Review

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What is the contribution of non-pharmacological procedures on the management of chronic migraine?

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Abstract

Chronic migraine (CM) is a common disorder that compromises the quality of life of patients, decreases functionality, is frequently misdiagnosed, and has poor response to treatment even when diagnosed. Rare and randomized controlled studies on chronic migraine have revealed limitations within current therapeutic options. While pharmacologic treatment includes acute and preventive treatment options, it may lead to some adverse effects, which challenge the tolerance of patients. An increased number of studies in recent years have shown that behavioral interventions such as cognitive behavioral therapy (CBT), biofeedback (BFD), relaxation techniques and neurostimulation procedures lead to a significant improvement in the treatment of chronic migraine. For this reason, such treatment options are recommended, especially in persistent cases with poor response to treatment. The treatment of chronic migraine is more challenging compared with episodic migraine (EM), and recent studies suggest that non-pharmacologic approaches and neurostimulation techniques will increase the chance of success in the treatment of chronic migraine.

Keywords: Behavioral therapy, chronic migraine, non-pharmacologic treatment

INTRODUCTION

Chronic primary headaches, such as chronic migraine (CM), are disorders that compromise the quality of life and have an approximate prevalence of 1-5% in the general population (1). CM develops from the episodic form to the chronic form (migraine transformation) over time and usually catches individuals in the most productive period of their lives. While in EM, headache attacks last less than 15 days per month, whereas CM has headache episodes that last for at least 15 days per month, for a total period of over 3 months, with headache attacks of at least 8 days that meet the diagnostic criteria for migraine (2). During CM, the rates of disability, anxiety, and depression associated with headache are high and the treatment is relatively difficult compared with the episodic form (3). At this point, pharmacologic therapy alone in CM may sometimes be inadequate in acute or prophylactic treatment. For this reason, it is necessary to evaluate patients in consideration with social, cognitive and emotional states (4).

Pain and emotion are intertwined and the human experience of pain includes both affective and nociceptive components. Based on the anatomic connections between emotion and pain, it can be stated that non-pharmacologic treatments such as yoga, cognitive behavioral therapy (CBT), biofeedback (BFD) and meditation, often used to increase emotional regulation, may strengthen migraine and pain management (5). In addition, studies have shown that invasive and noninvasive neurostimulation therapies combined with behavioral interventions can render successful results in treatment (6).

In recent years, promising studies on neuromodulation methods such as vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS), occipital nerve stimulation (ONS), sphenopalatine ganglion stimulation (SPG) and deep brain stimulation (DBS), have gained ground (7, 8).

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In this review, we address the non-pharmacologic treatment options towards a better management of patients with CM and a better understanding of its treatment.

METHODS

Using databases for which Mersin University holds subscriptions, mainly PubMed and Cochrane Library, Ovid, Medline and Taylor Francis, we completed a comprehensive review of studies that incorporate recent non-pharmacologic approaches to current CM treatment.

We made our search using the keywords and combinations of 'chronic migraine,' 'treatment,' 'non-drug based,' 'non-pharmacologic,' and 'behavioral therapy'. Including only reviews, randomized controlled trials (RCT), and open-label studies written in English, we tried to use those that had the widest group of patients. We have compiled current information from reviews and original articles including randomized controlled trials, open label studies, and cross-sectional studies. We included articles with high data-quality that were related to the heading of the review.

NON-PHARMALOGIC MANAGEMENTS

Although pharmacologic therapy is still the cornerstone of CM treatment, drug adverse effects, drug interactions, and comorbid diseases pose limitations in this treatment. Educating people about headaches and triggers, modifying lifestyles and developing an understanding about protective treatments are crucial for non-pharmacologic treatments. Of the modifiable risk factors, stress is thought to affect all age groups and to have an impact on the process of chronicity. Behavioral therapies, which aim to develop stress coping ability, have proven to be successful in the treatment of CM. Behavioral management needs to be tailored for the individual, because lifestyles of individuals and their exposure to stress show variety.

Behavioral therapies, which can be used by themselves or in combination, can be grouped under three categories: relaxation, BFD, and CBT. The most successful results have been obtained with regard to these three treatments (9, 10).

Relaxation Techniques

The use of relaxation techniques is mainly aimed at reducing sympathetic stimulation and muscle tonus, and at providing relaxation in the whole body. Patients are usually taught to perform a series of gradual relaxation techniques for 20 to 30 minutes per day. These techniques allow patients to learn about and to manage physiological responses. Patients are asked to integrate relaxation into their daily activities. At the same time, it alleviates pain by reducing peripheral sensory input due to distractions. Relaxation techniques include progressive muscle relaxation training, diaphragmatic breathing, meditation, autogenic training, and guided imagery.

Progressive muscle relaxation (PMR) is a systematic relaxation technique developed by Edmund Jacobson. During this training, patients are instructed to flex and loosen certain muscle groups, starting from the head down, and for each muscle group; these last for 10 and 20 seconds. Patients are asked to concentrate on their feelings during stretching and loosening. In further sessions, patients are asked to do this for a longer period, but with fewer muscle groups (4 or 7), and then only loosening exercises without the stretching. This allows for the interaction between muscular and mental levels. Video and audio programs can be used to increase this concentration (10). In a study involving 35 patients with migraine and 46 healthy controls, six-week PMR-training was performed to 16 patients with migraine and 21 healthy controls, who were then compared using contingent negative variation (CNV) measurements to investigate cortical information. In conclusion, although no meaningful difference between patients with migraine and healthy controls were identified in CNV measurements, there was a decrease in the monthly frequency of headaches and the number of days with headache in the migraineurs after the PMR training (11). Studies on PMR have revealed a decrease in headache frequency and days with headache in migraineurs. Indeed, PMR was granted Grade A status by the United States Headache Consortium (12). However, most of the studies are old, were conducted by the International Headache Society (IHS) prior to the identification of definitive diagnostic criteria for migraine and in some of the studies, one or two sessions of PMR were performed, which was found to be inadequate in some other studies. These studies were not specifically performed on patients with CM. Moreover, little is known about the mechanism of the PMR-stimulated impact, and the theory of a reduction of a possible sympathetic stimulation still remains current (13). In an internet-based study that involved 39 patients and 47 healthy controls, PMR plus autogenic training was performed on 11 patients with migraine and 16 with mixed-type headaches, and PMR plus cognitive stress-coping therapy was applied on 12 patients with tension headaches. The 50% response rate was 38.5% in groups that received PMR plus therapies, and was identified as 6.4% in the control group, but no significant difference was found between the headache types. However, again in this study, the number of patients with migraine was low, and it is not known how many of these had CM (14).

During diaphragmatic breathing, patients are asked to lie eyes closed, in a relaxed environment in the supine position with hands on the side and palms facing up. During this time, they are asked to use the diaphragm, keeping movement of the thorax to a minimum, and to take a slow and deep breaths. They are then expected to reduce the pause time during breaths. With an average of 10 breaths per minute, exhaling should last longer than inhaling. During this exercise, they repeat the word "relax" in a sincere manner, and when they do this regularly, they automatically start to breathe this way.

During these exercises, the patient is asked to try to block any negative or upsetting ideas. Sometimes during the day, patients may need to remind themselves to take deep and slow breaths. This exercise flexes and relaxes 16 different muscle groups and by time, patients understand the sensory difference between flexing and relaxation (10).

During autogenic training, individuals perform 6 specific conditioning exercises, which result in relaxation. These include procedures such as respiratory exercises, extremity weight exercises, forehead cooling exercises, solar plexus warmth exercises, and limb warmth exercises, which aim to raise a consciously directed awareness, similar to hypnosis (15). Diaphragmatic breathing and autogenic training reduce respiratory symptoms (shortness of breath, chest tightness, hyperventilation), cardiac symptoms (increased pulse rate), and chronic muscle tension, and they are commonly used interventions, especially for the treatment of anxiety.

Mental imagery relaxation (guided imagery) aims to divert the attention of the patient from an upsetting/painful situation. Patients imagine that they are in a pleasant, peaceful place and are asked to replace the discomfort and upsetting situation with this sedating image. It is a type of mental escape. In a study that involved 40 male and female patients with migraine, the patients were divided into guided imagery, BFD and control groups, each group receiving 6 training sessions. Pre- and post-treatment results were assessed, and although patients talked about a subjective healing, no statistically significant difference was found. Patients subjectively reported that guided imagery had a positive impact by changing migraine pain perception (16). Another recent study involved 60 patients with chronic tension-type headache (CTTH). Patients were divided into 3 treatment groups of 20 people. The first group was the "guided-imagery tape group," the second group was the "guided-imagery perceived happy memory group," and the third group was the control group. They were asked to recall their happiest moments, with audio accompaniment, for a duration of 3 weeks, and 3 times per week. As a result, the frequency, severity and duration of headache were observed to be reduced in the guided imagery groups compared with the control group. However, no patients with migraine were included in this study (17). Relaxation techniques are often used in combination with BFD, stress management and CBT.

Meditation

Meditation, which combines breathing and relaxation with physical exercise, is a self-regulating mind-body practice that involves focusing voluntary and sustainable focus on a selected object. The aim here is the relaxation of the entire body by the patient, ensuring that they remove themselves from stressful situations that trigger headache by using these exercises. In a study involving 19 patients with EM, patients received meditation for 34±11 minutes per day for a period of 8 weeks. The study showed that the meditation was safe and applicable; however no statistically meaningful difference was identified in the frequency, duration, and severity of headache due to the low number of participants (18). In another study involving 60 patients with migraine, 30 patients were given conventional care whereas the other 30 patients were given yoga plus conventional care. The yoga group received conventional care with yoga for 5 days per week for duration of 6 weeks. Although healing was observed in both groups, the yoga group demonstrated greater improvement in the frequency and severity of headache (19).

In a study involving 72 patients with EM, patients received yoga therapy for 3 months. A significant impact of yoga treatment was observed with regard to the frequency and severity of headache (20). In conclusion, yoga therapy can be recommended as an adjuvant therapy for patients with migraine.

Biofeedback

During BFD, patients monitor and control body responses with the help of specific tools and trained therapists. The aim here is to reduce the excitability and ensure relaxation in the entire body (6). BFD uses scientific bases for measurement. The purpose is that the patient obtains the target response using the knowledge and learns to manage it. This technique involves monitoring involuntary physiological processes. Thermal BFD, electromyographic (EMG) BFD, and electrodermal BFD are the three most widely used forms of BFD. BFD is a simple physiologic re-training, and its therapeutic processes incorporate cognitive and psychological variables. The most commonly used types are thermal and EMG BFD. For instance, EMG BFD helps the patient to learn how to manage striated muscles in tension-type headaches. The patient learns how to relax muscles that are over-stretched under psycho-physiologic stress conditions (such as migraine). EMG measurement may be used as a strain indicator. Thermal BFD, used in the treatment of migraine, uses skin temperature measurements of the distal parts of the body. The skin temperature is primarily regulated by the cardiovascular system and is closer to autonomic nervous system activity than the somatic nervous system. Sympathetic activity leads to many changes during stress, one of which is the tightening of smooth muscles that surround the peripheral vessels. This contraction slows down the peripheral blood flow, causing the skin temperature to decline. Parasympathetic activity, on the other hand, leads to relaxation of smooth muscles and an increase of blood flow, resulting in an increased body temperature. Through thermal BFD, patients learn ways to increase skin temperature against the stress. When combined with autogenic training, autogenic feedback occurs. Specialists usually perform BFD techniques during weekly face-to-face clinical sessions (21). The duration of treatment depends on the clinical response and the ability of the patient to maintain the target level. These approaches are most appropriate for younger patients and those whose medications have contraindications because there are few adverse effects and complications.

Two studies evaluated the efficacy of BFD in patients with migraine and chronic daily headache with drug overuse. In the first, which involved 27 patients with migraine with medication overuse, only one of the two groups received pharmacologic treatment and the other group received BFD and pharmacologic treatment. At the end of 1-year follow-up, headache in the BFD group was significantly reduced compared with the control group (22). In another study involving 61 patients with migraine, two groups were formed and one group was treated with only pharmacologic therapy, whereas the other group was treated with BFD with pharmacologic treatment. Although no significant difference in recovery rates between the groups was observed in the one-year follow-up, in the 3rd-year follow-up, there was a significant decrease in headache frequency and drug intake in the group receiving BFD compared with the group receiving only pharmacologic treatment (23). In a study conducted in Korea with 32 female patients with migraine, BFD-autogenic training was given to 17 patients and the other 15 patients were monitored only. As a result, a significant difference in headache index was detected between the two groups. In the BFD group, a 50% or higher level of decrease was observed compared with the follow-up group. The study also showed that BFD reduced headache, depression and anxiety rates in migraine and was an effective non-pharmacologic treatment (15). In another study involving 37 patients with migraine, thermal BFD was administered to patients in addition to neurofeedback and 70% of patients had a 50% response rate in headache frequency after 14.5 months of follow-up (24). However, none of these studies involved only patients with CM according to the IHS criteria, and almost all of the studies were about combined treatments, including BFD. No studies investigating the association between BFD and CM by itself was found.

More recently, alternative forms of distribution have been developed that will change the number and frequency of sessions based on the characteristics of the patients. Prior to 1970, the literature on these treatments consisted mainly of clinical interpretation. The current literature has increasingly expanded to include psychological variables, headache-related disabilities and its impact on quality of life (21).

Cognitive Behavioral Therapy

Cognitive behavioral therapy mainly is an option of therapy aimed at stress management, which is enabled through changes in behavior, thoughts and feelings, and improving lifestyle change management and coping mechanisms. Intensive CBT treatments include patient education, self-regulation skills training, as well as stress and pain-coping mechanisms. They reduce the severity of pain by changing the pain experience in people who report chronic pain. Although some studies have shown that CBT reduces pain severity, patients with headache have not been included in these studies (25).

In a study involving 80 patients with primary headache (35 migraine, 14 tension-type headache, 31 migraine plus GTB), patients received 10 sessions of CBT for a month, which resulted in a significant improvement in headache frequency, medication intake rate, and quality of life. This is one of the rare studies where CBT was administered alone (26). In a study with 135 adolescents and children with CM, amitriptyline treatment in addition to 10 sessions of CBT was given and as a result, amitriptyline treatment with CBT was recommended as a first-line therapy for children with CM (27). The effectiveness of CBT on chronic headache or migraine still remains unclear. Among the CBT-based studies involving patients with chronic headache and migraine, there are no studies evaluating the efficacy of CBT alone on CM. These studies usually explore the association between migraine and CBT combined treatments including relaxation, BFB or placebo. While the durations of these studies and the additional therapies differ, it was observed that CBT reduced the intensity and frequency of migraine when combined with other therapies, while failing to demonstrate a meaningful precedence by itself. A longer-term study and observation is needed in patients with chronic headache because the benefit level was identified to have reduced within a few weeks following the completion of CBT (28, Table 1).

Complementary and Alternative Medicine (CAM)

Patients around the world who do not receive any benefits from pharmacologic remedies in the treatment of headache are seeking alternative medical methods. Alternative medicine began to gain popularity in the late 1970s and patients applied this treatment alone or in combination with medications. Complementary and alternative medicine (CAM) is currently used in many countries as an adjunct to pharmacologic treatment in the treatment of primary headaches. These treatments are comprehensive and include diet, herbal therapy, hyperbaric oxygen therapy, and manual therapies. Although there is increasing evidence as to the ease of tolerance and efficacy of CAM, there is still uncertainty about many approaches for which more clinical trials are needed (29). Although these treatments are recommended, they are the options that have not been specifically studied within the context of CM. There are few studies available on this subject in Turkey, and a clinical study conducted in 2014 with 110 patients with primary headache intended to provide epidemiologic data about the awareness about implementation and benefits of CAM methods. The best-known CAM methods were identified as massage, acupuncture, yoga, exercise, psychotherapy, and the most commonly used CAM methods were identified as massage and exercise. The largest group in this study consisted of migraine (69.1%) and only five patients with CM were included (30).

Diet and Lifestyle

Some food and drinks are considered as potential migraine triggers and physcians have long been interested in this topic. When triggers are identified, protection from these is possible and attacks can be reduced. The World Health Organization

Table 1. Behavioral therapy studies including chronic migraine patients

First author, year, reference number	Study design	Number of participants, (number in treatment group)	Intervention	Duration	Results
Meyer et al., 2016 (11)	RCT	81 M or healty control (PMR:37)	PMR	6-weekly sessions	Significant reduction of migraine frequency (24%, p=0.017) and headache days (29%, p=0.046) in migraine group. iCNV amplitudes showed a normalization in migraineurs. PMR has clinical efficacy for migraine prophylaxis
Devineni et al., 2005 (14)	RCT	86 (39 M,TTH, mixed type headache and 47 healty controls)	PMR+autogen training, PMR+cognitive stress coping therapy	8 weekly sessions	No difference between headache groups including TTH, migraine and mixed type headache. Significant difference in reduction of headache disability, medication overuse and headache symptoms in headache group versus waiting list. (p=0.003)
Abdoli et al., 2012 (17)	RCT	60 CTTH (40 guided imagery, 20 control)	Guided imagery	3 weekly sessions, 3 times each week	Guided imagery groups showed significantly improvement in headache frequency, severity and duration versus control group. Migraine patients were not included in this study.
John et al., 2007 (20)	RCT	72 EM	Yoga	12 weekly sessions	Headache intensity, frequency, total pain rating index, symptomatic medication use significantly lower in the yoga group compared to the self-care group.
Kang et al., 2009 (15)	RCT	32 M (BFB:17)	BFB-autogenic training	4 weekly sessions, 2 sessions a week, totally 8 sessions	50% responder rate was greater in BFB group versus monitoring group. Also anxiety and depression scores were lower in BFB arm.
Stokes et al., 2010 (24)	RCT, open label study	37 M	BFB-neurofeedback	3 times a week during 6 months, totally 40 sessions	26 patients (70%) experienced 50% reduction in the frequency of their headaches.
Nash et al., 2004 (26)	RCT	80 (35 M, 14 TTH, 31 M+TTH)	CBT	4 weekly sessions, totally 10 sessions	Significant improvement in headache frequency, medication intake rate and quality of life. 50% of participants experienced 50% reduction in headache frequency.
Hernandez-Rief et al., 2006 (35)	RCT	26 CM (massage and control group)	massage	30-minute massage twice a week during 5 weeks	Patients reported less pain, more headache free days, fewer sleep disturbances and distress symptoms.
Lawler et al., 2006 (36)	RCT	47 EM (massage and control group)	massage	Once a week during 5 to 10 weeks	Improvement in migraine frequency and sleep quality in massage group versus control group.
Kelman et al., 2007 (32)	Cross sectional study	1207 migren (491 CM)	Diet and lifestyle		Triggering by stress, hunger, smell, neck pain, smoking, sleeping late, exercise and eating habits were found to be more frequent in chronic migraine patients than in episodic migraine group.

RCT: randomized controlled trial; M: migraine; PMR: progressive muscle relaxation; TTH: tension type headache; CTTH: chronic tension type headache; EM: episodic migraine; CM: chronic migraine; CNV: contingent negative variation; BFB: biofeedback; CBT: cognitive behavioral therapy

(WHO) reported that one of the seven elements of good headache management was identification of predisposing factors and triggers, and modifying lifestyle for prevention. However, there is no definitive evidence for most triggers; there is limited research about triggers and few studies have evaluated the effectiveness of recommendations (31). Many trigger factors including stress, menstruation, hunger, alcohol, sleep deprivation, smoking, sexual activity, travel, temperature, and smell have been identified in the studies to date. The largest study involving 1207 patients evaluated triggers in patients with EM (with or without aura) and CM. Triggers were detected in 75.9% of patients with an average of 6.9 triggers per individual. Stress, hormones, hunger, air, irregularity of sleep, smell, neck pain, light, alcohol, cigarette, heat, food, exercise and physical activity were determined as triggers, respectively. Four hundred ninety-one patients with CM were included and the identification of triggers according to migraine types was only considered in this study. Stress, hunger, smell, neck pain, smoking, sleeping late, exercise and eating habits were found to be more frequent triggers in the CM group than in the EM group (32).

Lifestyle changes can provide an improvement in migraine including measures such as sleeping regularly, eating, exercising and avoiding stress. Patients are asked to keep a diary of triggers such that they can determine their lifestyle. While it is comparatively easier for patients to avoid certain triggers such as alcohol, certain foods, bright light, and noisy environments, it may be more difficult to avoid triggers such as hormones, travel, change of climate, and stress. Behavioral interventions are introduced at this point, in addition to changes in diet and lifestyle (31). Regarding eating habits, the main things to note are to having regular eating habits, avoiding hunger and avoid foods that are thought to be triggers. These foods are mainly monosodium glutamate, nitrates, alcohol, excessive caffeine consumption, and less commonly, tyramine and chocolate (9). Trigger-related studies are usually cross-sectional studies, which are based on retrospective patient experience. The fact that they are based on patient experiences limits the effectiveness of the studies. Although these studies have produced hypotheses, they do not support strong causal inferences. Only stress, noise and hunger have been verified based on experimentation and many triggers are yet to be investigated (33). Triggers have mostly been associated with migraines although they have been observed in other types of headaches (34). There have not been any studies in the field of CM about the impact of avoiding triggers and changing lifestyle on alleviating headache.

Manual Therapies

The most common manual therapies are massage therapy, physiotherapy and chiropractic spinal manipulative therapies.

Massage

Massage therapies include classic massage, trigger point massage, and myofascial release massage applied to abnormal muscle tissue. One of the two studies on massage therapy involved 26 patients with CM, the other was performed with 48 patients with EM. Both studies showed that massage reduced migraine attacks, but a reduction in the severity of attacks was observed only in the CM group (35, 36). Another recent study was conducted on 64 patients with migraine, 21 of whom received lymphatic drainage, 21 received traditional massages, and the remaining 22 patients were placed on a waiting list and were not given any treatment. As a result, no statistically significant difference was detected between the lymphatic drainage and massage groups in terms of frequency of headache and number of days with headache; however these two groups was found statistically superior to the waiting list group (37).

Physiotherapy

Modern physiotherapy concentrates on rehabilitation and exercise, whereas manual therapy emphasizes postural correction, soft tissue exercises, stretching and mobilization techniques. Mobilization is the movement of joints within their physiologic range of motion. Musculoskeletal abnormalities identified in patients with headache caused physiotherapy to be considered as a treatment option. A study from the United States of America involving 30 patients with migraine with a minimum of 5 attacks per month showed that the group that received physiotherapy plus BFB and relaxation techniques had much more distinct improvement than the group that received physiotherapy only. The study concluded that physiotherapy, when applied as an additional treatment could be useful when other techniques failed. The lack of a control group in this study renders it insufficient (38).

Chiropractic spinal manipulation (CSMT)

Chiropractic spinal manipulation (CSMT) is a technique that uses slow and high amplitude propulsive movements over specified joints, passively within the anatomic limit but beyond the normal physiologic movement limit. Although there are studies in which CSMT was used, there were no control groups in these studies. In conclusion, CSMT was shown to reduce migraine frequency and pain severity and it has been observed to be a viable option as an alternative preventive treatment. There is no standard duration of these techniques; the application type and duration vary according to the applicant. That is, there is no specific dose determined in manual therapies (39).

Neuromodulation Procedures

Neuromodulation procedures target peripheral and central structures and are effective in many cases of primary chronic headaches over many mechanisms. Studies on this issue have gained impetus over the last two decades. Although migraine is primarily a central pathology, interventions for peripheral cranial structures reduce pain. Such interventions reduce pain through the activation of the afferent Aß fibers and gateway control mechanisms, and the descension of supraspinal

pathways (40). Electrical nerve stimulation is a non-destructive method of pain control comprised of two types. Invasive types are applied via surgically implanted tools, and noninvasive types are applied transcutaneously.

The invasive methods require risk-free surgical procedures and, if possible, should be administered to patients with chronic headaches who fail to respond to non-invasive techniques or have failed in medical treatment (7). Invasive methods include invasive occipital nerve stimulation (iONS), combined occipital and supraorbital nerve stimulation, invasive vagus nerve stimulation (iVNS), and sphenopalatine ganglion stimulation (SPGS). iONS is the most frequently used one method; however, its impact mechanism is not clearly known (41). Nine articles related to iONS were found after 2000, five of which were conducted on patients with CM.

The number of patients included in two of these studies was large, and only in one, patients were followed up for a long period (12 months), and in the other one, even though there was a large patient group they were followed for a short period (3 months). Although patients expressed a decrease in the severity of pain and the number of days with headache, the study with 12-month follow-up involving 157 patients with CM showed no statistically meaningful difference in the 50% response rate of the active and sham stimulation groups. However, it can be said that iONS can be recommended because the 30% response rate was better in the active stimulation group (42). In the PRISM study involving 125 patients episodic and chronic migraine no statistically meaningful difference was observed between active stimulation and sham stimulation groups after the 3-month follow-up (43). A recently published meta-analysis revealed that the 50% response rate in headache frequency and severity was not different in the active and sham stimulation groups in patients with CM (44). Despite the low number of studies performed on CM with regard to combined stimulation of invasive occipital and supraorbital pain, the decrease in the frequency and severity of pain was found to be superior to iONS alone. However, there are not enough studies and those present had a low number of participants (7). Although iVNS is often used in the treatment of epilepsy or persistent depression, several studies have been conducted in CM. In a study involving 10 CM patients with epilepsy, a 50% or more reduction in headache severity and frequency was detected in eight patients (80%), five of whom were completely pain-free during the first 6 months of treatment (45). Studies on SPGS to date have been evaluated predominantly in trigeminal autonomic cephalalgia, especially cluster headache. In only one study, SPGS was applied to 11 patients with EM and medication overuse headache, and reduced pain was observed in 5 of them, but in this study, CM was not specifically observed (46).

The battery life of implants used in invasive methods may not be sufficient in longer-term studies depending on the frequency and intensity of the stimulation and there may often be a need for new surgical procedures. Rechargeable implants can be used as a precaution, however this makes the study more costly. Often, secondary infections and paresthesia on the treatment site are observed after surgery.

Non-invasive methods; Non-invasive methods studied within the context of primary headaches are transcutaneous supraorbital nerve stimulation (tSNS), non-invasive transcutaneous occipital nerve stimulation (tONS), and non-invasive/transcutaneous vagus nerve stimulation (nVNS). Without any need for surgical intervention, these methods work by causing electrical depolarization of the underlying structures through dermal electrical stimulation (9). tSNS is also known as electrical trigeminal nerve stimulation (eTNS). In a tSNS study involving 67 patients with EM, tSNS was observed to reduce the frequency of attacks, number of days with headache, and analgesic intake. However, there are no studies related to tSNS in the context of primary chronic headaches (47). In a study involving 43 patients with CM with resistance to tONS, patients received transcranial direct stimulation or tONS for a duration of 3 months and the number of days with headache was observed to be reduced in both groups following treatment. The 30% response rate was observed as 42% in the tONS group (48). Another recent study evaluated the efficacy of tONS in 110 patients with migraine. Patients were divided into 5 groups (2 Hz, 100 Hz, 2/100 Hz, sham and topiramate group) and they received treatment for 1 month. The topiramate and tONS groups at different frequencies were found to be distinctively superior to sham stimulation, and the best response rate, 50%, was observed in 100 Hz tONS and topiramate groups (49).

nVNS can be applied through the cervical region or the ear. Four studies were found with nVNS used in acute or prophylactic treatment. There are two studies on acute nVNS and only one involves patients with CM. In this study, a total of 50 patients, 36 with CM and 14 with EM, were given cervical nVNS during 131 attacks over 2 weeks. The rate of 50% or more reduction in pain according to a visual analogue scale (VAS) was detected in 64.6% of patients at the end of the 2nd hour, and the pain-free (zero pain) rate was identified in 39.6% of patients. At the end of the 2nd hour for 131 episodes in total, the 50% response rate was seen in 51.1% of patients (50). There are two studies on prophylactic nVNS. nVNS was administered to 40 patients with CM in RCTs prophylactically through the ear at the frequencies of 1 Hz and 25 Hz for 3 months, 4 hours daily. It was observed at 29.4% in the patients with a 50% response rate in 1 Hz nVNS group, and at 13.3% in the 25 Hz nVNS group. Looking at the results of this study, it can be said that 1 Hz nVNS treatment for CM is safe and effective; however, there are no similar studies about CM only and a further exploration is needed in this area (51). In a small case series study involving 4 patients with CM with depression and resistance to pharmacologic treatment, chronic VNS has been

Table 2. Neuromodulation trials for preventive treatment of chronic migraine

First author, year, reference number	Study design	Number of participants	Neurostimulation procedure	Follow-up (months)	Results
Silberstein et al., 2012 (42)	RCT	157 CM	iONS (105 active stimulation, 52 sham stimulation)	12	No significant difference in 50% responder rate (p=0.55), significant difference in 30% rate in active stimulation group (p=0.01) sgnificant reduction in number of headache days in active stimulation (p=0.008)
Lipton et al., 2009 (43)	RCT	125 M	iONS (63 active and 62 sham stimulation group)	3	No significant reduction difference in number of headache days in active stimulation group (-5.5 vs -3.9 days/month p=0.29)
Lenaerts ME et al., 2008 (45)	Retrospective, systematic study	10 CM	iVNS (10 active)	6	Eight (80%) had a reduction of monthly frequency of at least 50%., p<0.05. No difference in headache frequency in two migraineurs.
Schoenen et al., 2013 (47)	RCT	67 M	tSNS (34 tSNS, 33 sham)	3	Significant difference in reduction of migraine days (6.94 vs 4.88, p=0.023) and 50% responder rate significantly different (38.1% vs 12.1%, p=0.023) in active stimulation group.
Schoenen et al., 2016 (48)	RCT	43 CM	tONS (20 tDCS, 23 tONS)	3	No significant difference in reduction of total headache days (-16.4 vs 17) and 30% responder rate (47% vs 42%)
Liu Y et al., 2017 (49)	RCT	110 M	tONS (5 groups including 2 Hz, 100 Hz, 2/100 Hz, sham and topiramate group)	1	50% responder rate greater in tONS and topiramate group vs sham, but undergoing tONS at different frequencies didn't differ significantly, headache duration and intensity significantly decreases in tONS and toprimate group vs sham.
Barbanti et al., 2016 (50)	Open label study	50 M (36 CM, 16 EM)	nVNS	2 weeks	50% responder rate at 1 h 56.3%, at 2 h 64,6% and pain-free rate at 1 h 35.4%, at 2 h 39,6%
Straube et al., 2015 (51)	RCT	40 CM (1 Hz, 25 Hz groups)	nVNS	3	Reduction in headache days significantly larger in 1 Hz group (-7.0 vs -3.3, p=0.035)

iONS/tONS: invasive/transcutaneous occipital nerve stimulation; iVNS/nVNS: invasive/non-invasive vagal nerve stimulation; tSNS: transcutaneous supraorbital nerve stimulation

reported to lead to an improvement in depression as well as migraine, though the number of patients was insufficient (52). In another study involving 10 patients with EM and 10 CM, patients received cervical nVNS for 3 months, twice daily, and further improvement was observed in the EM group with regard to days with headache and the frequency of attacks (53). Again, a few studies reported positive results but the number of patients was also inadequate in these.

Non-invasive methods are generally well tolerated and have very few adverse effects, if any. Possible adverse effects during these procedures are local pain and redness at the side of application or dizziness. There are not enough studies on these treatments (Table 2). When these treatments become widespread, perhaps the number of medications taken during an attack will be reduced, which will be of benefit to patients with adverse effects, and at the same time, excessive use of drugs can thus be prevented. However, because the instruments used for stimulation are expensive, their use is likely to be limited. Invasive methods, on the other hand, are recommended for chronic headaches that are resistant to pharmacologic treatment and do not respond to non-invasive stimulation treatments, for the time being, due their adverse effects and difficulty of administration.

CONCLUSIONS

Migraine is amenable to modification by preventive treatment. It is important to take this into account in the follow-up of patients with migraine and to consider behavioral interventions. Although the number of studies on non-pharmacologic approaches has increased over the last two decades, the most up-to-date studies have been developed and researched in the United States; however, the level of availability and applicability of these treatments is low in Europe, the United States and in our country because of their potential cost implications. The fact that patients use different pharmacologic treatments also challenges standardization in these studies. Also in the majority of studies, behavioral interventions have been performed for 12-15 visits on average, and more sessions are needed in resistant cases such as chronic migraine. As the visits are prolonged, patient adjustment is compromised and many are unable to complete the visits.

Among the non-pharmacologic treatments, behavioral interventions seem to be effective in migraine; however, there are few chronic migraine-specific examples in these studies. Although BFD is the best studied in CM, these studies combine BFD with other behavioral interventions and there are no studies have shown its efficacy on CM by itself.

Although complementary and alternative medicine is promising, there is insufficient evidence on many modalities. Many other methods such as Tai Chi, meditation, aroma therapy, hydrotherapy, music-sound therapy, light treatment, hyperbaric oxygen therapy, dance therapy, and reflexology are still to be subjected to further research.

Neuromodulation procedures seem to be "shining star" of nonpharmacologic treatments; however, their use is limited because of the difficulty of administration and cost. VNS and ONS are the most widely researched components in this regard. Although VNS is effective in headache, for now it is used more widely for patients with epilepsy. Studies on the efficacy of VNS in migraine have gained impetus in recent years, and we are likely to obtain more information on its impacts in the near future. In view of current information, ONS is well tolerated and effective in headache.

As a result, there is scarcity of studies that directly compare behavior and pharmacologic treatments for headache, and the available evidence suggests that the level of improvement in headaches obtained by behavioral interventions can compete with those obtained using medication. Current behavioral therapies probably constitute only a fraction of what is possible in headache applications, and there is a need for an expanded knowledge base on the part of neurologists, as well as for large and randomized controlled studies.

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