oxforddictionaries.com. (2016). *comorbidity: definition of comorbidity in Oxford dictionary (American English)*. [online] Available at: http://www.oxforddictionaries.com/definition/american_english/comorbidity [Accessed 13 July 2016].

Ozturk, A., Degirmenci, Y., Tokmak, B. & Tokmak, A., 2013. Frequency of migraine in patients with allergic rhinitis. *Pakistan Journal of Medical Sciences*, 29(2), pp.528–531.

Pablo-ruiz-picasso.net. (2016). *Pablo Picasso - 900+ paintings, biography, quotes, video, monuments*. [online] Available at: http://www.pablo-ruiz-picasso.net/ [Accessed 13 July 2016].

Panconesi, A., 2008. Alcohol and migraine: Trigger factor, consumption, mechanisms. A review. The *Journal of Headache and Pain*, 9(1), pp.19–27.

Panconesi, A., Bartolozzi, M.L. & Guidi, L., 2011. Alcohol and migraine: What should we tell patients? *Current Pain and Headache Reports*, 15(3), pp.177–184.

Panconesi, A., Bartolozzi, M.L., Mugnai, S. & Guidi, L., 2012. Alcohol as a dietary trigger of primary headaches: what triggering site could be compatible?. *Neurological Sciences*, *33*(1), pp.203-205.

Parkman, H.P., 2013. Migraine and gastroparesis from a gastroenterologist's perspective. *Headache*, 53(Suppl 1), pp.4–10.

Patel, R.M., Sarma, R. & Grimsley, E., 2006. Popular Sweetner Sucralose as a Migraine Trigger. *Headache*, 46, pp.1303–1305.

Paulino, J. & Griffin, C., 2001. *The Headache Sourcebook*. In Chicago: McGraw-Hill Professional: pp.1-287.

Pavlović, J.M., Buse, D.C., Sollars, C.M., Haut, S. & Lipton, R.B., 2014. Trigger Factors and Premonitory Features of Migraine Attacks : Summary of Studies. *Headache :The Journal of Head and Face Pain*, 54(19), pp.1670–1679.

Pavlović, J.M., Stewart, W.F., Bruce, C.A., Gorman, J.A., Sun, H., Buse, D.C. & Lipton, R.B., 2015. Burden of migraine related to menses: results from the AMPP study. *The The Journal of Headache and Pain*, 16(1), pp.1–11.

Pelzer, N., Stam, A.H., Haan, J., Ferrari, M.D. & Terwindt, G.M., 2013. Familial and sporadic hemiplegic migraine: Diagnosis and treatment. *Current Treatment Options in Neurology*, 15(1), pp.13–27.

Peng, K.P. & Wang, S.J., 2014. Epidemiology of headache disorders in the Asia-Pacific region. *Headache*, 54(4), pp.610–618.

Peres, M.F.P., Mercante, J.P.P., Guendler, V.Z., Corchs, F., Bernik, M. a., Zukerman, E. & Silberstein, S.D., 2007. Cephalalgiaphobia: A possible specific phobia of illness. The *Journal of Headache and Pain*, 8(1), pp.56–59.

Peroutka, S.J., 2014. What turns on a migraine? A systematic review of migraine precipitating factors. *Current Pain and Headache Reports*, 18(10), p.454 (1–6).

Peroutka, S.J., Price, S.C., Wilhoit, T.L. & Jones, K.W., 1998. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. *Molecular Medicine (Cambridge, Mass.)*, 4(1), pp.14–21.

Pesaturo, K.A. & Wooding, F.G., 2009. Modern Management of the Migraine Headache. *American Journal of Lifestyle Medicine*, 3(2), pp.147–159.

Petrusic, I., Zidverc-Trajkovic, J., Podgorac, A. & Sternic, N., 2013. Underestimated phenomena: higher cortical dysfunctions during migraine aura. *Cephalalgia*, 33(10), pp.861–867.

Pinkerman, B. & Holroyd, K., 2010. Menstrual and nonmenstrual migraines differ in women with menstrually-related migraine. *Cephalalgia*, 30(10), pp.1187–1194.

Pizzolato, R., Villani, V., Prosperini, L., Ciuffoli, A. & Sette, G., 2011. Efficacy and tolerability of pregabalin as preventive treatment for migraine: A 3-month follow-up study. The *Journal of Headache and Pain*, 12(5), pp.521–525.

Podoll, K. & Robinson, D., 2000. Illusory splitting as visual aura symptom in migraine. *Cephalalgia*, 20, pp.228–232.

Podoll, K. & Robinson, D., 2002. Splitting of the body image as somesthetic aura symptom in migraine. *Cephalalgia*, 22(1), pp.62–65.

Polit, D.F. & Beck, C.T., 2004. *Nursing Research: Principles and Methods*. In Philadelphia: Lippincott Williams & Wilkins: pp.1-758.

Pompili, M., Serafini, G., Innamorati, M., Serra, G., Dominici, G., Fortes-Lindau, J., Pastina, M., Telesforo, L., Lester, D., Girardi, P. & Tatarelli, R., 2010. Patient outcome in migraine prophylaxis: the role of psychopharmacological agents. *Patient Related Outcome Measures*, *1*, pp.107-118.

Porter, R.S. & Kaplan, J.L., 2011. *The Merck Manual of Diagnosis & Therapy*. In New York: Merck Sharp & Dohme Corp: pp.1-3800.

Powers, C., Szeto, S., Pangtay, D., Bort, T., Cervi, M. & Cady, R., 2000. Evaluation of migraineurs' preferences for naratriptan over conventional first-line agents. *Archives of Family Medicine*, 9(8), pp.753–758.

Prince, P.B., Rapoport, A.M., Sheftell, F.D., Tepper, S.J. & Bigal, M.E., 2004. Brief Communication The Effect of Weather on Headache. *Headache*, 44, pp.596–602.

Pruzan, P., 2016. *Research Methodology: The Aims, Practices and Ethics of Science*. In Switzerland: Springer International Publishing: pp.1-326.

Queiroz, L.P., Friedman, D.I., Rapoport, A.M. & Purdy, R.A., 2011. Characteristics of migraine visual aura in Southern Brazil and Northern USA. *Cephalalgia*, 31(16), pp.1652–1658.

Quintela, E., Castillo, J., Muñoz, P. & Pascual, J., 2006. Premonitory and resolution symptoms in migraine: A prospective study in 100 unselected patients. *Cephalalgia*, 26, pp.1051–1060.

Rabbie, R., Derry, S. & Moore, R.A, 2013. Ibuprofen with or without an antiemetic for acute migraine headaches in adults (Review). *The Cochrane Database of Systematic Reviews*, (4), pp.1–65.

Raddant, A.C. & Russo, A.F., 2011. Calcitonin gene-related peptide in migraine: intersection of peripheral inflammation and central modulation. *Expert Reviews in Molecular Medicine*, 13, p.e36 1-22.

Radtke, A. & Neuhauser, H., 2009. Prevalence and burden of headache and migraine in Germany. *Headache*, 49(1), pp.79–89.

Rahimtoola, H., Buurma, H., Tijssen, C., Leufkens, H. & Egberts, A., 2002. Incidence and determinants of migraine prophylactic medication in the Netherlands. *European Journal of Clinical Pharmacology*, 58(2), pp.149–155.

Rahimtoola, H., Buurma, H., Tijssen, C.C., Leufkens, H.G. & Egberts, A.C.G., 2003. Migraine prophylactic medication usage patterns in The Netherlands. *Cephalalgia*, 23(4), pp.293–301.

Ramadan, N., Silberstein, S. & Freitag, F., 2000. Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting : Pharmacological Management for Prevention of Migraine. pp.1–56.
Available at: http://tools.aan.com/professionals/practice/pdfs/gl0090.pdf [Accessed 5 May 2016].

Ramage-morin, P.L. & Gilmour, H., 2014. Prevalence of migraine in the Canadian household population. *Health Reports*, 25(6), pp.10–16.

Ravishankar, K., 2010. Migraine the new understanding. *The Journal of the Association of Physicians of India*, 58, pp.30–33.

Reed L., M., Fanning M., K., Serrano, D., Buse C., D. & Lipton B., R., 2015. Persistent Frequent Nausea Is Associated With Progression to Chronic Migraine: AMPP Study Results. *Headache*, 55(1), pp.76–87.

Reuter, U., Del Rio, M.S., Diener, H.C., Allais, G., Davies, B., Gendolla, A., Pfeil, J., Schwalen, S., Schäuble, B. & Van Oene, J., 2010. Migraines with and without aura and their response to preventive therapy with Topiramate. *Cephalalgia*, 30(5), pp.543–551.

Richman, P.B., Allegra, J., Eskin, B., Doran, J., Reischel, U., Kaiafas, C. & Nashed, A.H., 2002. A randomized clinical trial to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headache. *The American Journal of Emergency Medicine*, 20(1), pp.39–42.

Richman, P.B., Reischel, U., Ostrow, a, Irving, C., Ritter, A., Allegra, J., Eskin, B., Szucs, P. & Nashed, A.H., 1999. Droperidol for acute migraine headache. *The American Journal of Emergency Medicine*, 17(4), pp.398–400.

Riederer, F., Baumgartner, H., Sándor, P.S., Wessely, P. & Wöber, C., 2011. Headache in 25 consecutive patients with atrial septal defects before and after percutaneous closure-a prospective case series. *Headache*, 51(8), pp.1297–1304.

Ritchie, J. & Lewis, J., 2003. *Qualitative Research Practice: A Guide for Social Science Students and Researchers*: In Sage Publications Ltd: pp.1-356.

Robbins, L., 2015. Refractory (Difficult-to-Treat) Headache. In *Advanced Headache Therapy*. Springer International Publishing Switzerland, Chapter 2 pp. 49–114.

Robbins, L., 2015. Letters to the editor. *Headache*, 55(4), p.575.

Roberts, J.E. & deShazo, R.D., 2012. Abdominal Migraine, Another Cause of Abdominal Pain in Adults. *The American Journal of Medicine*, 125(11), pp.1135–1139.

Robertson, C.E. & Garza, I., 2012. Critical analysis of the use of onabotulinumtoxinA (botulinum toxin type A) in migraine. *Neuropsychiatric Disease and Treatment*, 8, pp.35–48.

Rockett, F.C., Castro, K., de Oliveira, V.R., da Silveira Perla, A., Fagundes Chaves, M. & Schweigert Perry, I., 2012. Perceived migraine triggers: Do dietary factors play a role. *Nutrición Hospitalaria*, *27*(2), pp.483-489.

Rockett, F.C., de Oliveira, V.R., Castro, K., Chaves, M.L.F., da S Perla, A. & Perry, I.D., 2012. Dietary aspects of migraine trigger factors. *Nutrition Reviews*, 70(6), pp.337–356.

Rosenfeld, G.C. & Loose, D.S., 2014. *Pharmacology*. *Journal of Chemical Information and Modeling*. In Baltimore: Lippincott Williams & Wilkins: pp.1-376.

Rossiter, D. ed., 2013. *South African Medicines Formulary (SAMF)*. In Cape Town: Health and Medical Publishing Group of the South African Medical Association: pp.1-654.

Rothrock, J.F., 2008. The truth about triggers. *Headache*, 48(3), pp.499–500.

Rozen, T.D., 2004. Migraine prodrome: a nose on a face. *The Lancet*, 363(9408), p.517.

Ruiz, L. & Ferrandi, D., 2009. Topiramate in migraine progression. *The Journal of Headache and Pain*, 10(6), pp.419–422.

Russell, G., Abu-Arafeh, I. & Symon, D.N.K., 2002. Abdominal migraine: evidence for existence and treatment options. *Paediatric Drugs*, 4(1), pp.1–8.

Russell, M.B., 2010. Genetics of menstrual migraine: The epidemiological evidence. *Current Pain and Headache Reports*, 14(5), pp.385–388.

Russell, M.B., 2008. Is migraine a genetic illness? The various forms of migraine share a common genetic cause. *Neurological Sciences*, 29(S1), pp.52–54.

Russell, M.B. & Ducros, A., 2011. Sporadic and familial hemiplegic migraine: Pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *The Lancet Neurology*, 10(5), pp.457–470.

Russell, M.B., Kristiansen, H.A., Šaltyté-Benth, J. & Kværner, K.J., 2008. A cross-sectional population-based survey of migraine and headache in 21,177 Norwegians: The Akershus sleep apnea project. The *Journal of Headache and Pain*, 9(6), pp.339–347.

Russell, M.B. & Olesen, J., 1996. A nosographic analysis of the migraine aura in a general population. *Brain*, 119 (2), pp.355–361.

Saberi, A., Nemati, S., Shakib, R.J., Kazemnejad, E. & Maleki, M., 2012. Association between allergic rhinitis and migraine. *Journal of Research in Medical Sciences*, 17(6), pp.508–512.

Sadeghi, O., Askari, G., Nasiri, M. & Maghsoudi, Z., 2015. The association Between Riboflavin Intake and Incidence of Migraine Symptoms: A Review on Evidences Between 1994-2014. *Scientific Journal of Ilam University of Medical Sciences*, 23(2), pp.103–110.

Sadeghi, O., Nasiri, M., Bayatiyani, F.A., Rasad, H., Pahlavani, N., Maghsoudi, Z. & Askari, G., 2015. Migraine and Magnesium: Review of Evidences. *Journal of Clinical Exellence*, 3(2), pp.15–28.

Sakai, F. & Igarashi, H., 1997. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia*, 17(1), pp.15–22.

Samaie, A., Asghari, N., Ghorbani, R. & Arda, J., 2012. Blood magnesium levels in migraineurs within and between the headache attacks: A case control study. *Pan African Medical Journal*, 11, p.46 1-4.

Sándor, P.S., Di Clemente, L., Coppola, G., Saenger, U., Fumal, A., Magis, D., Seidel, L., Agosti, R.M. & Schoenen, J., 2005. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology*, 64(4), pp.713–715.

Sándor, P.S., Morath, G.P., Hess, K., Kaube, H., Agosti, R.M. & Regard, M., 2006. Prosopagnosia as symptom of migraine with aura: A case report. *Cephalalgia*, 26(3), pp.345–348.

Santos, I.S., Goulart, A.C., Passos, V.M., del Carmen Molina, M., Lotufo, P. & Bensenor, I.M., 2014. Obesity, abdominal obesity and migraine: A cross-sectional analysis of ELSA-Brasil baseline data. *Cephalalgia*, 35(5), pp.426–436.

Santos, I.S., Griep, R.H., Alves, M.G.M., Goulart, A C., Lotufo, P. A, Barreto, S.M., Chor, D. & Benseñor, I.M., 2014. Job stress is associated with migraine in current workers: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *European Journal of Pain (London, England)*, 2, pp.1290–1297.

Sauro, K.M. & Becker, W.J., 2009. The stress and migraine interaction. *Headache*, 49(9), pp.1378–1386.

Scheidt, J., Koppe, C., Rill, S., Reinel, D., Wogenstein, F. & Drescher, J., 2013. Influence of temperature changes on migraine occurrence in Germany. *International Journal of Biometeorology*, 57(4), pp.649–654.

Scher, A.I., Bigal, M.E. & Lipton, R.B., 2005. Comorbidity of migraine. *Current Opinion in Neurology*, 18(3), pp.305–310.

Schiffman, S.S., Buckley, C.E., Sampson, H.A., Massey, E.W., Baraniuk, J.N., Follett, J.V. & Warwick, Z.S., 1987. Aspartame and susceptibility to headache. *The New England Journal of Medicine*, 317(19), pp.1181–1185.

Schmidt, R.F. & Willis, W.D. eds., 2007. *Encyclopedia of Pain*. In New York: Springer Reference: pp.1-2803.

Schoonman, G.G., Evers, D.J., Ballieux, B.E., de Geus, E.J., de Kloet, E.R., Terwindt, G.M., van Dijk, J.G. & Ferrari, M.D., 2007. Is stress a trigger factor for migraine? *Psychoneuroendocrinology*, 32(5), pp.532–538.

Schoonman, G.G., Evers, D.J., Terwindt, G.M., van Dijk, J.G. & Ferrari, M.D., 2006. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia*, 26(10), pp.1209–1213.

Schramm, S.H., Obermann, M., Katsarava, Z., Diener, H.-C., Moebus, S. & Yoon, M.-S., 2013. Epidemiological profiles of patients with chronic migraine and chronic tension-type headache. *The Journal of Headache and Pain*, 14(1), pp.1-8.

Schuh-Hofer, S., Richter, M., Geworski, L., Villringer, A., Israel, H., Wenzel, R., Munz, D.L. & Arnold, G., 2007. Increased serotonin transporter availability in the brainstem of migraineurs. *Journal of Neurology*, 254(6), pp.789–796.

Schulman, E.A. & Brahin, E.J., 2008. Refractory headache: Historical perspective, need, and purposes for an operational definition. *Headache*, 48(6), pp.770–777.

Schulman, E. A., Lake, A.E., Goadsby, P.J., Peterlin, B.L., Siegel, S.E., Markley, H.G. & Lipton, R.B., 2008. Defining refractory migraine and refractory chronic migraine: Proposed criteria from the refractory headache special interest section of the American Headache Society. *Headache*, 48(6), pp.778–782.

Schulman, E. & McGeeney, B.E., 2013. Current concepts in refractory migraine. *Current Treatment Options in Neurology*, 15(1), pp.40–55.

Schulte, L.H., Jürgens, T.P. & May, A., 2015. Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? *The Journal of Headache and Pain*, 16(14), pp.1–5.

Schürks, M., Buring, J.E. & Kurth, T., 2011. Migraine features, associated symptoms and triggers: a principal component analysis in the Women's Health Study. *Cephalalgia*, 31(7), pp.861–869.

Schwedt, T.J., 2007. Serotonin and migraine: The latest developments. *Cephalalgia*, 27(11), pp.1301–1307.

Schwedt, T.J., Demaerschalk, B.M. & Dodick, D.W., 2008. Patent foramen ovale and migraine: A quantitative systematic review. *Cephalalgia*, 28(5), pp.531–540.

Semiz, M., Şentürk, I.A., Balaban, H., Yağız, A.K. & Kavakçı, Ö., 2013. Prevalence of migraine and co-morbid psychiatric disorders among students of Cumhuriyet University. *The Journal of Headache and Pain*, 14(1), p.34 1-6.

Senaratne, R., Van Ameringen, M., Mancini, C., Patterson, B. & Bennett, M., 2010. The prevalence of migraine headaches in an anxiety disorders clinic sample. *CNS Neuroscience and Therapeutics*, 16(2), pp.76–82.

Seng, E.K. & Holroyd, K.A., 2014. Behavioral migraine management modifies behavioral and cognitive coping in people with migraine. *Headache*, 54(9), pp.1470–1483.

Shahbeigi, S., Fereshtehnejad, S.M., Mohammadi, N., Golmakani, M.M., Tadayyon, S., Jalilzadeh, G. & Pakdaman, H., 2013. Epidemiology of headaches in Tehran urban area: A population-based cross-sectional study in district 8, year 2010. *Neurological Sciences*, 34(7), pp.1157–1166.

Shahien, R. & Beiruti, K., 2012. Preventive agents for migraine: focus on the antiepileptic drugs. *Journal of Central Nervous System Disease*, 4, pp.37–49.

Shapero, G., Dowson, A., Lacoste, J.P. & Almqvist, P., 2006. Improved migraine management in primary care: results of a patient treatment experience study using zolmitriptan orally disintegrating tablet. *International Journal of Clinical Practice*, 60(12), pp.1530–1535.

Shapiro, R.E., 2008. Caffeine and headaches. *Current Pain and Headache Reports*, 12(4), pp.311–315.

Sheikh, H.U. & Mathew, P.G., 2012. Acute and preventive treatment of migraine headache. *Techniques in Regional Anesthesia and Pain Management*, 16(1), pp.19–24.

Shepherd, A.J., Hine, T.J. & Beaumont, H.M., 2013. Color and spatial frequency are related to visual pattern sensitivity in migraine. *Headache*, 53(7), pp.1087–1103.

Sheth, J.N. & Malhotra, N.K. eds., 2011. *Wiley Encyclopedia of Marketing*. In West Sussex: Wiley: pp.1-1732.

Shukla, R., Khanna, V.K., Vinod, P., Sankhwar, M.L. & Yadav, R.S., 2009. Platelet dopamine: D2 receptor binding in patients with migraine. *Cephalalgia*, 29(5), pp.532–538.

Silberstein, S.D., 1999. Menstrual migraine. *Journal of Women's Health & Gender-Based Medicine*, 8(7), pp.919–931.

Silberstein, S.D., 2004. Migraine pathophysiology and its clinical implications. *Cephalalgia*, 24 (S2), pp.2–7.

Silberstein, S.D., 2006. Preventive treatment of migraine. *Trends in pharmacological sciences*, 27(8), pp.410–415.

Silberstein, S.D., 2012. Migraine: Headache: Merck Manual Professional. *The Merck Manual Professional Version*, pp.1–4. Available at: http://www.merckmanuals.com/professional/neurologic_disorders/headache/migraine.html [Accessed 9 February 2014].

Silberstein, S.D., 2013. Gastrointestinal Manifestations of Migraine: Meeting the Treatment Challenges. *Headache*, 53(S1), pp.1–3.

Silberstein, S.D., 2014. Migraine : Preventative Treatment. *Current Medical Research Opinion.*, 17(S1), pp.1–9.

Silberstein, S.D. & Collins, S.D., 1999. Safety of Divalproex Sodium in Migraine Prophylaxis: An Open-Label, Long-term Study. *Headache*, 39(9), pp.633–643.

Silberstein, S.D., Dodick, D.W., Aurora, S.K., Diener, H.-C., DeGryse, R.E., Lipton, R.B. & Turkel, C.C., 2015. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. *Journal of Neurology, Neurosurgery, and Psychiatry*, 86(9), pp.996–1001.

Silberstein, S.D. & Goadsby, P.J., 2002. Migraine: preventive treatment. *Cephalalgia*, 22(7), pp.491–512.

Silberstein, S.D., Holland, S., Freitag, F., Dodick, D.W., Argoff, C. & Ashman, E., 2012. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults report of the quality standards subcommittee of the American academy of neurology and the american headache society. *Neurology*, 78(17), pp.1337–1345.

Silberstein, S.D. & Kori, S.H., 2013. Dihydroergotamine: A Review of Formulation Approaches For the Acute Treatment of Migraine. *CNS Drugs*, 27(5), pp.385–394.

Silberstein, S.D., Lipton, R.B. & Dodick, D.W., 2014. Operational diagnostic criteria for chronic migraine: Expert opinion. *Headache*, 54(7), pp.1258–1266.

Silberstein, S.D. & McCrory, D.C., 2003. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache*, 43(2), pp.144–66.

Silva-Néto, R.P., Almeida, K.J. & Bernardino, S.N., 2014. Analysis of the duration of migraine prophylaxis. *Journal of the Neurological Sciences*, 337(1), pp.38–41.

Silva-Néto, R., Peres, M. & Valença, M., 2014. Odorant substances that trigger headaches in migraine patients. *Cephalalgia*, 34(1), pp.14–21.

Simon, H., 2012. Migraine headaches University of Maryland Medical Center. Available at: http://umm.edu/health/medical/reports/articles/migraine-headaches [Accessed 2 March 2014].

Sinert, M.R. & Epstein, B.J., 2009. Topiramate for Use in Adult Migraine Prophylaxis. *Journal of Pharmacy Technology*, 25(2), pp.100–110.

Singh, N.N. & Sahota, P., 2013. Sleep-Related Headache and its Management. *Current Treatment Options in Neurology*, 15(6), pp.704–722.

Singh, Y., 2006. *Fundamental of research methodology and statistics*. In New Delhi: New Age International Publishers: pp.1-314.

Sjöstrand, C., Savic, I., Laudon-Meyer, E., Hillert, L., Lodin, K. & Waldenlind, E., 2010. Migraine and olfactory stimuli. *Current Pain and Headache Reports*, 14(3), pp.244–251.

Smitherman, T.A., Kolivas, E.D. & Bailey, J.R., 2013. Panic disorder and migraine: Comorbidity, mechanisms, and clinical implications. *Headache*, 53(1), pp.23–45.

Solomon, S., 2001. Migraine variants. *Current Pain and Headache Reports*, 5(2), pp.165–169.

Solomon, S., Frishberg, B., Hu, X.H., Markson, L. & Berger, M., 2001. Migraine treatment outcomes with rizatriptan in triptan-naive patients: A naturalistic study. *Clinical Therapeutics*, 23(6), pp.886–900.

Snow, V., Weiss, K., Wall, E.M. & Mottur-Pilson, C., 2002. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Annals of Internal Medicine*, *137*(10), pp.840-849.

Srinivasa, R. & Kumar, R., 2010. Migraine variants and beyond. *Journal of Association of Physicians of India*, 58(Supplment April 2010), pp.14–17.

Stang, P.E. & Osterhaus, J.T., 1993. Impact of migraine in the United States: Data from the National Health Interview Survey. *Headache*, 33(1), pp.29–35.

Stanic, I. & Sretenovic, L.J., 2013. The frequency of postdromal symptoms in patients suffering from migraine. *The Journal of Headache and Pain*, 14(S1), p.117.

Stark, R.J., Valenti, L. & Miller, G.C., 2007. Management of migraine in Australian general practice. *Medical Journal of Australia*, 187(3), pp.142–146.

Steiner, T.J., Ahmed, F., Findley, L.J., MacGregor, E.A. & Wilkinson, M., 1998. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. *Cephalalgia*, 18, pp.283–286.

Steiner, T.J., Birbeck, G.L., Jensen, R.H., Katsarava, Z., Stovner, L.J. & Martelletti, P., 2015. Headache disorders are third cause of disability worldwide. *The Journal of Headache and Pain*, 16(1), pp.1–3.

Steiner, T.J., Scher, A. I., Stewart, W.F., Kolodner, K., Liberman, J. & Lipton, R.B., 2003. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia*, 23(7), pp.519–527.

Steiner, T.J., Stovner, L.J. & Birbeck, G.L., 2013. Migraine: the seventh disabler. *Cephalalgia*, 33(5), pp.289–90.

Stewart, W.F., Lipton, R.B. & Liberman, J., 1996. Variation in migraine prevalence by race. *Neurology*, 47(1), pp.52–59.

Stewart, W.F., Wood, C., Reed, M.L., Roy, J. & Lipton, R.B., 2008. Cumulative lifetime migraine incidence in women and men. *Cephalalgia*, 28(11), pp.1170–1178.

Stickler, G.B., 2005. Relationship between cyclic vomiting syndrome and migraine. *Clinical pediatrics*, 44(6), pp.505–508.

Stokes, M., Becker, W.J., Lipton, R.B., Sullivan, S.D., Wilcox, T.K., Wells, L., Manack, A., Proskorovsky, I., Gladstone, J., Buse, D.C. & Varon, S.F., 2011. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). *Headache*, *51*(7), pp.1058-1077.

Stokes, D.A. & Lappin, M.S., 2010. Neurofeedback and biofeedback with 37 migraineurs: a clinical outcome study. *Behavioral and Brain Functions*, *6*(1), pp.1-10.

Stolte, B., Holle, D., Naegel, S., Diener, H. & Obermann, M., 2015. Vestibular migraine. *Cephalalgia*, 35(3), pp.755–270.

Stovner, L.J., Hagen, K., Jensen, R., Katsarava, Z., Lipton, R.B., Scher, A.I., Steiner, T.J. & Zwart, J.A., 2007. The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia*, 27(3), pp.193–210.

Sun-Edelstein, C. & Mauskop, A., 2009. Role of magnesium in the pathogenesis and treatment of migraine. *Expert Review of Neurotherapeutics*, 9(3), pp.369–379.

Sun-Edelstein, C. & Rapoport, A.M., 2016. Update on the Pharmacological Treatment of Chronic Migraine. *Current Pain and Headache Reports*, 20(1), pp.1–8.

Sutherland, A. & Sweet, B. V., 2010. Butterbur: An alternative therapy for migraine prevention. *American Journal of Health-System Pharmacy*, 67(9), pp.705–711.

Sweetman, S.C., 2009. *Martindale: The Complete Drug Reference*. In London: Sweetman, C.S, ed. Pharmaceutical: pp.1-3694.

Takele, G.M., Haimanot, R.T. & Martelletti, P., 2008. Prevalence and burden of primary headache in Akaki textile mill workers, Ethiopia. The *Journal of Headache and Pain*, 9(2), pp.119–128.

Takeshima, T., Ishizaki, K., Fukuhara, Y., Ijiri, T., Kusumi, M., Wakutani, Y., Mori, M., Kawashima, M., Kowa, H., Adachi, Y. & Urakami, K., 2004. Population-Based Door-to-Door Survey of Migraine in Japan: The Daisen Study. *Headache*, *44*(1), pp.8-19.

Tepper, S.J., Evidence-based Basics on Nutraceuticals: Herbs, Minerals, Vitamins, and Supplements in Migraine Management.
Available at: http://www.nvhi.net/docs/Nutraceuticals.pdf [Accessed 15 July 2016].

Tepper, S.J., 2012. Opioids Should Not Be Used in Migraine. *Headache*, 52(S1), pp.30–34.

Tfelt-Hansen, P.C., 2010. History of migraine with aura and cortical spreading depression from 1941 and onwards. *Cephalalgia*, 30(7), pp.780–92.

Tfelt-Hansen, P.C., 2011. Published and not fully published double-blind, randomised, controlled trials with oral naratriptan in the treatment of migraine: A review based on the GSK Trial Register. The *Journal of Headache and Pain*, 12(4), pp.399–403.

Tfelt-Hansen, P.C., 2013. Relatively slow and long-lasting antimigraine effect of dihydroergotamine is most likely due to basic pharmacological attributes of the drug: a review. *Cephalalgia*, 33(13), pp.1122–1131.

Tfelt-Hansen, P.C. & Koehler, P.J., 2008. History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward. *Cephalalgia*, 28(8), pp.877–886.

Tfelt-Hansen, P.C. & Koehler, P.J., 2011. One hundred years of migraine research: Major clinical and scientific observations from 1910 to 2010. *Headache*, 51, pp.752–778.

Tfelt-Hansen, P.C.,, Saxena, P.R., Dahlöf, C., Pascual, J., Lainez, M., Henry, P., Diener, H.-C., Schoenen, J., Ferrari, M.D. & Goadsby, P.J., 2000. Ergotamine in the acute treatment of migraine. *Brain*, 123(1), pp.9–18.

Theeler, B.J., Kenney, K., Prokhorenko, O. A., Fideli, U.S., Campbell, W. & Erickson, J.C., 2010. Headache triggers in the US military. *Headache*, 50(5), pp.790–794.

Thissen, S., Vos, I.G., Schreuder, T.H., Schreurs, W.M.J., Postma, L. A & Koehler, P., 2014. Persistent Migraine Aura: New Cases, a Literature Review, and Ideas About Pathophysiology. *Headache*, 54, pp.1290–1309.

Thomsen, L.L., Eriksen, M.K., Romer, S.F., Andersen, I., Ostergaard, E., Keiding, N., Olesen, J. & Russell, M.B., 2002. An epidemiological survey of hemiplegic migraine. *Cephalalgia*, 22(5), pp.361–375.

Tietjen, G.E., Brandes, J.L., Peterlin, B.L., Eloff, A., Dafer, R.M., Stein, M.R., Drexler, E., Martin, V.T., Hutchinson, S., Aurora, S.K. & Recober, A., 2009. Allodynia in migraine: association with comorbid pain conditions. *Headache*, *49*(9), pp.1333-1344.

Todd, J., 1955. The syndrome of Alice in Wonderland. *Canadian Journal Medical Association*, 73(9), pp.701–704.

de Tommaso, M., 2012. Prevalence, clinical features and potential therapies for fibromyalgia in primary headaches. *Expert Review of Neurotherapeutics*, 12(3), pp.287–296.

Truter, I., 2015. Prescribing patterns of anti-migraine medicines in South Africa using a claims database. *International Journal of Clinical Pharmacy*, 37, pp.447–451.

Truter, I. & Kotze, T.J.V.W., 1996. An investigation into the prescribing of analgesics. *South African Medical Journal*, 86(11), pp.1394–1397.

Tuchin, P.J., Pollard, H. & Bonello, R., 2000. A randomized controlled trial of chiropractic spinal manipulative therapy for migraine. *Journal of manipulative and Physiological Therapeutics*, 23(2), pp.91–95.

Turner, L. ed., 2010. *Daily Drug Use*. In Cape Town: The Tincture Press: pp.1-607.

Tzourio, C., Gagnière, B., El Amrani, M., Bousser, M.-G. & Alpérovitch, A., 2003. Lay versus expert interviewers for the diagnosis of migraine in a large sample of elderly people. *Journal of Neurology, Neurosurgery, and Psychiatry*, 74(2), pp.238–241.

Unger, J., 2006. Migraine Headaches: A Historical Prospective, a Glimpse into the Future, and Migraine Epidemiology. *Disease-a-Month*, 52(10), pp.367–384.

Vangoghgallery.com. (2016). [online]
Available at: http://www.vangoghgallery.com/catalog/image/0612/Starry-Night.jpg [Accessed 15 July 2016].

Varkey, E., Cider, A., Carlsson, J. & Linde, M., 2011. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia*, 31(14), pp.1428–1438.

Vetvik, K.G., MacGregor, E.A., Lundqvist, C. & Russell, M.B., 2014. Prevalence of menstrual migraine: A population-based study. *Cephalalgia*, *34*(4), pp.280-288.

Viana, M., Genazzani, A. a, Terrazzino, S., Nappi, G. & Goadsby, P.J., 2013. Triptan nonresponders: do they exist and who are they? *Cephalalgia*, 33(11), pp.891–896.

Viana, M., Linde, M., Sances, G., Ghiotto, N., Guaschino, E., Allena, M., Nappi, G., Goadsby, P. & Tassorelli, C., 2014. EHMTI-0024. The typical duration of migraine aura: a prospective diary-based study. *The Journal of Headache and Pain*, 15(1), p.D71.

Viana, M., Linde, M., Sances, G., Ghiotto, N., Guaschino, E., Allena, M., Terrazzino, S., Nappi, G., Goadsby, P.J. & Tassorelli, C., 2016. Migraine aura symptoms: Duration, succession and temporal relationship to headache. *Cephalalgia*, *36*(5), pp.413-421.

Viana, M., Sprenger, T., Andelova, M. & Goadsby, P.J., 2013. The typical duration of migraine aura: a systematic review. *Cephalalgia*, 33(7), pp.483–490.

Villalón, C.M., Centurión, D., Valdivia, L.F., De Vries, P. & Saxena, P.R., 2002. An introduction to migraine: from ancient treatment to functional pharmacology and antimigraine therapy. *Proceedings of the Western Pharmacology Society*, 45, pp.199–210.

Vlajinac, H.D., Dzoljic, E.D., Sipetic, S.B. & Kostic, V.S., 2004. Hereditary patterns of Belgrade university female students with migraine and nonmigraine primary headache. *Journal of Neurology*, 251(8), pp.973–976.

Vo, M., Ainalem, A., Qiu, C., Peterlin, B.L., Aurora, S.K. & Williams, M.A., 2011. Body mass index and adult weight gain among reproductive age women with migraine. *Headache*, 51(4), pp.559–569.

Vogler, B., Rapoport, A.M., Tepper, S.J., Sheftell, F. & Bigal, M.E., 2006. Role of melatonin in the pathophysiology of migraine: Implications for treatment. *CNS Drugs*, 20(5), pp.343–350.

Vuković, V., Lovrencić-Huzjan, A., Bosnar-Puretić, M. & Demarin, V., 2009. The efficacy of gabapentin in migraine prophylaxis: an observational open label study. *Acta Clinica Croatica*, 48(2), pp.145–151.

Vuković, V., Plavec, D., Galinović, I., Lovrenčić-Huzjan, A., Budišić, M. & Demarin, V., 2007. Prevalence of vertigo, dizziness, and migrainous vertigo in patients with migraine. *Headache*, 47(10), pp.1427–1435.

Wacogne, C., Lacoste, J.P., Guillibert, E., Hugues, F.C. & Le Jeunne, C., 2003. Stress, anxiety , depression and migraine. *Cephalalgia*, 23, pp.451–455.

Walach, H., Betz, H.D. & Schweickhardt, A., 2001. Sferics and headache: A prospective study. *Cephalalgia*, 21(6), pp.685–690.

Wang, J., Huang, Q., Li, N., Tan, G., Chen, L. & Zhou, J., 2013. Triggers of migraine and tension-type headache in China: A clinic-based survey. *European Journal of Neurology*, 20(ii), pp.689–696.

Wang, L.P., Zhang, X.Z., Guo, J., Liu, H.L., Zhang, Y., Liu, C.Z., Yi, J.H., Wang, L.P., Zhao, J.P. & Li, S.S., 2011. Efficacy of acupuncture for migraine prophylaxis: A single-blinded, double-dummy, randomized controlled trial. *PAIN*®, 152(8), pp.1864–1871.

Wang, S.J., Chung, C.S., Chankrachang, S., Ravishankar, K., Merican, J.S., Salazar, G., Siow, C., Cheung, R.T.F., Phanthumchinda, K. & Sakai, F., 2008. Migraine disability awareness campaign in Asia: Migraine assessment for prophylaxis: Research submission. *Headache*, 48(9), pp.1356–1365.

Wang, S.J., Fuh, J.L., Lu, S.R., Juang, K.D. & Wang, P.H., 2003. Migraine prevalence during menopausal transition. *Headache*, 43(5), pp.470–478.

Wang, S.J., Fuh, J.L., Young, Y.H., Lu, S.R. & Shia, B.C., 2000. Prevalence of migraine in Taipei, Taiwan: A population-based survey. *Cephalalgia*, 20(6), pp.566–572.

Weiller, C., May, A, Limmroth, V., Jüptner, M., Kaube, H., Schayck, R.V, Coenen, H.H. & Diener, H.C., 1995. Brain stem activation in spontaneous human migraine attacks. *Nature Medicine*, 1(7), pp.658–660.

Wells, N.E.J. & Steiner, T.J., 2000. Effectiveness of eletriptan in reducing time loss caused by migraine attacks. *Pharmacoeconomics*, 18(6), pp.557–566.

Wells, R.E., Burch, R., Paulsen, R.H., Wayne, P.M., Houle, T.T. & Loder, E., 2014. Meditation for migraines: A pilot randomized controlled trial. *Headache*, 54(9), pp.1484–1495.

Winawer, M.R. & Connors, R., 2013. Evidence for a shared genetic susceptibility to migraine and epilepsy. *Epilepsia*, 54(2), pp.288–295.

Winkler, A.S., Dent, W., Stelzhammer, B., Kerschbaumsteiner, K., Meindl, M., Kaaya, J., Matuja, W.B.P. & Schmutzhard, E., 2010. Prevalence of migraine headache in a rural area of northern Tanzania: A community-based door-to-door survey. *Cephalalgia*, 30(5), pp.582–592.

Winter, A.C., Berger, K., Buring, J.E. & Kurth, T., 2009. Body mass index, migraine, migraine frequency and migraine features in women. *Cephalalgia*, 29(2), pp.269–278.

Wöber, C., Brannath, W., Schmidt, K., Kapitan, M., Rudel, E., Wessely, P. & Wöber-Bingöl, Ç., 2007. Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia*, *27*(4), pp.304-314.

Wöber, C., Holzhammer, J., Zeitlhofer, J., Wessely, P. & Wöber-Bingöl, Ç., 2006. Trigger factors of migraine and tension-typeheadache: Experience and knowledge of the patients. The *Journal of Headache and Pain*, 7(4), pp.188–195.

Woldeamanuel, Y.W., Andreou, A.P. & Cowan, R.P., 2014. Prevalence of migraine headache and its weight on neurological burden in Africa: A 43-year systematic review and meta-analysis of community-based studies. *Journal of the Neurological Sciences*, 342(1-2), pp.1–15.

Woodruff, A.E., Cieri, N.E., Abeles, J. & Seyse, S.J., 2013. Abdominal migraine in adults: a review of pharmacotherapeutic options. *The Annals of Pharmacotherapy*, 47(6), p.e27.

World Health Organization, 2011. Atlas of headache disorders and resources in the world 2011. Available at: https://extranet.who.int/iris/restricted/handle/10665/44571 [Accessed 23 February 2014].

World Health Organization, 2001. *WPRO | Health Research Methodology: A Guide for Training in Research Methods*. In World Health Organization - Regional Office for the Western Pacific, ed. WPRO | WHO Western Pacific Region. Available at: http://www.wpro.who.int/health_research/documents/HR_Methodology/en/ [Accessed 9 March 2014].

World Health Organization, 2003. WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services: Introduction to drug utilization research. *Introduction to Drug Utilization Research. Geneva: World Health Organization*, pp.1-49.

World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama*, *310*(20), pp.2191. [Accessed 9 July 2016]

Yadav, R.K., Kalita, J. & Misra, U.K., 2010. A study of triggers of migraine in India. *Pain Medicine*, 11, pp.44–47.

Yamada, K., Moriwaki, K., Oiso, H. & Ishigooka, J., 2011. High prevalence of comorbidity of migraine in outpatients with panic disorder and effectiveness of psychopharmacotherapy for both disorders: A retrospective open label study. *Psychiatry Research*, 185(1-2), pp.145–148.

Yang, A.C., Fuh, J.L., Huang, N.E., Shia, B.C., Peng, C.K. & Wang, S.J., 2011. Temporal associations between weather and headache: Analysis by empirical mode decomposition. *PLoS ONE*, 6(1), pp.1–6.

Yang, G., Baad-Hansen, L., Wang, K., Xie, Q. & Svensson, P., 2014. Effect of negative emotions evoked by light , noise and taste on trigeminal thermal sensitivity. *The Journal of Headache and Pain*, 15(1), pp.1–12.

Yavuz, B.G., Aydinlar, E.I., Dikmen, P.Y. & Incesu, C., 2013. Association between somatic amplification, anxiety, depression, stress and migraine. *The Journal of Headache and Pain*, 14(1), p.53.

Yilmaz, M., Gurger, M., Atescelik, M., Yildiz, M. & Gurbuz, S., 2015. Meteorologic parameters and migraine headache: ED study. *The American Journal of Emergency Medicine*, 33(3), pp.409–413.

Ying, G., Fan, W., Li, N., Wang, J., Li, W. & Tan, G., 2014. Clinical Characteristics of Basilar-Type Migraine in the Neurological Clinic of a University Hospital. *Pain Medicine*, 15, pp.1230–1235.

Young, W.B., Silberstein, S.D., Nahas, S.J. & Marmura, M.J., 2011. *Jefferson Headache Manual*. In New York: Demos Medical Publishing. pp.1-224.

Yu, S., Liu, R., Yang, X., Zhao, G., Qiao, X., Feng, J., Fang, Y., Cao, X., He, M. & Steiner, T.J., 2012. Body mass index and migraine: A survey of the Chinese adult population. The *Journal of Headache and Pain*, 13(7), pp.531–536.

Yuan, K., Zhao, L., Cheng, P., Yu, D., Zhao, L., Dong, T., Xing, L., Bi, Y., Yang, X., von Deneen, K.M. & Liang, F., 2013. Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. *The Journal of Pain*, *14*(8), pp.836-844.

Zahid, M., Sthanadar, A.A., Kaleem, M., Latif, M., Sthanadar, I.A., Ali, P.A., Sthanadar, I.A., Ismail, M., Imtiaz, N. & Shah, M., 2014. Prevalence and Perceptions about Migraine among Students and Patients in Khyber Pakhtunkhwa Province , Pakistan. *Advances in Bioscience and Biotechnology*, 5, pp.508–516.

Zebenholzer, K., Andree, C., Lechner, A., Broessner, G., Lampl, C., Luthringshausen, G., Wuschitz, A., Obmann, S.-M., Berek, K. & Wöber, C., 2015. Prevalence, management and burden of episodic and chronic headaches—a cross-sectional multicentre study in eight Austrian headache centres. *The Journal of Headache and Pain*, 16(1), pp.1–9.

Zebenholzer, K., Frantal, S., Pablik, E., Lieba-Samal, D., Salhofer-Polanyi, S., Wöber-Bingöl, C. & Wöber, C., 2016. Reliability of assessing lifestyle and trigger factors in patients with migraine - findings from the PAMINA study. *European Journal of Neurology*, 23(1), pp.120–126.

Zebenholzer, K., Rudel, E., Frantal, S., Brannath, W., Schmidt, K., Wöber-Bingöl, C. & Wöber, C., 2010. Migraine and weather: A prospective diary-based analysis. *Cephalalgia*, 31(4), pp.391–400.

Zhang, Y. & Wildemuth, B.M., 2009. Qualitative Analysis of Content. In *Applications of Social Research Methods to Questions in Information and Library Science*. p. 421. Available at: http://www.ischool.utexas.edu/~yanz/Content_analysis.pdf [Accessed 12 April 2014].

Zidverc-Trajkovic, J., Petrusic, I., Podgorac, A., Radojicic, A. & Sternic, N., 2013. Other cortical dysfunctions during visual and sensitive migraine aura. *The Journal of Headache and Pain*, 14(S1), p.P115.

Zivadinov, R., Willheim, K., Jurjevic, A., Sepic-Grahovac, D., Bucuk, M. & Zorzon, M., 2001. Prevalence of migraine in Croatia: A population-based survey. *Headache*, 41(8), pp.805–812.

Zivadinov, R., Willheim, K., Sepic-Grahovac, D., Jurjevic, A., Bucuk, M., Brnabic-Razmilic, O., Relja, G. & Zorzon, M., 2003. Migraine and tension-type headache in Croatia: A population-based survey of precipitating factors. *Cephalalgia*, 23(5), pp.336–343.

Appendices

Appendix A

MIGRAINE QUESTIONNAIRE FOR PHARMACISTS

PHARMACY NUMBER _____

1. How many migraine patients visit this pharmacy on average per month? _____

2. What is the average age _____

of a migraine patient in this pharmacy? _____ years

3. What percentage of migraine patients are female? _____%

4. What percentage of migraine patients visit the pharmacy:

With a prescription _____% Average age:_____years

For OTC treatment/Pharmacist-Initiated Therapy _____% Average age:_____years

5. Of those visiting the pharmacy to fill a prescription, what percentage of prescriptions are from:

General practitioners _____ % Average age:_____years

Specialists _____% Average age:_____years

6. Does your pharmacy sell a “migraine cocktail”? _____

If yes, which active ingredients (and dosages) are in your “migraine cocktail”?

_____

_____

_____

7. On average, how many migraine patients buy a “migraine cocktail” from your pharmacy in a

month? _____

8. What is the price of the “migraine cocktail”?_____

9. Approximately how many migraine patients do you refer to a doctor or specialist for correct diagnosis each month? _____

Appendix B

MIGRAINE QUESTIONNAIRE FOR PATIENTS

FACILITATOR NUMBER_____

QUESTIONNAIRE NUMBER - _____

PLEASE COMPLETE THE FOLLOWING QUESTIONNAIRE BY CIRCLING THE CORRECT RESPONSE OR WRITE YOUR ANSWER IN THE SPACE PROVIDED.

1. DEMOGRAPHIC INFORMATION

1.1 Gender		Female		Male
1.2 **Age**	20-29 years	30-39 years	40-49 years	50-60 years
1.3 Ethnic Group	White	Coloured	Black	Indian
Other (please specify)				

2. MIGRAINE HISTORY

2.1 At what age did you have your first migraine attack?			_____years
2.2 Who diagnosed your headache as migraine?			
Self	Pharmacist	Doctor	Specialist
Other (please specify)			
2.3 Are your migraines as a result of illness or injury?			
yes	no	not sure	
If yes, please specify:-			
2.4 How many migraines do you get on average?			
per month _____	per year _____		
2.5 How many days do you suffer from migraine on average?			
per month _____	per year _____		
2.6 How long do your migraine attacks on average last? _____			
2.7 On a scale of 1-10, how severe is the pain associated with your average migraine?			

mild	1	2	3	4	5	6	7	8	9	10	extreme

2.8 Has the frequency of your migraine changed through the years?			
increased	decreased	stayed the same	not sure
2.9 Has the intensity of pain associated with your migraine changed through the years?			
increased	decreased	stayed the same	not sure
2.10 On average how many days of work are lost per year due to your migraine? _____			
2.11 Do other members of your family suffer from migraine?			
yes	no	no sure	
If yes, specify the family members who suffer from migraine:-			
mother	father	sister	brother	aunt
uncle	grandmother	grandfather	cousin
other (specify)			

3. FEMALE MIGRAINEUR (if male go to section 4)

3.1 Are your migraines related to your menstrual cycle?		
yes	no	not sure
3.2 Do you only get migraines related to your menstrual cycle (that is during the five day period of the two days before the start of your cycle and three days after the start of your of your cycle)?		
yes	no	not sure
3.3 Do female contraceptives affect your migraines?		
yes	no	not sure	not using any
3.4 Does hormonal replacement therapy affect your migraines?		
yes	no	not sure	not using any
3.5 Did your migraines increase or decrease with menopause?		
increase	decrease	stayed the same	not sure	not menopausal

4. MIGRAINE DESCRIPTION

4.1 Do you have an aura before a migraine?						
yes	no	sometimes	not sure			
4.2 If yes, what type of aura do you experience? Please circle all those that you experience.						
4.2.1 Visual aura:-	zig-zag lines	flashing lights	blurred vision	halos		
Other(specify:						
4.2.2Sensory aura:-	numbness	pins and needles				
tinnitus	vertigo	Speech impairment				
Other(specify):-						
4.3 Are there factors that trigger your migraine?						
yes	no	not sure				
If you have triggers, which of the following trigger your migraine? Please circle all the triggers that can trigger your migraine.						
4.3.1 Weather Changes:-	thunder storm	wind	heat	cold		
Other (specify):						
4.3.2 Stress:-	emotional	work based	financial	environmental		
4.3.3 Excessive stimuli:-	flashing lights	strong odours	exercise			
4.3.4 Food:-	cheese	chocolate	red wine	caffeine	yeast	MSG
artificial sweeteners	skipping meals	processed food				
Other(specify):						
4.3.5 Sleep:-	excessive sleep	insufficient sleep				
4.3.6 Hormonal factors						
4.3.7 Smoking						
4.3.8 Other factors: (specify)						

4.4 Which of these symptoms do you experience during a migraine attack? Circle all those that you experience.			
constipation	diarrhoea	nausea	nausea with vomiting
vision changes	difficulty concentrating	fatigue	weakness
vertigo	feeling light headed	hives	food cravings
mood changes	neck pain	numbness	tingling
sensitivity to light	sensitivity to sound	sensitivity to smell	
neck pain	pain on one side of the head	throbbing pain	
Other(specify)			
4.5 Do you suffer from any of the following conditions?			
depression	anxiety	chronic fatigue	rhinitis
hypertension	fibromyalgia	diabetes	irritable bowel syndrome
Other: (specify)			

5. MIGRAINE MEDICATION

5.1 What medication do you use to abort a migraine attack if any?
Medications:-

5.2 Are you on prophylactic medication?	yes	no	not sure
If yes, what medication are you taking?			
5.3 What medications have you tried and what were the reason for stopping the medication, if any?			
Medication			
Reason for stopping	did not work	side effects	
Other (specify):			
Medication			
Reason for stopping	did not work	side effects	
Other (specify):			
Medication			
Reason for stopping	did not work	side effects	
Other (specify):			
5.3.1 Are you on medication for any other chronic conditions?	yes	no	
If Yes:-			
Condition:-	Medication:-		
Condition:-	Medication:-		
Condition:-	Medication:-		
Condition:-	Medication:-		
Condition:-	Medication:-		
5.4 Have you tried alternative medication?	yes	no	
If yes, which of the following have you tried?			
5.4.1 Natural remedies			
Herbs:	feverfew	butterbur	valerian
Omegas			
Other (specify)			

5.4.2 Vitamins/Minerals:-				
vitamin B2	vitamin B6	potassium	magnesium	zinc
Co-enzyme Q10				
5.4.3 Mind-body medicine:-				
meditation	yoga	acupuncture	tai chi	hypnotherapy
5 4.4 Manipulative and body-based practices:-				
chiropractic spinal manipulation		massage therapy		physiotherapy
5.4.5 Botox treatment				
5.4.6 Other(specify):-				
5.5 If you have tried alternative medicine, what has worked for you and what has not work?				

Worked	**Did not work**

6. DESCRIBE A TYPICAL MIGRAINE ATTACK

THANK YOU FOR YOUR PARTICIPATION

COMPLETED QUESTIONNAIRES CAN BE RETURN TO THE PLACE THAT YOU RECEIVED IT FROM OR IT CAN BE FAXED OR E-MAILED TO THE RESEARCHER.

Fax: 0860240 4824

Email: berns65@live.co.za

If you would like feedback on this research, please fill in the following:

Name: _____

Postal address / fax /email to where the information can be sent.

_____

_____

_____

_____

Appendix C

PO Box 77000
Nelson Mandela Metropolitan University
Port Elizabeth
6031

LETTER OF PERMISSION (Pharmacist)

Title of the research project	Relationship between migraine triggers, aura and treatment
Principal investigator	Bernadette Louwrens
Contact telephone number	0837660633

I, _____, as a professional involved in the care of persons suffering from migraine, I hereby grant permission for the above-mentioned research project to be conducted through my facilities.

I as the pharmacist in charge, agree to complete a short questionnaire on migraine patients that visit my premises. Furthermore, I agree that my premises will serve as a distribution and collection point for a questionnaire-based survey of migraine patients. No further involvement by either me or my colleagues will be required with regards to the questionnaire

All information pertaining to the questionnaire has been provided to me by the principal researcher and I will carry no liability for any problems incurred.

I understand that patient confidentiality will be maintained.

Facility: _____

Signature: _____ Date: _____

Appendix D

Nelson Mandela Metropolitan University
for tomorrow

PO Box 77000
Nelson Mandela Metropolitan University
Port Elizabeth
6031

LETTER OF PERMISSION (FACILITY)

Title of the research project	Relationship between migraine triggers, aura and treatment
Principal investigator	Bernadette Louwrens
Contact telephone number	0837660633

I, _____, as a professional involved in the care of persons suffering from migraine, I hereby grant permission for the above-mentioned research project to be conducted through my facilities.

I agree that my premises will serve as a distribution and collection point for a questionnaire-based survey of migraine patients. No further involvement by either me or my colleagues will be required with regards to the questionnaire

All information pertaining to the questionnaire has been provided to me by the principal researcher and I will carry no liability for any problems incurred.

I understand that patient confidentiality will be maintained.

Facility: _____

Signature: _____ Date: _____

Appendix E

PATIENT INFORMED CONSENT LETTER

Faculty of Health Sciences, Department of Pharmacy

Tel. (+27) 833467709

berns65@live.co.za

Researcher: Bernadette Louwrens **Date:**_____

NMMU REC-H Ref: H14-HEA-PHA-003

Dear Sir/Madam

You are being asked to participate in a migraine research study entitled: Relationship between migraine triggers, auras and treatment. The aim of the study is to determine if any relationship exists between auras and triggers factors experienced by migraineurs and which treatment are effective in treating migraine.

In order to participate, you are required to complete this form thereby giving written consent. Your participation is completely voluntary and will involve answering a questionnaire. If you choose not to participate there shall be no penalty to you. If you agree to participate, you are free to withdraw at any time during the study. Withdrawing from the study will not affect your current or future medical care in any way. It is important to remember that participation in this study will not benefit you in any way nor will it cause you any harm. No changes to your current medication or medical records will be made. Participation in this study will not incur any additional costs to you as the participant.

This research may be presented at scientific conferences or in scientific publications, but your identity will remain confidential at all times. No information will be able to be tracked back to you.

If you have any questions, please feel free to contact the researcher using the following details:
Telephone: 083 346 7709
E-mail: berns65@live.co.za

This informed consent statement has been prepared in compliance with current statutory guidelines. If you understand and accept the conditions and are willing to participate, please sign your name and initials below.

_____ _____
Participant's name and initials Participant's signature

Yours sincerely
Researcher:
Bernadette Louwrens

Appendix F

Copies to:
Supervisor: Prof I Truter

Summerstrand South
Faculty of Health Sciences
Tel. +27 (0)41 504 2956 Fax. +27 (0)41 504 9324
Nouwaal.Isaacs@nmmu.ac.za

Student number: 183072710

Contact person: Ms N Isaacs

28 May 2014

MS B LOUWRENS
DEPARTMENT OF PHARMACY
SOUTH CAMPUS

RE: OUTCOME OF PROPOSAL SUBMISSION

QUALIFICATION: **MPHARM**
FINAL RESEARCH/PROJECT PROPOSAL:
RELATIONSHIP BETWEEN MIGRAINE TRIGGERS, AURAS AND TREATMENT

Please be advised that your final research project was approved by the Faculty Postgraduate Studies Committee (FPGSC) subject to the following amendments/recommendations being made to the satisfaction of your Supervisor:

COMMENTS/RECOMMENDATIONS

1. Concerns were raised regarding the self-definition and/or without prescription (page 12) migraine: how does one know this is an accurate diagnosis or that the individual is suffering from a migraine?
2. Explain the terms basilar, vestibular migraines etc on page 8.
3. Is the methodology a mixed method or triangulated methodology, given the quantitative and qualitative aspects?
4. Appendix A
   Is the question about females in order to establish the percentages of both genders?
5. Page 14 – Population of Interest What about the Pharmacists?
6. Research design (Page 15)
   - What is meant by a verbal questionnaire?

- It was indicated that questionnaires would be given to patients with migraines who frequently visits the shop. Be more specific, frequent is too vague.

7. Page 17 – First sentence of pilot study Replace the word trail with “trial”.
8. Page 18 – Ethics What about autonomy?
9. Page 18 – Reliability of study
   Describe the strategies that would be used to ensure this.
10. Page 19 – Validity
    How would this be ensured? 11. Referencing

- List all the authors when using the reference for the first time throughout the proposal.
- The Olesen reference on page 5 was not listed within the reference list.
- The first two references (Stephen & Siliberstein/Olesen) within point 1.3 (Definition) say the same thing.
- Page 8 – HIS
  Insert the date.
- Page 13
  Use more recent references (Brink & Wood, 1998:284). - Et al was used inconsistently.

Faculty Postgraduate Studies Committee (FPGSC) reference number: **H14-HEA-PHA-003**. FPGSC grants ethics approval.

Please be informed that this is a summary of deliberations that you must discuss with your Supervisor.

Please forward a final electronic copy of your appendices, proposal and REC-H form to the Faculty Postgraduate Studies Committee (FPGSC) secretariat.

We wish you well with the project.

Kind regards,

pp
Ms N Isaacs
Manager: Faculty Administration
Faculty of Health Sciences