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Treatment Update of Chronic Migraine

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Abstract
Purpose of Review Although chronic migraine (CM) is a common disorder that severely impacts patient functioning and quality of life, it is usually underdiagnosed, and treatment responses often remain poor even after diagnosis. In addition, effective treatment options are limited due to the rarity of randomized controlled trials (RCTs) involving patients with CM. In the present review, we discuss updated pharmacological, non-pharmacological, and neurostimulation treatment options for CM.
Recent Findings Pharmacological treatments include both acute and preventive measures. While acute treatment options are similar between CM and episodic migraine (EM), preventive treatment with topiramate and botulinum toxin A exhibited efficacy in more than two RCTs. In addition, several studies have revealed that behavioral interventions such as cognitive behavioral therapy, biofeedback, and relaxation techniques are associated with significant improvements in symptoms. Thus, these treatment options are recommended for patients with CM, especially for refractory cases. Neurostimulation procedures, such as occipital stimulation, supraorbital transcutaneous stimulation, non-invasive vagal nerve stimulation, and transcranial direct current stimulation, have shown promising results in the treatment of CM. However, current studies on neurostimulation suffer from small sample size, no replication, or negative results.
Summary Although CM is less responsive to treatment compared to EM, recent advance in pharmacological, non-pharmacological, and neurostimulation treatments may provide more chance for successful treatment of CM.

Keywords Behavioral treatment · Chronic daily headache · Chronic migraine · Headache · Migraine · Pharmacological treatment

This article is part of the Topical Collection on *Chronic Daily Headache*

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Introduction

Chronic migraine (CM) is defined as more than 15 headache days per month over a 3-month period, at least eight of which are migraine, in contrast to episodic migraine (EM), which is defined as less than 15 headache days per month [1]. CM is associated with more severe symptoms than EM and has been reported to affect 1–5% of the general population [2–4]. When compared to individuals with EM, individuals with CM are more likely to experience headache-related disability, decreased headache-related quality of life (HRQoL), greater health care utilization, higher levels of anxiety and depression, and reduced responsiveness to treatment [5].

Although CM is often resistant to treatment, recent advances may provide greater opportunity for successful management of CM. Several pharmacological treatments have

proven effective in the treatment of CM [6]. Furthermore, the efficacy of behavioral interventions such as relaxation training, stress management, cognitive behavioral therapy (CBT), and biofeedback in migraine treatment has been well-established [7, 8]. Acceptance and commitment therapy (ACT) has also demonstrated significant efficacy in several studies [9, 10]. Recent studies have investigated both invasive and non-invasive neurostimulation therapies for the treatment of CM, mainly for those with symptoms refractory to conventional treatment. Such methods include vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS), occipital nerve stimulation (ONS), supraorbital transcutaneous stimulation (STS), sphenopalatine ganglion (SPG) stimulation, transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) [11, 12, 13•, 14].

This review will provide an update on pharmacological, non-pharmacological, and neurostimulation treatment options for CM, with the aim of improving the management and understanding of CM.

Methods

We performed a systematic search using PubMed (incorporating MEDLINE) to identify updated studies reporting on the treatment of CM. The search included full papers and abstracts published in English between October 19, 2011 and October 20, 2016. Papers published in languages other than English that included adequate English abstracts for our review were also included. Searches were performed on October 20, 2016, using combinations of the keywords "chronic migraine" and "treatment." Search strings were entered as free text with no limits to minimize the possibility of omitting relevant records. Authors (SJC, TJS, and MKC) retrieved 959 records from the PubMed search and subsequently reviewed these records for relevance. Finally, 44 original articles and 31 review articles were selected. Additional searches were performed using fewer or wider search terms to ensure that all potentially relevant studies had been identified, following which an additional 48 articles were included for review (Fig. 1).

Results

Pharmacological Treatments

Acute Treatment of CM

Acute treatment of CM is principally similar to that utilized for EM, as both aim to improve current headache symptoms [15]. However, the effectiveness and optimization of acute treatment options for CM are rather limited when compared to those for EM [16]. Relative to patients with EM, those with CM exhibited lower pain free rates at 2 h and rates of sustained pain freedom at 24 h after acute treatment [17•]. Moreover, the addition of triptans or non-steroidal anti-inflammatory drugs (NSAIDs) for acute migraine treatment beyond baseline pain control medication is not associated with improvements in CM-related disability [16]. Furthermore, although appropriate acute treatment can aid in reducing immediate pain, patients with CM are at increased risk for medication overuse headache (MOH) due to the frequency of headache episodes. Therefore, clinicians have recommended that medication be used only in certain cases and no more than twice per week [17••]. NSAIDs, triptans, dihydroergotamine, and antiemetics may be used for acute treatment of CM, although opiates should be avoided because of the high risk of MOH and medication dependency [18].

Recently, new formulations of preexisting drugs have emerged for acute migraine treatment. Nasal powder sumatriptan (AVP-825) [19, 20] and orally inhaled formulation of

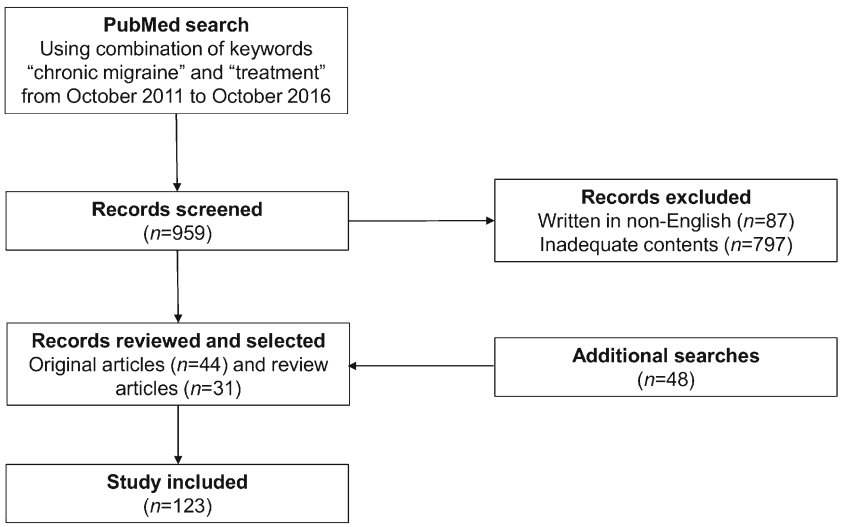

Fig. 1 Process of study selection

dihydroergotamine mesylate [21] are likely to arrive on the market soon. The sumatriptan ionophoretic transdermal system (Zecuity®) was available in USA but was recently withdrawn from the market due to skin irritation, burns, and potentially low efficacy [22].

Triptans may cause vasoconstriction and are contraindicated in patients with vascular disorders. Calcitonin gene-related peptide (CGRP) receptor antagonists do not cause vasoconstriction and have shown promise in acute treatment of migraine [23]. Recent studies have reported that the effects of CGRP antagonists are similar to those of triptans, without the risk of vascular side effects [24, 25]. However, further investigation is required to confirm the safety and efficacy of these new formulations and CGRP receptor antagonists.

Ultimately, migraine-specific medications with favorable recurrence rate or longer half-life within the recommended frequency range are recommended for the effective treatment of acute CM symptoms, although greater focus should be placed on preventive treatment and improving quality of life [26].

Preventive Treatment of CM

Only a few drugs have proven effective for the preventive management of CM. For example, topiramate and botulinum toxin A (BT-A) have proven effective in more than two RCTs [27–31], while valproate, gabapentin, tizanidine, and amitriptyline (not placebo controlled) each exhibited efficacy in a single RCT for the preventive treatment of chronic headache conditions, including CM [32–35]. No evidence for the efficacy of selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors has been observed for the prevention of CM [36].

Two RCTs have reported that topiramate is effective for preventive management of CM [27, 30]. In the TOPCHROME study, a mean topiramate dose of 100 mg/day was associated with reduced frequency of migraine relative to a placebo group and was also effective for patients with MOH [27]. This result was also observed in the Topiramate Chronic Migraine Study, in which significant improvements in quality of life were observed in patients with CM, relative to a placebo group [27, 30]. Because the effect of topiramate in CM appears approximately 4 weeks after drug administration, the observation period should be longer than 4 weeks [37].

Two RCTs have also reported that treatment with BT-A is effective for patients with CM (Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT 1 and PREEMPT 2)) [28, 29]. In these studies, BT-A treatment was associated with significantly reduced headache frequency, headache intensity, and number of triptan doses and improved quality of life in patients with CM, regardless of medication overuse history. To confirm the effectiveness of BT-A treatment, repeated administration (two to three treatments) at intervals of 12 weeks is recommended [38]. Additional studies have supported the efficacy of BT-A in patients with MOH [39]. Although no difference in efficacy has been observed between BT-A and topiramate in CM prevention, rates of side effects and treatment failure were lower in patients receiving BT-A treatment [40]. Open label studies have also observed that repeated cycles of BT-A (beyond five cycles) and 195-U BT-A show some efficacy in patients with CM who experience MOH [41]. BT-A 195-U has also shown superior efficacy to BT-A 155-U in patients with MOH during a 2-year treatment period in a real-life clinical setting, with similar safety and tolerability profiles [42].

Several reports have been published regarding emerging drugs for the prophylactic treatment for CM. Calcitonin gene-related peptide is one promising target for preventive migraine treatment. Because CGRP antagonists are associated with hepatotoxicity, CGRP ligand and receptor monoclonal antibodies that bypass liver metabolism have been developed, which have a long half-life and are not metabolized in the liver [23]. ALD403, TEV48125, and LY2951742 target the CGRP molecule itself, while AMG334 targets the CGRP receptor [23, 43–47]. The phase III trial of ALD403 for CM is ongoing, though TEV-48125 showed good tolerance in phase I and II trials involving patients with high-frequency EM and CM [43, 44, 48, 49]. Furthermore, a phase IIb RCT demonstrated that subcutaneous injection of TEV-48125 (900 mg in all three 28-day treatment cycles) was tolerable and effective, thus supporting the further development of TEV-48125 for the preventive treatment of CM in a phase III trial [44]. Phase II studies aimed at evaluating the efficacy and safety of AMG334 in CM prevention recently reported a promising result [50]. An experimental study has reported that oxytocin decreases activation of CNS trigeminal neurons in migraine models [51]. The results of a phase II trial (TI-001, intranasal oxytocin) for treatment of chronic migraine will be published in the near future [52] (Table 1).

Non-pharmacological Treatments

Cognitive behavioral therapy (stress management training), biofeedback therapy, and relaxation training are recommended behavioral modalities with grade A evidence for the prevention of migraine [8, 53]. Such treatment is recommended for all patients with CM undergoing pharmacological treatment, although behavioral therapy is considered as an alternative for patients with EM who exhibit poor tolerance to pharmacological treatment or medical contraindications [54, 55]. Nevertheless, only a few studies have been published regarding behavioral treatment options for CM, and the number of participants in the intervention group was usually under 20 (Table 2).

Table 1 Randomized trials of behavioral therapy including adult and pediatric patients with chronic migraine

First author, year, reference number	Number of participants, (number in treatment group)	Intervention	Duration	Outcomes	Results
Mo'tamedi et al, 2012 [9]	30 CM or CTTH (ACT:11)	ACT, 90 min	8 weekly session	MIDAS, affective distress, sensory aspect of pain	MIDAS↓, affective distress↓,
Powers, 2013 [10], Kroner, 2016 [58]	135 CM aged 10-17 years (CBT:64).	Amitriptyline with CBT (coping skills, biofeedback, relaxation training) vs. Headache education, 1 hour	10 weekly sessions, 5 boosters at 12th, 16th week, 3rd,6th,9th month	PedMIDAS, 50% reduction of headache days, ≤ 4 headache days/mon at 20-week, 12-month	PedMIDAS ↓ 50% reduction of headache days ↓ 47% vs 20% at 20-week 72% vs 52% at 12-month
Bakhshani et al, 2015 [64]	40 CM or CTTH (na)	MBSR, 90 min, daily home practice	8 weekly sessions	Pain intensity,Quality of life	Pain intensity ↓ Quality of life ↓
Grazzi et al, 2002 [66]	61 TM with MOH (biofeedback: 19)	Biofeedback-assisted relaxation, 20 min	8 weekly sessions	Headache days, Analgesic medication use, recurrence at 3 years	Headache days↓ Analgesic medication ↓ recurrence at 3 years ↓
Rausa et al, 2016 [67]	27 CM or CTH with MOH (biofeedback:15)	Biofeedback, acquisition, maintenance, exposure, 1 hr	9 weekly sessions	Headache frequency, Analgesics intake. Return to episodic headache	Return to episodic headache: 67% vs 17% at 8 weeks. 47% vs 17% at 1 year

number of participants, *CM* chronic migraine, *CTTH* chronic tension-type headache, *TM* transformed migraine, *MOH* medication-overuse headache, *MBSR* mindfulness-based stress reduction, *CT* acceptance and commitment therapy, *MIDAS* Migraine Disability Assessment Scale, *PedMIDAS* pediatric Migraine Disability Assessment Scale, *na* not available, ↓ decreased

Cognitive Behavioral Therapy

Traditional CBT is focused on stress management, whereas recent trends include ACT, mindfulness mediation-based interventions, and behavioral interventions for common comorbidities [56•, 57•]. The efficacy of CBT for pediatric patients with CM has been reported in two well-designed RCTs [10, 58]. Ten sessions of 1-h individual CBT vs. ten headache education sessions were conducted in patients taking 1 mg/kg/day of amitriptyline for 20 weeks. The number of headache days during which participants experienced at least 50% reduction in symptoms was significantly greater in the CBT group than in the headache education group at the conclusion of the study (66 vs. 36%, $p < 0.001$) and at the 12-month follow-up (88 vs. 69%, $p < 0.001$), respectively [10].

The ACT is characterized by willingness to experience rather than control of pain (acceptance) and the pursuit of broader life values (committed action). Only one trial of ACT intervention among female patients with CM or chronic tension-type headache (CTTH) reported greater improvements in disability (45 vs. 7%) and affection and distress (45 vs. 0%) in intervention the group [9].

Mindfulness-based interventions focus on directing attention to bodily sensations such as breathing, as well as nonjudgmental awareness of the present [56•, 57•]. However, such methods require intensive training (> 2 h per session) in meditation, yoga, and body scanning as well as daily practice [59]. The suggested mechanisms underlying the effects of mindfulness meditation-based analgesia involve alterations in resting state functional connectivity, endogenous opioid pathways (some controversy), or immune functions [60–63]. In a trial that included patients with CM or CTTH, the intervention group reported lower pain intensity and greater improvements in some quality of life parameters when compared with the control group [64].

CBT trials have been associated with such limitations as low number of participants, non-assessment of headache days, and inadequate controls, although the primary aim of such methods is to improve quality of life and reactions to pain, rather than pain itself [7, 57•]. Nonetheless, ACT or mindfulness-based intervention has merits in self-regulation, long-term therapeutic benefits, and efficacy for comorbidities such as depression, anxiety, or fibromyalgia [65].

Biofeedback With/Without Relaxation Techniques

During biofeedback, participants monitor and attempt to control bodily responses (e.g., blood pressure, temperature, and muscle tension) with the aid of specific instruments and trained therapists. Two studies have evaluated the efficacy of biofeedback for participants with MOH with transformed migraine or chronic daily headache. One study reported that the biofeedback group reported a lower

Table 2 Neurostimulation randomized controlled trials for preventive treatment of chronic migraine

Neurostimulation techniques	Author names, year, reference number	Number of participants	Outcomes
ONS	Saper et al., 2011, [73]	110	No significant difference in 3-month response rate (≥50% reduction in headache days): 39% for adjustable stimulation group vs. 6% for preset stimulation vs. 0% medical management. Lead migration in 12/51 (24%) subjects
	Silberstein et al., 2012, [74]	132	No significant difference in 50% reduction in mean visual analogue scale for headache intensity ($p = 0.55$) Significant difference in percentage of 30% reduction ($p = 0.01$). Significant reduction in number of headache days (6.1 vs. 3.0, $p = 0.008$), migraine-related disability ($p = 0.001$).
	Lipton et al., 2009, [75]	125	No significant reduction in migraine days (−5.5 vs. −3.9, $p = 0.29$). There was a trend towards a greater difference between treatment arms for those not overusing medication (−5.9 vs.-2.6) in comparison with the medication overuse subgroup (−5.0 vs. −4.8)
	Dodick et al., 2015, [76]	154	Significant reduction in headache days (6.7 ± 8.4, $p < 0.001$), MIDAS score (50.9 ± 71.9, $p < 0.001$), patient's rating of headache relief (65.4%), and quality of life improvement (69.8%) after 52 weeks
STS	Schoenen et al., 2013, [77]	67	Significant difference in mean number of migraine days (6.94 vs. 4.88, $p = 0.023$) 50% response rate in migraine days (38.1 vs. 12.1%, $p = 0.023$), monthly migraine days (3.55 ± 2.94 vs. 3.89 ± 1.89, $p = 0.044$), and acute migraine drug intake 7.25 ± 7.31 vs. 9.28 ± 5.69, $p = 0.044$) in treatment group at third month
nVNS	Silberstein et al., 2012, [89]	59	No significant change in the number of headache days per month (−1.4 vs. −0.2, $p = 0.56$). Tolerability was similar between treatment and sham groups after 2 months
tDCS	DaSilva et al., 2012, [92]	13	Ten sessions of active of sham tDCS for 20 min. Improved in visual analogue scale for pain intensity ($p = 0.02$) and length of migraine episodes ($p = 0.02$)

ONS occipital nerve stimulation, *STS* supraorbital transcutaneous stimulation, *nVNS* non-invasive vagal nerve stimulation, *tDCS* transcranial direct current stimulation, *MIDAS* Migraine Disability Assessment Scale

number of headache days and a lower risk of MOH relapse relative to the control group at the 3-year follow-up, though not at the 1-year follow-up [66]. Another trial reported the efficacy of EMG biofeedback in returning to episodic headache at 8 weeks and 1 year [67].

Relaxation techniques include progressive muscle relaxation, diaphragmatic breathing, autogenic training, guided imagery, and meditation. Such techniques aim to reduce muscle tension and sympathetic arousal, which may be associated with stress or illness [54]. Relaxation techniques have been used in conjunction with biofeedback and CBT [64, 66, 68], although no isolated randomized trials for CM have been conducted to date.

Other Non-pharmacological Treatment Options

Behavioral therapy for insomnia has been reported to reduce headache frequency in patients with CM [69]. Behavioral treatment with stimulus control and sleep restriction (restrict time in bed to total sleep time plus 30 min) achieved 26.9 and 48.9% reductions in headache frequency at post-treatment and at the 6-week follow-up, respectively. In comparison, the lifestyle modification control group (regular dinner, stretching, liquid intake) achieved 36.2 and 25% reductions in headache frequency at post-treatment and at follow-up, respectively, a difference that was not statistically significant.

Behavioral therapy and exercise have also shown promise for the treatment of CM, although few trials have been conducted [70]. Chronic migraineurs tend to pursue multiple complementary and alternative treatments, although such patients often report minimal satisfaction or dissatisfaction [71]. The efficacy of non-pharmacological therapy including behavioral therapy may depend on the types, duration, schedules of training and booster sessions, comorbidities, participant adherence, and the experience of the therapist.

Neurostimulation

Although pharmacological treatment has been a mainstay for CM treatment, the effectiveness of medication can be limited by side effects, drug interactions, comorbid conditions, and refractory cases. Recent technological developments in neurostimulation have provided greater opportunity for the successful treatment of CM. Non-invasive neurostimulation

modalities include STS, TMS, non-invasive vagal nerve stimulation (nVNS), and tDCS. Invasive treatment modalities for migraine/headache include ONS and implanted VNS [11, 12, 13•, 14]. Results of neurostimulation RCTs for CM treatment were summarized in Table 2.

Occipital Nerve Stimulation

Occipital nerve stimulation is likely to reduce pain via peripheral and central mechanisms. Stimulation of the occipital nerve inhibits nociceptive activity in small c-fiber and A-delta fibers. Centrally, ONS reduces activation of brain regions involved in pain processing [72]. Four multicenter RCTs have examined the efficacy of ONS in the treatment of CM. The Occipital Nerve Stimulation for the Treatment of Intractable Chronic Migraine (ONSTIM) study included an adjustable stimulation group, preset stimulation group, and sham group. Although there was no significant statistically significant improvement over baseline when comparing the adjustable stimulation group (27%) with the present stimulation group (9%) or medically managed group (4%), a numerical advantage appeared to be associated with the adjustable stimulation group. Because the number of subjects in the ancillary group was small, reliable comparisons could not be made. Common side effects included lead migration (24%), infection (18%), and implantation failure (4%) [73].

The St. Jude study included 177 patients with CM. The active control group exhibited a 17.1% reduction (≥50% improvement in headache pain) of headache days, whereas this value was 13.5% in the sham group. Although this primary endpoint did not reach statistical significance, rates of 40, 30, and 20% reduction were statistically significant [74].

The Precision Implantable Stimulator for Migraine (PRISM) study included 132 patients with CM and involved a 12-week blinding phase, followed by an open-label phase. Although statistically significant reductions in headache days per month were not observed at the 12-week follow-up (−5.5 vs. −3.9 days/month, $p = 0.29$), there was a trend of greater difference between patients with medication overuse (−5.9 vs. −4.8) and those without (−5.9 vs. −2.6) [75].

A recent randomized, multicenter, double-blinded, controlled study composed of 12-week blind period and 50-week open period reported a significant improvement in number of migraine days (6.7 ± 8.4, $p < 0.001$), MIDAS score (50.9 ± 71.9, $p < 0.001$), patient's rating of headache relief (65.4%), and quality of life improvement (69.8%) [76].

Supraorbital Transcutaneous Stimulation

The mechanism of STS is similar to that of ONS. The Cefaly® device is the first STS device targeted for migraine treatment and is currently available in the USA and Europe for migraine prophylaxis. The use of this device has also been supported by a multicenter RCT that included 67 patients with migraine, in which treated patients experienced a significantly greater reduction in headache days relative to controls [77]. One mail-based survey including patients with either EM or CM indicated that the overall patient satisfaction rate was 54%, with a side effect rate of 4.3% [78]. All side effects were minor and transient. Two small-size open trials for combined STS and ONS have also reported significant improvement in patients with CM [79, 80].

Transcranial Magnetic Simulation

When TMS is delivered to the scalp, the magnetic field induces a secondary current in the adjacent brain tissue, leading to depolarization. By manipulating the location of stimuli and other parameters, TMS can induce functional activation or deactivation in the brain [81, 82].

Transcranial magnetic stimulation pulses can be delivered in rapid succession (repetitive TMS, rTMS) or singly (single pulse TMS, sTMS). Two randomized RCTs of sTMS for acute treatment of migraine with aura reported favorable outcomes [83, 84]. The US Food and Drug Administration (FDA) recently approved sTMS for the acute treatment of migraine with aura [85]. Although RCT data regarding TMS treatment for CM are unavailable, a post-marketing open-label study for sTMS including 131 patients with CM and 59 patients with EM reported that 62% of patients experienced pain relief [86]. Furthermore, rTMS delivered at the hot spot of the right abductor digiti minimi on alternate days for 3 days in 17 patients with CM and 8 patients with EM resulted in significant improvements in headache frequency, intensity, and functional disability after 7 days [87].

Non-invasive Vagal Nerve Stimulation

Although the exact mechanism underlying the efficacy of VNS in pain relief remains poorly understood, research suggests that VNS may result in inhibition of glutamate release in the trigeminal nucleus caudalis [88].

One small-size ($n = 59$) RCT of nVNS was conducted for the treatment of CM. Vagal nerve stimulations were performed three times a day, with 6–8 h between each session. Each session consisted of two 90-s stimulations delivered to the right vagus nerve at 5–10-min intervals. Although the study failed to show significant reduction in treatment group at the end randomized phase, the treatment group experienced 1.4 day reduction for 2 months in the number of headache days, whereas the sham-treated group exhibited 0.2-day reduction for 2 months. A small proportion (11.0%) of the treatment group showed >50% reduction in headache days. The rates of adverse effects (AEs) were similar between the treatment and sham groups, and no severe events were reported [89].

An open-label study of nVNS treatment for CM and comorbid MOH has also been conducted. Patients underwent 5 days of detoxification, followed by 6 months of nVNS treatment. The 2-h pain-free rate following the first acute treatment was 21%, and no serious adverse effects were reported [90].

Sphenopalatine Ganglion Stimulation

The sphenopalatine ganglion contains parasympathetic efferents to meningeal blood vessels, the lacrimal gland, and nasal mucosa and has been implicated in autonomic headache features, which have been reported in up to 73% of adult migraineurs. Therefore, the SPG may represent one therapeutic target in patients with CM.

One small, open-label study has examined the effect of SPG in migraine treatment. Among ten patients with migraine (two EM and eight CM), two (one EM and one CM) were pain-free after SPG stimulation. Three experienced reductions in pain, while the remaining five experienced no change in pain [91].

Transcranial Direct Current Stimulation

tDCS utilizes a weak current to alter the modulation of cortical excitability. Cathodal tDCS inhibits neuronal firing, while anodal tDCS increases neuronal firing. An RCT examined the efficacy of tDCS in 13 patients with CM. Stimulation (2 mA) was applied over the motor (anodal) and orbitofrontal (cathodal) cortices for 20 min over a period of 4 weeks. Significant improvements in headache duration and intensity were observed in the active tDCS group [92].

Conclusions

Although individuals with CM experience more severe symptoms, higher levels of disability, and more profound decreases in quality of life than those with EM, their symptoms are often resistant to treatment. Several RCTs have demonstrated the efficacy of both BT-A and topiramate for the preventive treatment of CM. Recent trials of CGRP and CGRP receptor monoclonal antibodies have also produced promising results. Cognitive behavioral therapy, biofeedback therapy, and relaxation training are also associated with significant improvements in individuals with CM. Some neurostimulation studies have reported promising results for the treatment of CM treatment, particularly in patients with symptoms refractory to previous treatments. RCTs have documented the efficacy of occipital nerve stimulation, STS, and tDCS in the treatment of CM, although some studies reported contradictory results.

Compliance with Ethical Standards

Conflict of Interest Soo-Jin Cho declares grant support from the Korean Neurological Society and Hallym University Research Fund 2016, lecture honoraria from Yuyu Pharmaceutical Company, and serving as a site investigator of a multicenter trial for Eli Lilly and Company.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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