

LEVEL 6 ASSESSMENT SPECIFICATION

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A Systematic Review of the Treatment of Migraine: A Health Perspective.

Abstract

Migraine affects a lot of people with its symptoms being quite debilitating and long lasting. The main aim of this systematic review was to compile and evaluate the efficacy of a varied amount of migraine treatments. Online databases and libraries that have been made public and free were used to accumulate a vast number of trials and studies within the field of migraine treatment. 8 key studies were then chosen based on their relevance to the subject field. All results were summarised to which the efficacy of each intervention was evaluated. This review also found that the target audience for migraine treatment is female so it is unclear on how some treatment will react with a male population.

These findings revealed that all treatment used offered at least mild pain relief and some offering 35% reduction monthly migraine days.

Introduction

A migraine has been categorised as a severe headache that may cause a throbbing pain and predominantly affects one side of the head or upper part of the face. It can also cause dizziness, nausea, blurred vision, and irritability (Crevits, Vanacker & Verraes, 2012). There are several types of migraine, to which all may cause a severe headache, but some can be accompanied by symptoms unique to the specific type. Some types are more common than others. The most common type being Migraine without aura. This condition can last anywhere between 4 hours to 3 days, and the most common associated symptoms are a throbbing headache on one side of head, nausea and or vomiting, and photophobia - which is a heightened sensitivity to light (Nyholt et al, 2014).

Migraine with Aura is a condition that presents itself with a pre-headache sign. The sign is usually a mild visual impairment. Common types of impairment are found in the forms of blind spots, flashing or flickering lights, zig zag patterns, coloured lines, and temporary blindness. A headache may not always occur during an attack and the auras may last anywhere from 5 minutes to one hour (Lampl et al, 2005).

Chronic migraine can be found in the form of a frequent and severe headache, nausea & vomiting and an increased sensitivity to light, sound and smell. A chronic migraine is categorised as a reoccurring headache for at least 15 days per month, with 8 of these being inclusive of migraine symptoms and to have happened for a minimum of 3 months. This type can be debilitating and life altering for those who suffer from them (Ruiz et al, 2015).

Brainstem aura formerly known as Basilar type migraine, is a much rarer form and occurs with more severe neurological symptoms. The symptoms associated with this condition are – Tinnitus, Vertigo, Diplopia (double vision), unsteadiness when walking (Ataxia), Syncope, pins and needles, and changes in vision in both eyes. Disorientation and confusion are both likely, in some rare cases all of the symptoms may occur at the same time. Brainstem aura can be devitalizing to the point of prevent sufferers from driving and attending work (Sui-Yi et al, 2021).

Vestibular Migraine which is also known as Migrainous vertigo- Vertigo. This condition presents in the form of severe dizziness and balance problems, as well as other common migraine symptoms. Some of which are Photophobia, Phonophobia (heightened sensitivity to sound), a sensation of movement (Vertigo), sensitivity to smells (Osmophobia) and Cranial Allodynia an increased sensitivity to touch on the face or head (Wurthman et al, 2014). This type can be temporarily disabling to those who are experiencing an attack, therefore vestibular migraine is part of its own classification of headache – ICHD3 (Mostardini, Nola & Giovani, 2014). A bout of this migraine can last any time from 5 minutes to 3 days (Kutay et al, 2017). Another rare type of migraine is a Hemiplegic migraine. This condition is made up of two types. Familial – when the condition has been passed down a generation, if a parent experiences Hemiplegic migraine, there is a 50% chance, their child will develop the condition in later life. The other type is Sporadic – The condition occurs even though there is no record of it within the family.

When experiencing this condition, the main symptom is weaknesses on one side of the body, accompanied by speech & communication difficulties and visual disturbances (Sugrue et al, 2014).

A 2014 study cited that migraine is more common amongst women compared to men. This citation would remain inline with the gender population percentages used for the trails that have been selected for this review. Moreover, a separate type of the condition known as Menstrual migraine, specifically only affects women as there is a strong link between migraine occurrence during the menstrual cycle (Vetvik et al, 2014).

Although some types of migraine may cause more severe affects than others, any type can cause debilitating, painful and exhausting circumstances that may interrupt daily life. Due to their complex way of occurring and no obvious trigger points (Pacheve & Ivan, 2013) this can make the condition, extremely difficult to treat and to prevent. Therefore, a vast range of medicinal and herbal strategies have been trialled and used as a way of combating and preventing the occurrence of a migraine.

This systematic review will look at a wide range of past studies performed to treat migraine and will discuss the findings from 8 key studies that have been published within the last 5 years.

Study identification:

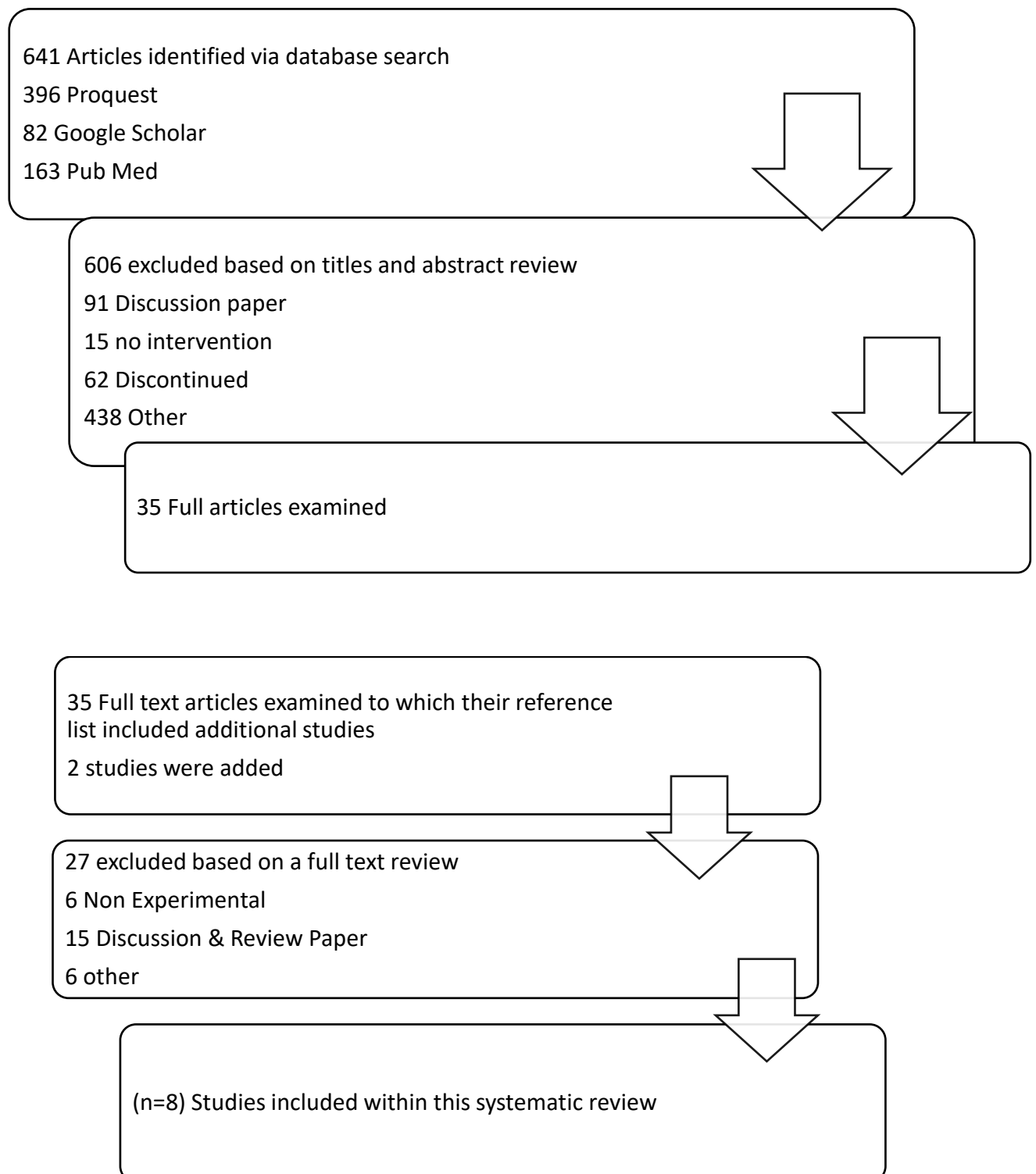
To acquire past studies for this review, a systematic search was conducted via online resources and libraries that were accessible without the use of paywall subscriptions. The resources used were PROQUEST, PUBMED & Google Scholar, as the articles included within these databases were either free to read online or included with a university subscription. For the preliminary search of studies there were no year restrictions put in place, the search was then refined down to key studies which have been published within the last 5 years.

The search terms used throughout remained the same as this would allow the only relevant studies to be included. The key terms were “Migraine”, “Treatment” & “Study”. Only peer reviewed and full text articles were considered.

Inclusion Criteria:

All three resources were used to assess and to allow for a more refined search based on the inclusion criteria. The following had to be included: 1. The study participants needed to be affected by migraine condition for a set amount of time. 2. There would be an intervention of a proposed treatment for migraine. 3. Study was not discontinued. 4. The study design was experimental but safe. 5. Was peer reviewed. 6. Published in English or could be translated into. 7. Was ethical and fair. Figure 1 displays the series of research and assessment that found the key studies.

Figure 1



Criteria for assessment of study quality:

The study refinement and choice were determined via the resources and aided by an assessment of relevance, validity and reliability. All 8 studies that were chosen to be key studies provided information and results that remain in line with the review question. The study quality was helped determined through a series of assessment questions. 1. Were all the trial participants involved affected by migraine for a minimum set time? 2. Did the study use an intervention? 3. Was the intervention experimental? 4. Was it safe and ethical? 5. Did it take place within the last 5 years? 6. Has it been peer reviewed? If the study remained in line with the assessment questions it was considered to be a key article.

Results

Study summary:

In total, 641 studies were found via a database search on three online resource platforms. 606 of these were excluded due to lack of relevance, protocol and other factors. The remaining 35 were at first glance the most relevant and appropriate to be used. With further assessment it was apparent that only 8 of these would be identified as key studies. A summary of results table for the key studies can be seen below in Table 1. The minimum age requirement for all studies were 18 and for those that included a maximum age it was 75. The mean age for all participants used, calculated to be 45.4. Both Male and Female participants were used although, 3 studies used only Female (Messoud et al, 2021; Ordas et al, 2020; Smith et al, 2020). Female participants were also the predominant choice with a total of 2114 participants across all studies, of which 1996 of these are female (96%). This would perhaps remain in line with previous literature citing that migraine is more commonly associated with a female gender (Ghosh et al, 2010; Marino et al, 2010; Quintas et al, 2013).

The study population size was not evenly dispersed either, as one study had only 20 participants (Knife et al, 2015) and another had 748 (Smith et al, 2020).

5 out of 8 studies lasted in duration of 12 weeks or 3 months with the remaining 3 being conducted for much longer. Stark et al, 2019's study lasted 8 months,

Rapoport et al, (2019) continued for 11 months and finally Smith et al, (2020) had a duration of 60 weeks.

Study Design:

4 out of 8 studies included an intervention classified as a medical procedure (Rapoport et al, 2019; Knife et al, 2015; Lipton et al, 2019; Ordas et al, 2020), 3 were in the form of a pharmaceutical analgesic drug (Messoud et al, 2021; Smith et al, 2020; Stark et al, 2019) and only 1 used a herbal medicinal approach (Jung et al, 2019).

Half of all studies used a Double-blind strategy accompanied with placebo (Lipton et al, 2019; Rapoport et al, 2019; Messoud et al 2021; Smith et al, 2020) and the remaining 4 used an array of different approaches. The vary in study design will be explored more within the discussion.

Summary of Results

Table 1

Study	Study Design	Age Mean	Gender – Male/Female (n)	Inclusion Criteria	Intervention	Trial Duration	Efficacy Outcome	Adverse Effects
Raport et al, 2019	Double Blind *Acute Management	43.8	296 (60 M) (236 F)	• 2- 8 Migraine days monthly • <12 Head ache days monthly • 18+	REN	11 months	Significant pain relief or pain free at 2 hours (Acute Management)	Continued Migraine (Low)
Jung et al, 2019	interventional, single-arm, pre-post study	51.5	37 (7 M) (30 F)	• 19 – 65 • International diagnosis	Shinbaro	12 weeks	4.1 fewer migraine days per month	5% Minor occipital Neuralgia & Moderate

				is of migraine – classification of headache disorders • 4 migraine days in a month for 3 months minimum				Migraine Attack
Knife et al, 2015	open label Prospective	53.1	20 (4 M) (16 F)	• 18+ • CRH Headache Disorder – ICHD 3 • Eligible for NVNS therapy	nVns	3 months	5.1 monthly reduction in Migraine days	Very mild neck twitching & skin irritation – no Serious
Lipton et al, 2019	Double blind *Acute Management	42.3	107 (23M) (84 F)	• 18-75 • Episodic migraine category - ICHD3 • 12-month history of 2-8 attacks per month • Minimum 48h headache free	DFN-02	12-week study	Significant reduction in pain or pain free 2 hours – 24 hours (Acute Management)	No clinically meaningful adverse effects

Messoud et al 2021	DB – Placebo Controlled	46.4	674 (F)	• 18+ • Documented proof of inadequate response to migraine medication ~ (10 years)	Fremanezumab	12 weeks	4.4-4.8 Fewer Monthly migraine days	Nasopharyngitis & Injection Site Erythema
Ordas et al 2020	Quasi Experimental – Control	41.9	21 (F)	• 18+ • 6 month chronic phase categorised as ICHD3	Transcutaneous Supraorbital Stimulation	3 months	A mean reduction of 4 days per month for severe headaches	Mild uncomfortable and mild paraesthesia
Smith et al 2020	Double blind – randomized – placebo controlled	39.8	748 (F)	• 18+ • Maximum 14 migraines per month • 6 + months	Eptinezumab	60 weeks	3.9-5.3 reduction per month for episodic migraine	No serious Tolerability observed
Stark et al 2019	multicentre , retrospective chart review	44.6	211 (M 26) (185F)	• 18+ • 15 or more days per month with severe headache – 6+	OnabotulinumtoxinA	8 months	5.6 – 7.1 reduction in migraine days per month	No serious Adverse affects were recorded

Study Quality:

Although there were slight variations in study size and duration, the quality of trial was determined via an effective use and administration of an intervention. All 8 were successful in doing so, with half having opted for different approaches, to which all

were able to remain in line with clinical standards and no ethical guidelines were breached.

All studies were able to publish an efficacy outcome, and none were discontinued after later review

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Discussion

Intervention Efficacy:

Throughout the systematic review, the primary aim was to compile and evaluate an effective treatment for migraine.

All trials used an experimental intervention on participants who were in most need for a treatment solution, with all programmes spanning a minimum of 12 weeks and one study lasting longer than a year.

As seen in Table 1, the efficacy outcome provides an insight into the results of each intervention. Each treatment found at least some temporary alleviation of a migraine and others proved to be more effective by cutting down the mean average of migraine days occurring per month. The least effective interventions, through the perspective of a chronic migraine sufferer could perhaps be the two that are noted as *Acute Management (Rapoport et al, 2019 & Lipton et al, 2019) these offered pain free at 2 hours to the 24-hour mark, but there no noted decrease in average migraine days per month. Both trials were medical procedures which were administered during a migraine attack.

The remaining six studies produced results that saw a significant decrease in mean average days per month of a migraine occurring. The lowest decrease being at the low end of the Smith et al, (2020) study (3.9-5.3) to which an Analgesic drug known as Eptinezumab was administered to 748 female participants over a 60 week period. Comparing this outcome with study that found the highest decrease in mean average migraine days per month (5.6-7.1), Stark et al, (2019) conducted their study on 211 participants (87% female) using a pharmaceutical drug known as OnabotulinumtoxinA during an 8-month period. For both the Smith and Stark study, who's inclusion criteria required a maximum of 14 severe headache days per month for Smith and a minimum of 15 days per month for Stark, there is a low to top end reduction of 28-35% in monthly migraine days. These results would seem to be

effective, providing the use of pharmaceutical drugs are not un-welcomed by a personal health perspective.

A 2008 research study on the safety and efficacy of Herbal medicine, found their role in treatment of some mild illnesses and diseases to be a safer and natural solution to some ailments (Bent, 2008). For this systematic review, there was one trial that used a herbal medicine, Jung et al, (2019) conducted a trial on the efficacy and role of Shinbaro when used to treat migraine. Shinbaro is a traditional medicine made up of 6 herbs native to Japan and has been approved to treat bone and joint disorders, and some other inflammatory diseases. Preclinical trials have displayed effective treatment and pain alleviation for Osteoarthritis, these results prompted further research into the herbal medicine to which a migraine trial was formed. The results found that when treating 37 participants (81% female) within an interventional single arm pre & post study for 12 weeks, there was a mean reduction of 4.1 fewer monthly migraine days. The inclusion criteria for this trial required participants to experience 4 or more migraines per month, with an average reduction of 4.1 per month this would imply the use of Shinbaro to be incredibly effective, although actual average migraines per month for each participant is unknown therefore making the actual effectiveness unclear. Albeit successful, as there is a significant reduction.

Adverse Events:

The key studies produced relatively low amounts of adverse events during their trials. There were 3 trials that recorded no clinically meaningful adverse reactions (Lipton et al, 2020; Stark et al, 2019; Smith et al 2020). The Smith study notably stands out in that regard as it used the largest population group of 748 participants. Rather counterintuitively, some adverse events heightened some migraine symptoms. During the Shinbaro trial (Jung et al, 2019) 2 out of 37 participants experienced a migraine attack and occipital neuralgia.

Comparatively and on a larger scale the treatments used, seemed to provide a very low risk of causing any serious harm. From a health and scientific study perspective, the 8 key studies would seem to be successful.

Limitations

As cited within the introduction, it has been found that women tend to make up the majority population of those who suffer from migraine (Vetvik et al, 2014), thus prompting the participant choice in these studies being mainly women. This then prompts the question, whether an all-male group would have responded the same way to the Fremanezumab, Eptinezumab and Transcutaneous Supraorbital Stimulation trials to which only females were used.

Further limitations to this systematic review would be Time Frame and Population size. These vary greatly and may affect efficacy outcomes.

Conclusion

A migraine can present itself in a complex way, as for some people with the condition, their triggers are unique to them and for others they are unknown. Therefore, a root cause to them and the production of a suitable solution has not been yet universally categorised or produced (Montagna, 2004).

The evidence made available for this systematic review has detailed that there is a varied amount of somewhat effective treatment for those with migraine. Although, as these are all pre-clinical trials, the public use of treatment has not yet been made available.

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