A review of current pharmacologic and non-pharmacologic therapies for the treatment of chronic migraine

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For my mother Robin, who has suffered with this disease for over 40 years, all the while providing unconditional love and kindness to those around her.

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Definition of Terms

Episodic Migraine*:* The ICHD-3 defines migraine as a recurrent headache disorder manifesting in attacks lasting 4-72 hours that is usually frontotemporal, with typical characteristics including unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia (Headache Classification Committee of the International Headache Society [HCC], 2013)

Chronic migraine: the ICHD-3 defines chronic migraine as a headache occuring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month (HCC, 2013) **Biofeedback**: A process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise Instruments measure physiological activity and rapidly "feed back" information to the user. The presentation of this information in conjunction with changes in thinking, emotions, and behavior supports desired physiological changes (Association for Applied Psychophysiology and Biofeedback, 2011)

Medication overuse headache: The ICHD-3 defines a medication overuse headache (MOH) as a headache occuring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication for more than 3 months that *usually* resolves after the overuse is stopped (HCC, 2013)

Photophobia: Eye discomfort in bright light

Phonophobia: An overwhelming fear of sound or noise

Introduction

Chronic migraine (CM) is a common and debilitating psychosocial-neurological disorder. The biological mechanisms underlying CM are currently unknown, but a number of risk factors for developing the disorder have been identified (Cho & Chu, 2015). Individuals with the disorder are plagued by frequent attacks of moderate to severe headache pain that can be difficult to treat. The International Headache Society [HIS] has published a classification system for diagnosing the various types of headache referred to as the International Classification of Headache Disorders (ICHD). According to this classification a migraine is a more chronic, frequent, and severe form of a headache that is also longer in duration. An episodic migraine (EM) is characterized by a 4-72 hour duration, unilateral location, pulsating quality, moderate to severe pain intensity, and aggravation by routine physical activity. In addition, during the attack the individual may experience either nausea and/or vomiting, or photophobia and phonophobia (Levin, 2013). Based on the criteria for migraine, CM is diagnosed when headache attacks occur on at least 15 days per month and at least eight of those meet the criteria for migraine (Levin, 2013).

As mentioned above, CM is a common disorder among the US population and throughout the world. A survey of 162,756 individuals 12 years and older revealed the prevalence of CM in the US to be nearly 1% (Buse et al., 2012). If extrapolated, the study results translate to greater than 1.5 million women and 500,000 men in the US living with this condition. The study also found that among respondents, the prevalence of CM was highest during midlife, which is often a period of great responsibility for individuals. Coping with the effects of migraine on more days than not while managing family life, work, and other responsibilities can be incredibly difficult for the individual and those providing support. A recent review (Cho, Song, & Chu, 2015) of

outcomes in individuals with CM found that disability measures, economic burden, and healthcare utilization are significantly higher among this group than individuals with EM. In this review they defined disability as reduction of function in school, work, or non-work activities, and the authors noted that CM sufferers have a significantly higher frequency of lost workdays and utilization of long-term sick leave. They also report that physical, emotional, and social function is impaired significantly, even between headache attacks. Other studies have shown that sufferers of CM have a higher prevalence of co-morbid conditions such as anxiety and depression (Buse, Manack, Serrano, Turkel, & Lipton, 2010; Payne et al., 2011). Additionally, since CM is exacerbated by physical activity, maintaining a healthy weight may be difficult. Subsequent weight gain could put individuals at risk for developing other chronic conditions such as diabetes or cardiovascular disease. In fact, there is evidence that individuals with CM are more likely to report being diagnosed with cardiac risk factors including hypertension, diabetes, high cholesterol, and obesity (Buse et al., 2010)

According to Levin (2013), despite its high prevalence and serious debilitating effects, CM remains underdiagnosed and poorly treated, with many therapeutic needs still left unmet. Although effective treatment options are limited, there are a multitude of possible therapeutic options that may be of some benefit. These include pharmacotherapy, prevention of medication overuse, surgery, behavioral therapy, lifestyle modification, trigger identification, and management of co-morbid conditions that can contribute to disease severity (Dougherty & Silberstein, 2015). Deciding which therapeutic option(s) to consider for patients can become complicated, especially as new research in the field is rapidly expanding our understanding of the disease and its treatment. It is important for primary care practitioners to become familiar with treatment options because educational and training options for clinicians in headache

medicine are limited (Minen, Monteith, Strauss, & Starling, 2015). Only 4% of patients consult headache specialists for treatment (Mauser & Rosen, 2014) with the rest likely seeking care from their primary care practitioner. A recent survey of members of the American Headache Society (Minen et al., 2015) found 82.4% of physician respondents strongly agreed there needs to be improved education for clinicians of all specialties.

Clinicians treating individuals with CM are faced with many challenges. Not only does each patient have different migraine triggers, co-morbidities, and life stressors, there are also a wide variety of treatment options available. Further, among the available treatment options there are differing amounts of evidence to support the use of each. The FDA-approved treatments for CM are severely limited and other treatments are commonly used despite lack of FDA approval. Behavioral and lifestyle therapies are supported as efficacious in the treatment of CM, adding to the complexity of management. Patient compliance is very important, as well as patient education on the part of the clinician. Comprehensive and up-to-date reviews of treatment options and their indications for use are needed to guide clinicians in optimizing the delivery of care to patients suffering with this debilitating condition.

The purpose of this review article is to identify and describe all of the current pharmacologic, surgical, and behavioral treatments available to treat CM. The goal of the treatments described will be to increase the frequency of days per month that patients do not experience a migraine. The final product should serve as a comprehensive review of available options, which can be used to aid in clinical practice.

Literature Review

This review of literature will cover the following topics: Definitions and diagnostic criteria for episodic, chronic, and medication overuse migraine, etiology of CM, disease-related disability, importance of adequate treatment, available treatments and their indications for use, patient education, and appropriate long-term monitoring. The body of the review will focus on treatments including botulinum toxin injections, oral medications for both acute and prophylactic therapy, anatomical nerve decompression, electric and magnetic nerve stimulation, behavioral therapy (biofeedback, cognitive behavioral therapy, and relaxation therapy), sleep hygiene, nutrition, exercise, avoidance of triggers, headache diaries, and the importance of addressing co-morbid factors. Finally, a multidisciplinary approach that relies on adequate patient education and patient involvement in the treatment plan will also be included in the review.

Diagnostic Criteria

The diagnosis of CM can be a difficult task as patients often present with headache of varying severity on many days out of the month. It is helpful for patients to complete a headache diary for one month prior to their visit documenting each headache occurrence, its duration, quality, associated symptoms, and any therapies they tried to relieve the headache. Clinically, the diagnosis of CM can be made if the patient has experienced greater than 15 headaches per month for longer than three months, and the headaches have features of a migraine on at least eight of those days out of the month. The migraine can be with our without an aura to meet diagnostic criteria and cannot be accounted for by any other diagnosis. A migraine is defined as a headache attack lasting 4-72 hours and must be associated with either nausea and/or vomiting, or photophobia and phonophobia, and must include two of the following symptoms: unilateral

location, pulsatile quality, pain rated moderate-severe in nature, and pain aggrevated by physical activity or resulting in avoidance of physical activity (HCC, 2013).

It is important to note that many patients who experience symptoms of CM are overusing medications in an effort to relieve their pain. However, this practice can actually cause rebound headaches and result in an even greater number of headaches. For this reason, it is essential to make efforts to determine if the headache syndrome is truly CM, or MOH. A MOH is defined as an interaction between a therapeutic agent used excessively and a susceptible patient with migraine. The criteria for excessive use of a therapeutic agent varies depending on the substance but is always at least greater than ten days per month for longer than three months (HCC, 2013). The most commonly overused medications are simple analgesics or those combined with caffeine (Katsarava & Obermann, 2013). However, the diagnosis of MOH can be made with overuse of any type of antiheadache drug including aspirin, paracetamol, opioids, barbiturates, Triptans, or ergots. If it is discovered initially that a patient is overusing medications they can be given a diagnosis of both CM and MOH until the true diagnosis can be established by decreasing/withdrawing medication use.

Etiology

In the past it was believed that migraine headache was a primarily vascular disorder caused by cerebral or meningeal vasodilation, however this theory is no longer accepted (Buture, Gooriah, Nimeri, & Ahmed, 2016) It is now widely accepted that migraine is a most often inherited neurovascular disorder with multiple processes and complex pathophysiologies that are affected by lifestyle and medication use. In terms of genetic susceptibility, a study by

Merikangas et al. (1988), found that the risk of migraine in relatives of patients with CM was three times greater than controls.

Overall, it is currently believed that migraine is a sub-cortical disorder involving activation of the trigeminovascular system and modulation of nociceptive trigeminal input within the central nervous system. The convergence of the trigeminal and cervical afferents on neurons in the trigemininocervical complex (TCC) within the brainstem explains the common clinical symptoms of pain in the ophthalmic and occipital regions of the head (Buture et al., 2016). It is believed that neurons in the TCC become hyperexcitable and sensory signal processing is altered, resulting in a reduced pain threshold and exaggerated pain response. This theory of central sensitization is though to play a role in the conversion of EM to CM (Dodick & Silberstein, 2006).

Peripheral sensitization is also believed to play a role as primary afferent nociceptive neurons express increased sensitization to external thermal or mechanical stimuli. This is thought to contribute to the throbbing nature of migraine and their aggravation during physical activity. In addition, a neurally mediated inflammatory response characterized by vasodilation, leakage of plasma proteins, and mast cell degranulation in meningeal tissue has been identified as a possible contributing factor (Blau & Dexter, 1981). Specifically, the release of neuropeptides involved in the pain mechanism of migraine including calcitonin-gene related peptide (CGRP) and substance P have been implicated (Moskowitz, 1993). However, despite the breadth of research on the etiology and pathophysiology of migraine the exact cause is not entirely clear. Therefore, a variety of treatments exist to relieve symptoms that are not only based on pathophysiologic research and targeting the cause of the disease, but also simple trial and error.

Disease-Related Disability

CM is a physically and emotionally disabling condition that affects sufferers on at least half of their days out of each month. CM has been associated with a number of psychiatric disorders including depression, dysthymia, panic disorder, generalized anxiety disorder, and suicide. It has also been associated with chronic fatigue syndrome, insomnia, restless leg syndrome, obesity, epilepsy, fibromyalgia, gastrointestinal disorders, and an increased risk of stroke, sub-clinical vascular brain lesions, coronary artery disease, and possibly hypertension (Wang, Chen, & Fuh, 2010). In addition to the co-morbid medical conditions the symptoms of CM including nausea, vomiting, photophobia, and phonophobia are enough to incredibly limit ones daily activity and ability to perform routine tasks. Recovery from each migraine often requires complete bed rest. As a result, sufferers experience a nearly constant interruption in everyday life including working and maintain relationships. A study by Bigal, Serrano, Reed, and Lipton, (2008), found that over a three-month period more than half of CM sufferers missed at least five days of household work and more than one third reported missing at least five days of family activities. Another study (Munakata et al., 2009) found that CM patients reported significantly more time missed at work or school and time when productivity was decreased by at least 50% than sufferers of EM. The same authors found that annual total costs associated with CM were 4.4-fold greater for those suffering with EM and were estimated to total $7,750 on average. In addition, the financial costs associated with medical care have been estimated to be significantly increased for CM sufferers, compounding the level of stress already burdening the individual and their families.

Treatment

Prophylactic pharmacology

Pharmacotherapy has long been the mainstay of treatment for CM. Medications for treating migraine are divided into either abortive agents or prophylactic agents. Abortive agents are not designed to be taken on a daily basis and when done so can result in medication-overuse headaches as discussed above. Migraine prophylactic therapy is indicated when migraine attacks begin to significantly impact a patients life despite the use of acute headache medication, headache trigger identification/management, and behavioral interventions (Pringsheim et al., 2012). The overall goal of prophylactic therapy is to increase migraine-free day and should strongly be considered to avoid overuse of acute medications and development of MOH. The medications used for prophylactic treatment that will be discussed in this section are divided into Level A and B recommendations, based on the level of research to support their use according to the American Academy of Neurology (AAN) and the American Headache Society (AHS). Currently only one medications is approved by the FDA for the treatment of CM, with a few others having approval for migraine prophylaxis.

Topiramate is a first-line preventative agent FDA-approved for migraine prophylaxis with three randomized placebo-controlled trials demonstrating its efficacy. It is an antiepileptic drug that exerts its effect by blocking calcium and sodium channels, inhibiting glutamatergic receptors, enhancing GABA activity, and inhibiting central activation of the trigeminal nucleus caudalis and upper spinal cord (Estemalik & Tepper, 2013). The recommended target dose is 100 mg/day due to higher incidence of reported side effects at higher doses (Pringsheim et al., 2012). Studies have shown that at when taken daily at doses between 50-100 mg/day it significantly increased migraine-free days compared to placebo (Starling & Vargas, 2015). In addition to

increasing the total number of headache-free days per month, topiramate also lessens the severity of symptoms experienced during migraine attacks and improves emotional function. A randomized, placebo-controlled study by Silberstein at al. (2009) demonstrated the medications ability to significantly decrease the severity of photophobia, phonophobia, unilateral and pulsatile pain, and pain worsened by physical activity. The same study also showed a decrease in the frequency of nausea and vomiting, and in the average use of abortive pain medications.

Divalproex sodium is another antiepileptic medication that is FDA-approved for migraine prophylaxis. Along with topiramate, it has a level-A recommendation from AAN and AHS for first-line prophylactic treatment (Silberstein et al., 2012). The mechanism by which the drug exerts its therapeutic effects is not entirely known, but it is thought that its ability to block sodium channels affects the neural component of migraine development. Studies have shown that daily use of divalproex sodium can reduce migraine frequency by at least 50% compared to placebo (Mulleners, McCrory, & Linde, 2015). However, a recent review article (Bagnato & Good, 2016) reported that it is often not prescribed as a first choice due to its propensity to cause weight gain and hepatotoxicity.

Beta-blockers have been proven effective for the prophylaxis of CM and metoprolol, propranolol, and timolol have a level-A recommendation from AAN and AHS (Silberstein et al., 2012). In addition, propranolol and timolol are FDA-approved medications for prevention of migraine, and metoprolol and propranolol are recommended as first-line drugs for prophylaxis in Europe (Antonaci, Dumitrache, De Cillis, & Allena, 2010). Like many of the prophylactic medications the mechanism by which beta-blockers exert their therapeutic effect is unclear. In an effort to uncover this mechanism Gerwig, Niehaus, Stude, Katsarave, and Diener (2012) used transcranial magnetic stimulation to test the effects of beta-blockers on the visual cortex. They

found a significant decrease in migraine frequency compared to control subjects and were able to suggest that beta-blockers may act in part by modifying central neuronal excitability. The choice to use a beta-blocker over another first-line preventative therapy should be made on an individual basis considering each patient's medical profile and comorbidities.

The antidepressants amitriptyline and venlafaxine have a level B recommendation from the AAN and AHS, meaning based on current evidence they are probably effective and should be offered for migraine prophylaxis (Silberstein et al., 2012). Amitriptyline is a tricyclic antidepressant that is also recognized as first-line prophylactic treatment in the European guidelines (Antonaci et al., 2010). It is hypothesized that its mechanism of action involves up-regulation of GABA receptors and inhibition of norepinephrine and serotonin reuptake, thus down regulating beta-adrenergic receptors, resulting in a decrease in neuronal excitation (Estemalik & Tepper, 2013). A study comparing amitriptyline vs. placebo on migraine prophylaxis (Couch, 2011) found that up to 46% of treatment group subjects experienced greater than 50% fewer headache days per month than placebo, with the major effect occuring in those subjects with at least 17 headache days per month. These results however did not pertain to the severity or duration of headaches that did occur.

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor with studies showing it is similarly effective as amitriptyline in reducing migraine frequency. In a double-blind, placebo-controlled study (Ozyalcin et al., 2005) considering the efficacy of extended-release venlafaxine vs. placebo, venlafaxine was found to significantly reduce migraines, decrease analgesic consumption, and increase daily activity with greater than 80% patient satisfaction. In addition, it is proposed that since venlafaxine has fewer drug interactions than tricyclic antidepressants it can be a safer alternative to amitriptyline in migraine prevention.

The angiotensin-converting enzyme inhibitor (ACEI) lisinopril and the angiotensin receptor blocker (ARB) candesartan have been given a level C recommendation for migraine prophylaxis indicating that they are possibly effective in treating CM (Silberstein et al., 2012). Their effects on reducing migraine have not shown a correlation with any degree of blood pressure reduction. Instead, it has been hypothesized that ACEIs and ARBs prevent mast cell degranulation, which is thought to result in meningeal irritation, vascular dilation, and stimulation of nociceptive inputs on the trigeminal nerve leading to migraine pain. (Ba'albaki & Rapoport, 2008). In one randomized, placebo-controlled study (Schrader, Stovner, Helde, Sand, & Bovim, 2001) 10 mg of lisinopril taken daily significantly decreased days with migraine, days with headache, and duration of headaches. Similarly, candesartan was shown to decrease days/hours with migraine and headache, level of disability, and number of sick days required (Trovnik, Stovner, Helde, Sand, & Bovim, 2003).

Calcitonin gene-related peptide (CGRP) targeted therapy is a newly developing category of prophylactic treatment. As discussed previously, CGRP has been discovered to play a role in the trigeminocervical complex pathway of migraine pain and elevated levels have been found in the external jugular vein during the headache phase of migraine (Cauchi & Robertson, 2016). It is believed that when CGRP is released it causes vasodilation and inflammation leading to the pain of migraine. This class of medications acts by either blocking release of CGRP or preventing the molecule from binding to its receptors (Tepper, 2016). Two classes of CGRP-blocking agents have been developed, one acting as a prophylactic agent and the other for acute relief. Neither class has received FDA-approval for treating migraine and are still undergoing clinical trials. In a recent randomized, placebo-controlled study, Bigal et al. (2015) compared a humanized monoclonal antibody targeting CGRP (TEV-48125) to placebo in CM patients who

were also using other preventative and acute therapies. They found that migraine frequency was significantly reduced, as well as acute drug consumption, photophobia, phonophobia, nausea, and vomiting. If granted FDA-approval, CGRP-antagonist may be a useful alternative to prophylactic and/or acute abortive migraine therapy with fewer side effects than currently available medications.

Abortive pharmacotherapy

There are multiple drug classes that have been shown to be effective for the abortive treatment of migraine. A recent review of acute migraine treatment (Becker, 2015) organized the medications into four different treatment strategies including: medications for mild to moderate severity migraine, severe migraine, refractory migraine, and for patients with contraindications to taking vasoconstrictive agents. Many individuals suffering with CM require an abortive therapy in addition to a daily prophylactic medication. The goal of acute therapy is migraine relief within to hours of medication administration, and ideally, freedom from pain for 24-48 hours following treatment (Marmura, Silberstein, & Schwedt, 2015). This practice however can lead to MOH as discussed previously. In addition, the medications used for CM are associated with clinically significant drug-drug interactions (DDIs) based on the pharmacokinetic and pharmacodynamic profiles of each (Lionetto et al., 2016). Therefore, providers should carefully review all medications their patients are taking to treat headaches and migraines at every visit, including those that can be purchased over-the-counter without a prescription.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered effective for acute treatment of mild to moderate migraine attacks and include: ibuprofen, acetylsalicylic acid (ASA), naproxen sodium, and diclofenac potassium. Selecting which NSAID to use should be based on the individual patient profile considering the differences in onset of action (OOA),

duration of action (DOA), and dosing requirements of each medication. For example, due to the rapid OOA and short DOA of ibuprofen and diclofenac sodium, repeated dosing may be necessary during a single attack. In addition, both have alternative formulations designed for faster absorption that result in significantly improved pain relief (Becker, 2015). With all medications for migraine, it is important to consider how the side effect profile of a given medication may interact with existing medical conditions. For example, ibuprofen may be a good choice in patients with gastrointestinal disease because it is less irritating to the gastric mucosa (Becker, 2015).

Acetaminophen (APAP) is another medication shown to be effective for abortive therapy of mild to moderate migraines, and has been given a level A rating based on available evidence (Marmura et al., 2015). In addition, according to Becker (2015), it can be combined with an antiemetic such as metoclopramide for relief of nausea associated with migraine. APAP is also included in non-opioid combination analgesics designed for migraine relief. One such medication with the brand name Excedrin is a combination of APAP, ASA, and caffeine. This particular combination has been shown to be significantly more effective at providing pain relief two hours following administration than Ibuprofen and placebo (Goldstein, Silberstein, Saper, Robert, & Lipton, 2015). However, it is important to remember that use of APAP, ASA, or their combination varieties should be kept to less than 15 days per month to avoid medication-overuse HA and worsening symptoms.

In addition to NSAIDs and acetaminophen, triptans also have a level A rating from the AHS, indicating they are established as effective for acute migraine treatment (Marmura et al., 2015) and recommended for severe attacks, or moderate attacks that do not respond to NSAIDs, APAP, or combination analgesics (Becker, 2015). Triptans are selective serotonin receptor

agonists that are thought to relieve migraine pain from a variety of mechanisms including blocking the release of neuropeptides at presynaptic central terminals in the dorsal horn (Nahas & Silberstein, 2008) and vasoconstriction. Unfortunately, their action as vasoconstrictors makes them contraindicated in patients with cardiovascular disease (Becker, 2015). There are seven oral triptans available including sumatriptan, eletriptan, almotriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan. A variety of these also come in subcutaneous, nasal, or patch forms, and sumatriptan specifically is available combined with naproxen. According to Becker (2015), they all have similar efficacy but individual patients respond to some better than others. It is thus recommended that if a patient has a sub-optimal response to one, a different triptan should be tried. Studies have shown that the combination of sumatriptan and naproxen significantly improved headache relief at 2 hours following administration, photophobia, phonophobia, and nausea compared to monotherapy with either (Brandes et al., 2007). Recently, the FDA approved a breath-powered intranasal sumatriptan dry powder that has been shown to work significantly faster than the oral tablet for up to two hours (Tepper, 2016). The breath-powered mechanism prevents the powder from being swallowed, which was a potential problem with the traditional liquid nasal spray.

Ergot derivatives are serotonin receptor agonists like triptans, however they are much less specific, resulting in a higher side effect profile (Becker, 2015). Similar to triptans, they are also contraindicated in patients with cardiovascular disaease due to their vasoconstrictive properties. Dihydroergotamine (DHE) nasal spray and the pulmonary inhaler formulation have level A ratings from the AHS (Marmura et al., 2015). A randomized, double-blind, placebo-controlled study found that subjects who used a DHE breath-synchronized inhaler were 39% more likely than controls to be headache free at two hours following administration (Aurora, Rozen, Kori, &

Shrewsbury, 2009). However, the IV, IM, and SC formulations have only been found to be probably effective and oral ergotamine, another commonly used ergot derivative has a level C rating from the AHS. Due to its side effect profile, dihydroergotamine is recommended for migraine attacks refractory to NSAIDs, APAP, and triptans. In addition, the nasal spray can be used with an anti-emetic for severe nausea and vomiting associated with migraine. The ergot derivatives should be used less than ten times per month in order to prevent MOH. A recent study in France found that 13.5% of patient taking ergotamine derivatives were overusing the medication, and in addition to increasing headache frequency can increase the risk of ischemic complications (Donnet et al., 2016).

Opioids have been shown to be effective in relieving pain during acute migraine attacks but should not be used frequently due to their risk for tolerance and dependence, as well as their side effect profile. Butorphanol nasal spray has a level A rating from the AHS, but the authors of a recent review on acute treatment suggest that despite the level A rating for efficacy over placebo, it should not be selected as a first-line agent (Marmura et al., 2015). Research shows that opioid use seems to make migraines subsequently more difficult to treat and more frequent despite initial pain relief by preventing reversal of migraine central sensitization (Stewart, 2012). Patients who may benefit from the occasional use of opioids include those with contraindications to ergot-type medications and triptans due to cardiovascular disease, those with contraindications to neuroleptic medications, pregnant women, and those who fail to respond to other types of medications (Levin, 2013).

Botulinum toxin injection

Onabotulinumtoxin A is currently the only FDA-approved medication for the prophylactic treatment of CM. The neurotoxin is produced by *Clostridium botulinum* and when

injected into muscle tissue, blocks acetylcholine release at the neuromuscular junction thereby creating a reversible, dose-dependent muscle relaxation. It is also thought that the injections may relieve migraine by reducing the release of nociceptive neurotransmitters including substance P, glutamate, and CGRP (Ashkenazi & Blumenfeld, 2013), preventing neurogenic inflammation and inhibiting peripheral and central pain sensitization. The treatment procedure involves 31 separate 0.1 mL injections in seven different head/neck muscle groups bilaterally where peripheral sensory nerves can be accessed. The specific muscle groups targeted include the frontalis, corrugator, procerus, occipitalis, temporalis, trapezius, and the cervical paraspinal muscles. The sensory nerves accessed from these injection sites include the supraorbital branch, supratrochlear branch, and auriculotemporal branches of the trigeminal nerve, the greater and lesser occipital nerve branches, the third occipital nerve, and the sensory rami of C3-C5 (Ashkenazi & Blumenfeld, 2013). For optimal efficacy, it is recommended that the procedure be completed every 12 weeks.

According to the FDA's prescribing information (2016), studies have shown that onabotulinumtoxin A injections result in clinically significant reductions in frequency of headache days and total cumulative hours of headache on headache days. The PREEMPT 2 study evaluating the effects of onabotulinumtoxin A showed significantly fewer headache days and number of migraines, shorter headache durations, reduced disability, and improved quality of life (Diener et al, 2010). The effects of onabotulinumtoxin A have been shown to increase after repeated cycles resulting in progressive improvements with each cycle continuing even after one year of sessions (Guerzoni, Pellesi, Baraldi, & Pini, 2016). In addition, onabotulinumtoxin A is safe to use with other prophylactic and abortive migraine medications described previously. Side effects associated with treatment that may lead to discontinuation

include neck pain (9%), worsening migraine (4%), muscular weakness (4%), and eyelid ptosis (4%).

Anatomical nerve decompression

Much like onabotulinumtoxin A injections, surgical nerve decompression for the treatment of CM was discovered incidentally following cosmetic brow-lift procedures involving resection of the corrugator supercilli muscle (Guyuron, Varghai, Michelow, Thomas, & Davis, 2000). Following this procedure, patients with CM reported improvement in symptoms. It is thought that extracranial trigger sites exist due to compression of the supraorbital, supratrochlear, zygomaticotemporal and/or the greater occipital nerves (Janis et al., 2014). Onabotulinumtoxin A offers a chemical means to decompress these nerves thus relieving pain, but the effects are temporary. These temporary effects have been used as a prognostic indicator for the success of nerve decompression and also to aid in identifying specific nerves that should be targeted (Lee, Monson, Liu, Reed, & Guyuron, 2013).

Studies have shown that surgical decompression can significantly and permanently improve or eliminate migraines and should be considered in patients refractory to medication management, or those in which pharmacotherapy is contraindicated. In fact, a retrospective study involving 18 patients who had undergone the procedure on various combinations of triggers sites found 17% had complete resolution of migraines, 50% had at least a 75% reduction in migraine frequency, duration, or intensity, 39% of patients were able to discontinue all migraine medications, and 100% of patients reported they would repeat the procedure (Poggi, Grizzell, & Helmer, 2008). Janis et al. (2014) reported that among the randomized controlled trials addressing the efficacy of peripheral nerve decompression for treating migraines; the percentage of participants that achieve either at least a 50% reduction in migraines or complete elimination

of symptoms is nearly 90%. In their review, Janis et al. (2014) go on to point out that surgical decompression of peripheral nerves is the most rigorously studied surgical procedure for migraine relief with well-demonstrated efficacy and sustainability, and minimal side effects. The most common side effects include transient numbness or parasthesias at the surgical site, incisional alopecia, controlled intra-operative bleeding, and transient uneven brow movement, and in a review of 14 studies (Ducic, Felder, & Fantus, 2014) none reported complications requiring patients return to the operating room.

Neuromodulation techniques

A variety of central and peripheral nerve stimulation methods have been studied as possible treatments for CM. According to a review by Magis & Schoenen (2012), techniques that have shown at least some improvement include: transcranial magnetic stimulation, transcranial direct current stimulation, occipital nerve stimulation, sphenopalatine ganglion stimulation, vagus nerve stimulation, and supraorbital nerve stimulation. However, it should be noted that these stimulation techniques have only been approved for off-label use. Occipital nerve stimulation has been shown to be effective with studies showing a greater than 50% improvement in migraine (Hann & Sharan, 2013; Schwedt, Dodick, Hentz, Trentman, & Zimmerman, 2007) and is the most widely used neuromodulatory technique. More recently, the combination of occipital and supraorbital nerve stimulation has shown to be significantly more effective. Specifically, the combination has been shown to markedly improve headache severity and frequency in 71% of patients, elicit resolution of associated neurological symptoms, and allow patients to return to their normal functional lifestyle in 50% (Hann & Sharan, 2013). The adverse effects from this study were more severe than those reported following anatomical nerve decompression and include lead migration, lead site allodynia, infections due to hardware

exposure, and requirement for reoperation due to surgical site infections or near electrode exposure.

Vagus nerve stimulation is a central neuromodulatory technique that has been studied for the treatment of CM. During the procedure, the stimulating electrode is implanted and wrapped around the vagus nerve in the neck. However, the high cost and the potential risks associated with the procedure have limited its use. Recently, a handheld non-invasive vagus nerve stimulating device has been developed that can be self-administered by patients. A 2016 (Silberstein et al.) prospective, multicenter, double-blind, sham-controlled study of this device found that participants who used the device three times daily at 6-8 hour intervals experienced a significant decrease in headache days over the eight month trial period. Interestingly, longer treatment durations were associated with greater reductions in the number of headache days indicating a slow accrual of benefits over time. Additionally, there were no serious adverse events reported with use of the device over the study period.

As another attempt to reduce the potential adverse events that have been reported with the use of implanted stimulation devices, the FDA has recently granted approval for a clinical trial of an electrical stimulation device called the StimRelieve Halo Migraine System. The device is implanted under the skin via an injection and a small battery pack is worn on the ear. This device would be significant as it is the smallest to date, making implantation less invasive and the implantable pulse generator responsible for reoperations and patient discomfort has been eliminated (Study of Wireless Nerve Stimulation in the Treatment of Chronic Migraine, 2016).

Percutaneous electrical nerve stimulation (PENS) has also been found to be effective in treating CM. The process is similar to acupuncture, in which needle probes are inserted into the skin at the dermatomal level corresponding to the location of headache symptoms. However, in

this case the needle probes are attached to an electric source and a low-level current is applied to the areas (Jenkins & Tepper, 2011). No device is left implanted under the skin with this method. In a study comparing PENS with needles alone for treating CM, Ahmed et al. (2000) found pain scores 48 hrs following PENS decreased by 59% compared with 15% for placebo. In addition, subjects also experienced a significant improvement in physical activity level, quality of sleep, reduction in frequency of headache, a reduction in the average daily requirement for analgesic therapy. Based on these results, PENS therapy is a useful complementary therapy for CM.

Another promising non-invasive neurostimulatory therapy is transcutaneous electrical nerve stimulation (TENS). In 2014 the FDA approved a battery-powered supraorbital TENS device that is designed for migraine prophylaxis named the STS Cefaly. When worn around the head, the device delivers biphasic electrical impulses to the supraorbital and supratrochlear nerves. In a 2013 study by Schoenen et al., patients who wore the TENS device for 20 minutes per day for 90 days found that daily use of the device decreased migraine days from baseline by 25% and migraine attacks by 19%. The authors compared these effects to those found with use of the preventative medication topiramate discussed earlier. They found topiramate to be overall more effective but noted the responder rate for the STS Cefaly was within the same range. A major benefit of the TENS device compared to prophylactic medication therapy is the excellent tolerance, safety, and lack of side effects of the device. In addition, use of the device can be combined with prophylactic medication to theoretically enhance relief without risk of interactions.

In addition to TENS, multiple studies have demonstrated the benefit of transcranial magnetic stimulation on migraine prophylaxis. However, there have been varying results depending on the frequency and duration of the treatment periods. In a study by Misra, Khalita,

and Bhoi (2013), patients were randomized to receive either three cycles of repetitive TMS (rTMS) every other day for four weeks, or sham stimulation. The treatments consisted of applying a stimulator to the area of the left frontal cortex for 412.4 seconds per cycle. During the treatment sessions all patients reported discomfort but none withdrew from the study due to this side effect and no other significant adverse effects were reported. Results of the study showed that rTMS significantly reduced headache frequency, headache severity, functional disability and rescue medication use. These results offer yet another non-invasive neuromodulation technique that can be safely used as an adjunct to other prophylactic migraine treatments.

Behavioral therapy

According to Morgan, Cousins, Middleton, Warriner-Gallyer, and Ridsdale (2016), a solely pharmacological approach to CM treatment often fails to take into account the social, cognitive and emotional factors associated with the onset, course and consequences of migraine. They add that the course of headaches and the development of CM is affected by psychological factors including locus of control, self-efficacy, and emotional states. In addition, stress has been identified as a triggering factor in greater than 75% of patients (Kelman, 2007). These factors play a role in perceived pain, quality of life and ultimately how each individual copes with managing their symptoms. There are a variety of behavioral therapies designed to address these psychological factors that contribute to CM and can result in improvements in self-management. The following psychological interventions are considered a possible alternative or adjunct to pharmacotherapy and/or surgical interventions and there is no evidence to suggest that one is superior to the others.

Biofeedback

Thermal (skin temperature), electromyographic (EMG) (electrical activity of head and neck muscles), and blood volume pulse biofeedback have been shown to be beneficial in managing migraine. Nicholson et al. (2011) described the technique as such:

> Biofeedback involves digital capture of physiological processes, which are converted into a medium (auditory, visual, or combined) that is displayed or "fed back" to the patient to facilitate the patient's ability to self-regulate or "control" the physiological processes found to be the most reactive during assessment.

According to Sun-Edelstein & Mauskop (2011), relaxation skills including diaphragmatic breathing or visualization are usually taught in conjunction with biofeedback to produce a relaxation response to the trained inputs. The technique is initially taught over multiple in-office sessions, but can eventually be completed by the patient on their own and practiced on a daily basis for prophylaxis and managements of acute migraine attacks. A study by Odawara, Hashizume, Yoshiuchi, & Tsuboi, (2015) found that following biofeedback therapy subjects showed a reduction in headache intensity, headache duration, and headache-related disability. They also identified improvements in psychological stress, depression, and anxiety. Campbell, Penzien, and Wall (2010) completed a review of non-pharmacological migraine treatments that included biofeedback. They reported that thermal biofeedback showed a 37% average improvement in headaches and EMG biofeedback resulted in a 40% average improvement in headache. They also reported on the efficacy of thermal biofeedback in conjunction with relaxation training in ten studies with an average improvement in headache frequency of 33%. In addition, studies have shown that biofeedback results in reduction of headache symptoms for

over one year and it can be concluded that it is a suitable treatment for the long-term prevention of migraine (Sun-Edelstein & Mauskop, 2011).

Cognitive behavioral therapy (CBT)

CBT interventions for migraine are diverse and include education and management of headache triggers, stress, and fear. It is most beneficial in patients with significant psychological or environmental problems that exacerbate headaches including chronic work stress, mood disorder, or adjustment problems (Sun-Edelstein & Mauskop, 2011). CBT requires a significant time commitment on behalf of the patient and provider, as multiple therapeutic sessions are required. The technique is designed to minimize the effects of stress and requires a therapist specifically trained in CBT to teach the skills necessary to identify and control stress. Studies have shown that CBT can result in a nearly 50% reduction in headache activity (Campbell et al., 2010). Morgan et al. (2016) conducted a study to evaluate participant experiences following a combined behavioral approach consisting of deep breathing, progressive muscle relaxation, and CBT. When asked about the effects of CBT over 50% of participants reported that CBT benefited them in some way, including managing triggers and improving coping strategies. A recent review (Minen et al., 2016) of electronic behavioral interventions found that CBT was the most commonly offered intervention with the greatest positive outcome in headache frequency, severity, intensity, and need for abortive migraine medication. The US Headache Consortium has found that CBT for migraine prophylaxis is supported by Grade A evidence (Campbell et al., 2010).

Relaxation training

According to a review by Sullivan, Cousins, and Risdale (2016) of psychological interventions used to treat migraine, the combination of CBT and relaxation therapy was the

most commonly used. Relaxation techniques have been studied as a means to prevent the onset of migraine and to reduce the intensity and duration of migraine once the attack has begun. It is used to decrease sympathetic arousal and physiologic responses to stress by enhancing awareness of tense and relaxed muscles (Sun-Edelstein & Mauskop, 2011). Techniques include deep breathing, progressive muscle relaxation, autogenic training, and meditative relaxation. Progressive muscle relaxation is a systemic relaxation technique that has been shown to decrease migraine frequency and after sufficient training, can be self-administered. A study by Meyer et al. (2016) confirmed the positive effect of PMR after six weeks of training on reducing frequency of migraine and suggested that with every successful relaxation exercise, patients develop greater confidence in their abilities to cope and control their own relaxation state. A 2010 review of relaxation techniques that included PMR, autogenic training, and meditation reported a 32% average improvement in headache frequency from pre- to post-treatment (Campbell et al., 2010). In terms of stress specifically, Keller, Meyer, Wohlbier, Overath, and Kropp, (2016) hypothesized that stress coping is reduced in migraine patients and found that meditation had the potential to combat the stress-enhancing strategies that are learned by many migraine patients. Interestingly, it has been demonstrated that the largest improvements in headache disability are seen when pharmacotherapy, CBT, relaxation training, and biofeedback are used in conjunction (Holroyd et al., 2010)

Acupuncture

Acupuncture has been shown to be a beneficial adjunct for the prophylactic treatment of migraine. The exact mechanism of action is unknown but it has been hypothesized that the therapy activates areas of the nervous system involved in the perception of pain, in addition to anti-inflammatory effects (Sun-Edelstein & Mauskop, 2011). A recent Cochrane review (Linde

et al., 2016) found that compared to placebo, 41% of participants' migraines decreased by at least 50% following treatment. However, the effect of acupuncture over sham treatment was not as effective with only a 9% difference in response between groups suggesting there may be a strong placebo effect associated with this method of treatment. Acupuncture was also compared with pharmacologic prophylaxis and found to be at least similarly effective as drug treatment. There have been no studies to date that have identified any significant adverse affects of acupuncture, and the therapy can be safely combined with pharmacologic or behavioral interventions. Thus, acupuncture should be considered as a treatment option, especially in patients who are unwilling or unable to tolerate prophylactic drugs.

Managing sleep disorders

Migraine and sleep disorders are common co-morbid conditions. Kim et al. (2016) found that nearly 20% of patients with migraine also suffer from excessive daytime sleepiness (EDS), and those with CM specifically have an increased prevalence. In addition, those with EDS and migraine reported more severe headache intensity, a higher psychological impact of their headaches, and a higher prevalence of comorbid depression. It has been observed that both sleep deprivation and excessive sleep are common triggers for migraine, thus regulating sleep patterns is an important aspect of overall treatment. Smitherman et al. (2016) evaluated the effect of CBT on individuals with migraine and comorbid insomnia. Participants in their study attended biweekly CBT sessions in which they learned skills pertaining to sleep restriction and stimulus control to reassociate the bedroom with sleep. The authors reported that at follow up participants who received CBT for insomnia experienced improved sleep and a 48.9% reduction in monthly headache frequency compared to a 25% reduction in the control group who received therapy regarding general lifestyle modification. Woldeamanuel & Cowan (2016) studied the impact of

regular lifestyle behaviors including regular mealtimes, sleep and exercise on episodic and CM. They found that regular sleep had an identical impact on the risk of having CM as the combination of all three lifestyle behaviors, indicating the prominent importance of sleep regulation. There is clear evidence that improving sleep patterns can result in fewer headaches and other co-morbid conditions such as depression. Thus, when evaluating patients with CM sleep should be assessed and sleep disorders such as insomnia and sleep apnea should be part of routine screening. If sleep disorders are recognized early, referral to a sleep specialist could optimize treatment goals.

Neutraceuticals

Magnesium. Magnesium is an abundant cation within the body and plays a variety of active roles within the cell, many of which are involved with the pathogenesis of migraine including: ATP production/function, glucose metabolism, regulation of vascular tone, concentration of serotonin receptors, nitric oxide synthesis, and release of inflammatory mediators (Sun-Edelstein & Mauskop, 2011). In addition, it has also been discovered that magnesium deficiency can elicit headache pain by generation of substance P (Moskowitz, 1984). A randomized controlled trial by Peikert, Wilimzig, and Khone-Volland (1996) found that a daily dosage of 600 mg elemental magnesium significantly reduced headache frequency, with over 50% of the study population experiencing a greater than 50% reduction in headaches from baseline. A separate study also comparing the 600 mg dose versus placebo found a significant reduction in migraine frequency and severity following a three-month treatment period (Koseoglu et al., 2008). The most common adverse effect associated with oral magnesium is diarrhea but toxicity can result in cardiac muscle weakness, respiratory paralysis, and death (Sun-Edelstein & Mauskop, 2011). Based on the current research, guidelines issued by the CHS

and EFNS support the use of 600 mg of elemental magnesium for migraine prophylaxis (Rajapakse & Pringsheim, 2016).

Coenzyme Q10. Coenzyme Q10 (coQ10) is an essential cofactor of the electron transport chain, protecting against mitochondrial degeneration and functional demise, while also stimulating endothelial release of nitric oxide and exerting anti-inflammatory effects (Rajapakse & Pringsheim, 2016). Studies have shown that daily doses ranging from 150-300 mg are effective in reducing frequency of migraine. A randomized controlled trial of the 300 mg dose taken daily for three months observed a significant reduction in migraine attacks compared to placebo (Sandor et al., 2005). Another study comparing the effects of 150 mg of coQ10 in patients with EM observed a greater than 50% reduction in the number of days with migraine headache in 61.3% of their study population compared to placebo (Rozen et al., 2002). In addition to the possible beneficial effects, adverse effects occurred in less than 1% of subjects and included, anorexia, dyspepsia, nausea, and diarrhea (Daniel & Mauskop, 2016). Based on this information the CHS recommends taking 300 mg of coQ10 daily for migraine prophylaxis, and the AAN, AHS, and EFNS guidelines state that coQ10 is possibly effective and may be considered for migraine prophylaxis (Rajapakse & Pringsheim, 2016).

Riboflavin (Vitamin B2). The evidence for use of riboflavin as a prophylactic measure is conflicting and various headache organizations have provided recommendations for its use. Riboflavin is a water-soluble B vitamin that functions as a cofactor in oxidation-reduction reactions of the Kreb's cycle and in cellular membrane stabilization (Taylor, 2011). A randomized controlled trial by Schoenen et al. (1998) found a once daily 400 mg dose to be effective in decreasing the frequency of migraine attacks by 50% in 59% of subjects. In addition, a pharmacogenetic study by Di Lorenzo et al. (2009) found that individuals with a specific

mitochondrial DNA haplogroup were more responsive to daily riboflavin, indicating that it may only help individuals with relatively decreased mitochondrial function (Daniel & Mauskop, 2016). Although the evidence is sparse the side effects are minimal, and supplemental riboflavin is generally recognized as safe. Based on this information the Canadian Headache Society (CHS) recommends 400 mg of riboflavin daily, and the AAN/AHS and the European Federation of Neurological Societies (EFNS) recommend considering riboflavin for prophylaxis stating it is possibly useful (Rajapakse & Pringsheim, 2016).

Herbal preparations

Butterbur. Butterbur is a perennial shrub native to Europe and parts of Asia. The purified extract of the leaves, rhizomes, and roots termed petasin, is pharmacologically active and has been shown to be effective in decreasing the frequency of migraine. According to Daniel & Mauskop (2016), butterbur has antihistamine properties and also inhibits the synthesis of leukotrienes, thus influencing the inflammatory cascade associated with migraine. In addition, a recent study by Slavin, Bourguignon, Jackson, & Orciga (2016) found that petasin decreased CGRP secretions by 24%, which may be important, as CGRP has been implicated in the pathophysiology of migraine and currently CGRP-antagonists are undergoing clinical trials. A study by Lipton et al. (2004) compared the effects of a twice-daily 75 mg dose of butterbur extract, with a twice-daily 50 mg dose, and placebo over a three-month period. The authors reported a 48% reduction in migraine frequency attack with the 75 mg dose, compared to a 36% reduction with the 50 mg dose, and a 26% reduction for placebo. They concluded that the 75 mg dose is more effective than placebo and well tolerated with burping reported as the only adverse effect. Another study compared the 50 mg dose to placebo and reported a significant decrease in migraine frequency following the three-month study period (Diener, Rahlfs, & Danesch, 2004).

It should be noted that butterbur contains pyrrolizidine alkaloids, which are hepatotoxic and have led to renal failure in individuals taking products that have not removed the toxic alkaloids. Patients should be advised to only use butterbur products that certify the alkaloids have been removed and that contain at least 15% petasins (Rajapakse & Pringsheim, 2016). Currently, the CHS and AHS recommends 75 mg of butterbur twice daily for migraine prophylaxis, and the EFNS states it is possibly useful for migraine prevention (Rajapakse & Pringsheim, 2016).

Medical marijuana. Although medical marijuana is not legalized in the majority of the United States, there have been a few studies examining the possibility for cannabinoids to prevent or relieve migraine. Cannabinoids exert serotenergic and dopaminergic effect on the central nervous system as well as anti-inflammatory effects. The evidence supporting the effectiveness of migraine medications like triptans, which are serotonin agonists suggests that cannabinoids may also be effective. There are currently no clinical trials available evaluating this hypothesis however, Rhyne, Anderson, Gedde, and Borgelt (2016), with the University of Colorado, conducted a retrospective chart review of patients prescribed medical marijuana for migraine. They found that the majority of patients used marijuana on a daily basis for both prophylaxis and acute treatment, and multiple forms were used including vaporized, edible, smoked, and topical. The authors reported that out of 121 patients, 85% reported a decrease in frequency of migraine, and 48% reported a decrease in prescription drug use. Adverse effects were reported in 11.5 % of patients and included somnolence and difficulty controlling the effects of marijuana, which were more likely to be reported among those using the edible form. These results indicate that medical marijuana may be an effective treatment for migraines with few side effects in states that have legalized the practice.

Physical therapy

Neck pain and other physical derangements of the head and neck have been identified in migraine patients. A study by Calhoun et al. (2010) found that the prevalence of neck pain directly correlated with headache frequency, even more so than the presence of nausea. Other research has shown that patients with migraine have a greater number of active myofascial trigger points in muscles of the head and neck, an altered neck posture, and decreased neck mobility. It is hypothesized that if present, these factors may contribute to the development of migraine and that physical therapy to improve these skeletal derangements may improve migraine (Fernandez-de-las-Penas, Cuadrado, & Pareja, 2006). Bevilaqua-Grossi et al. (2016) studied the effects of physical therapy by randomizing patients into groups receiving either migraine medication alone, or medication and biweekly 50-minute physical therapy sessions consisting of manual therapy and stretching maneuvers. They observed a clinically relevant improvement in headache frequency and intensity posttreatment, an increased cervical pain threshold, reduced nociceptive afferents in the craniocervical region, and enhanced patient satisfaction. In a 2011 review of manual therapies for the treatment of migraine Chaibi, Tuchin, and Russell reported findings that massage therapy, physiotherapy, and chiropractic spinal manipulative therapy may be equally effective as prophylactic medication. They concluded that manual therapy is a safe treatment with few adverse reactions and may be beneficial for patients not responding optimally to pharmacologic management.

Exercise

Exercise can be difficult for patients with CM to achieve. For some, exercise may be believed to be a trigger or exacerbating factor, and for others a regular exercise routine is difficult to maintain while managing a busy life plagued by migraines and near-daily headaches.

However, research has shown that therapeutic exercise provides beneficial effects on migraines including decreased frequency and intensity of pain (Gil-Martinez et al., 2013) and a linear relationship exists between low physical activity and increased migraine frequency (Varkey et al., 2009). Interestingly, research does not support the belief that aerobic exercise induces headache (Irby et al., 2015) rather, it is established that exercise can exacerbate a headache that is already occuring. In addition to improvement in migraine, regular exercise can also improve other conditions that are commonly co-morbid with migraine including sleep apnea, obesity, HTN, depression, and anxiety. The connection between aerobic exercise and improvement in migraine is not known.

Research has identified common mechanisms known to be operational in both migraine pathophysiology and exercise physiology involving biological markers such as CGRP and serotonergic function, as well as psychological and behavioral factors such as self-efficacy and locus of control. It is not yet known how these factors may interact to improve migraine. According to Irby et al. (2016) specific recommendations for exercise such as optimal types, intensity, and duration have yet to be established. Thus, it may be prudent at this time to follow the American Heart Association recommendations for physical activity (2016) when counseling patients which include: at least 30 minutes of moderate-intensity aerobic activity at least 5 days per week and moderate-to-high intensity muscle strengthening activity at least two days per week.

Avoidance of triggers

Careful identification and avoidance of triggers is perhaps one of the most important aspects of migraine prevention. Many different categories of triggers exist and are different between patients. However, there are many triggers that have been identified in a large number

of patients and thus, are important to educate patients about. These include environmental factors such as weather changes and sun exposure, psychological factors such as stress, alcohol including red wine, caffeine, certain foods, and missing meals. A study Wober, Holzhammer, Zeitlhofer, Wessely, & Wober-Bingol, (2006) found that weather changes, stress, and menstruation were the most frequently cited migraine triggers by participants. Although, triggers such as weather and menstruation often cannot be avoided, it does benefit patients to understand that they may be more susceptible to migraine attacks during these events and can thus take measures to limit their exposure to other triggers during these times.

It should be kept in mind that the concept of migraine triggers is complex, and as Goadsby and Silberstein (2013) report, “the response to a trigger depends on expectation to the response, prior conditioning, learning, memory, motivation, and meaning”. They also noted that female patients are more sensitive to individual triggers during menses. In an effort to organize and identify these triggers, patients should be encouraged to keep a record of their migraines or “headache diary”. The record should include each headache or migraine, the duration, any abortive therapy that was used, and any identifiable triggers. To simplify the process electronic headache diary applications have been developed for migraine patients that can be easily accessed from a cellular device or computer.

Methodology

Relevant research concerning therapies for increasing headache-free days in patients suffering from chronic migraine was identified by searching a number of biomedical research databases from January-August 2016. These databases included EBSCOhost, PubMed, and Google Scholar. In order to ensure that relevant studies were not missed, search terms remained broad but did include “chronic migraine” or “migraine” in the text and the search was limited to adult subjects and English language text. There were no restrictions placed on country of origin of the study or year published. An effort was made to primarily include research that has been conducted within the previous ten years but exceptions were made for articles of historical signifigance to the purpose of the paper. Other peer-reviewed medical resources were also consulted for portions of the paper including UpToDate, Clinical Key and DynaMed. In addition, positions from the American Headache Society, American Academy of Neurology, European Headache Federation, and British Association for the Study of Headache were reviewed.

Conclusions

As evidenced throughout this review, CM can be a debilitating disease with long-term health complications. Even reducing the frequency of monthly headache and migraine attacks can significantly improve ones health and quality of life without completely eliminating attacks. However, the pathophysiology of migraine is yet to be completely understood. As research improves, so do the available treatment options. There are currently a wide variety of treatment options that can make optimization of care a daunting task for both patients and practitioners. To date, the only FDA-approved therapy for CM specifically, is Botox injections. However, the widely accepted first-line therapy remains pharmacologic prophylactic treatment. In fact, insurance coverage of Botox injection therapy often requires that a patient fail management on multiple medications prior to approval. Thus, it is recommended that practitioners attempt a prophylactic medication from those discussed in this review, with the addition of acute abortive therapies for severe attacks. It must be kept in mind that abortive medications should be limited to no more than 10-15 days per month depending on the class, in order to prevent MOH. In addition to medications, there are a variety of nutritional supplements that are generally recommended as discussed in this review including magnesium, coQ10, riboflavin, and butterbur. Patients may also benefit from electric or magnetic stimulation, physical therapy, exercise, acupuncture, biofeedback, relaxation therapy, and/or CBT. The decisions regarding which therapies to attempt should be individualized to each patient's needs, and co-morbid illnesses that can impact migraine such as sleep apnea and HTN should be addressed. Finally, if conventional therapies have failed, plastic surgeons have recently begun performing surgical nerve decompression to alleviate the pain of migraine, but due to the invasive nature of this procedure, it has been limited to patients refractory to all other treatment methods.

In terms of routine care and follow-up, patients should be encouraged to keep a record of their headaches/migraines in the form of a headache diary that can be brought to each visit. Clinicians should carefully review frequency of headaches, abortive medication use, supplement use, alternative therapies, quality of life, and patient goals at each visit, and adjust treatment plans as necessary. The body of research on the pathophysiology of migraine and its treatment is rapidly expanding with new treatment options on the horizon such as CGRP antagonists. Keeping up to date with preventative measures and new treatments will enable practitioners to best serve their patient population.

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Abstract

Chronic migraine is a common illness among the population with long-term health consequences and a frequent complaint among patients presenting to their primary care provider. Thus, it is important that providers have a complete understanding of the available treatment options and when referral to a specialist is necessary. In addition to pharmacologic therapies for chronic migraine, a number of other options are available for patients including botulinum toxin injections, surgical interventions, behavioral therapy, physical therapy, and lifestyle changes including nutritional management. The mainstay of treatment has long been pharmacologic with a number of abortive and preventative medications available. However, research has shown that botulinum toxin injections and other measures including managing sleep disorders, physical therapy, and nutraceuticals can be effective as well, Thus, limiting the amount of medication an individual may need to take and decreasing the risk of developing medication over-use headache, which is a common problem among chronic migraine sufferers. The decisions regarding which therapies to attempt should be individualized to each patient's needs, and co-morbid illnesses that can impact migraine frequency and duration. Management of chronic migraine also requires a close patient-provider relationship and effective communication. Patients can benefit from keeping a headache diary to assist their provider in adjusting the treatment plan as necessary. Likewise, the provider is tasked with keeping up to date on the vast body of research and new treatment options which may improve the quality of life of their patients who suffer with this debilitating condition.

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