# HEADACHE AND NEUROGENIC PAIN EDITOR'S PICK 2021

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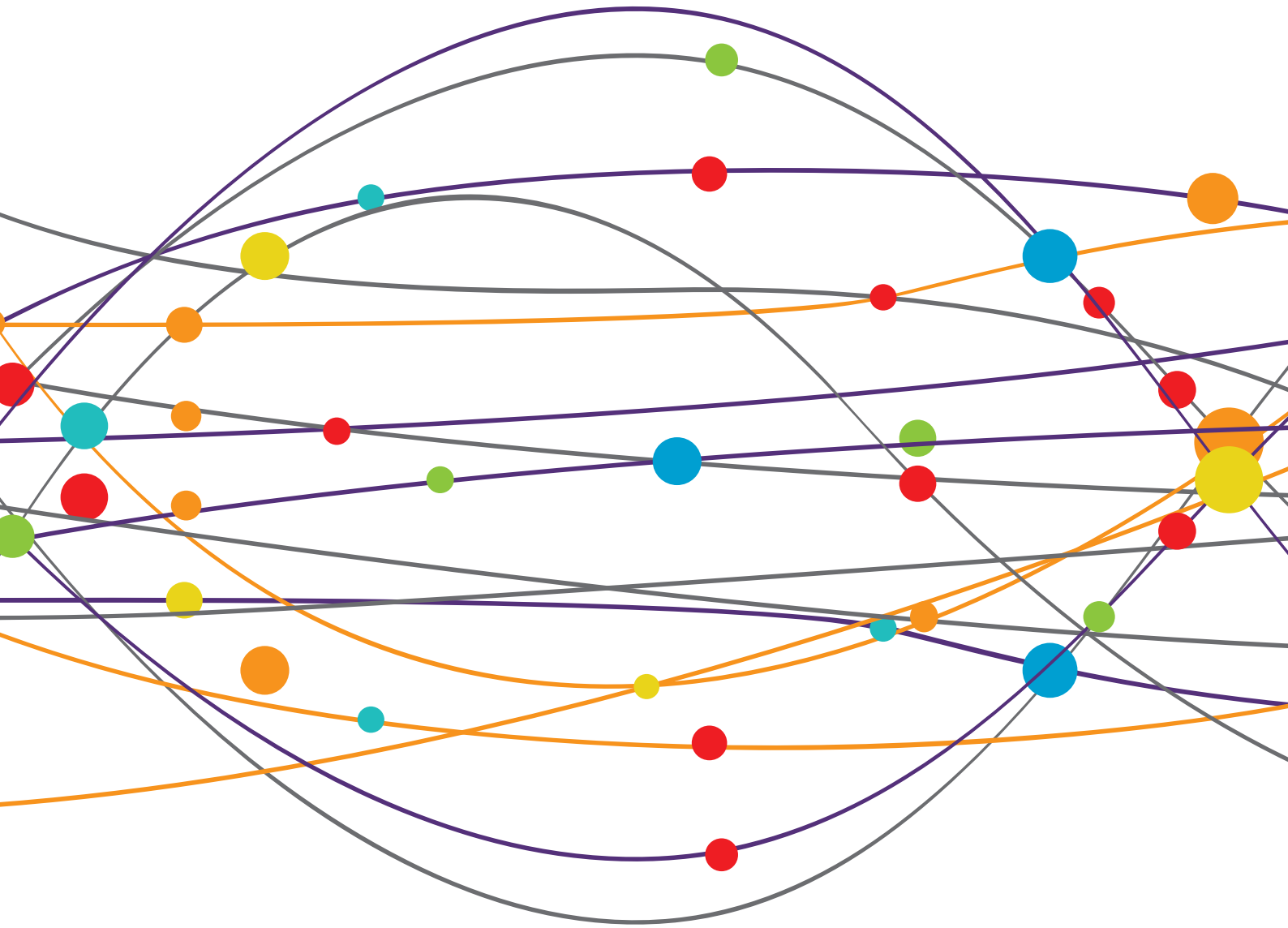

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# HEADACHE AND NEUROGENIC PAIN EDITOR'S PICK 2021

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PERSPECTIVE
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# A Neuroscience Perspective of Physical Treatment of Headache and Neck Pain

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The most prevalent primary headaches tension-type headache and migraine are frequently associated with neck pain. A wide variety of treatment options is available for people with headache and neck pain. Some of these interventions are recommended in guidelines on headache: self-management strategies, pharmacological and non-pharmacological interventions. Physical treatment is a frequently applied treatment for headache. Although this treatment for headache is predominantly targeted on the cervical spine, the neurophysiological background of this intervention remains unclear. Recent knowledge from neuroscience will enhance clinical reasoning in physical treatment of headache. Therefore, we summarize the neuro- anatomical and—physiological findings on headache and neck pain from experimental research in both animals and humans. Several neurophysiological models (referred pain, central sensitization) are proposed to understand the co-occurrence of headache and neck pain. This information can be of added value in understanding the use of physical treatment as a treatment option for patients with headache and neck pain.

**Keywords: physical treatment, headache, neck pain, pain, neurology, clinical reasoning, neurophysiology**

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## INTRODUCTION

Headache causes substantial pain and disability in people's daily life and delivers a high burden and cost to society that is estimated only in Europe at 173 billion Euro per year (1). The most prevalent primary headaches worldwide are tension-type headache (TTH) and migraine. These types of headache are frequently associated with neck pain (2, 3). A recent open population study reported a 1-year prevalence of neck pain of 68.4% and more in people with primary headache compared to people without primary headache (85.7 vs. 56.7%; OR 3.0, 95% CI 2.0–4.4). After adjusting for age, gender, education and poor self-rated health, the prevalence of neck pain (56.7%) was still significantly higher in people with only migraine (76.2%), migraine ánd TTH (89.3%), and only TTH (88.4%) in comparison with people without headaches (4). People with headache and neck pain frequently visit health care providers such as medical doctors (general practitioners, neurologists) and physical therapists in their quest for diagnosis and treatment (5). A broad pallet of treatment options is available, including reassurance, self-management strategies, pharmacological, and non-pharmacological treatments. Evidence for the effectiveness of physical therapy for headache is limited (6, 7). Despite this lack of solid scientific back-up, physical therapy is worldwide a frequently used alternative or complementary treatment and included in several

clinical guidelines as an alternative treatment option (The European Federation of Neurological Societies (EFNS) guideline, Italian guideline for primary headaches) (5, 8, 9). In daily practice, a combination of treatment options is often used, and the combination of pharmacological (acute and prophylactic drugs) and non-pharmacological (education, physical therapies, exercises, biofeedback) interventions is indeed considered to be an efficient approach in headache disorders (10). Additional research concerning non-pharmacological prophylactic treatment strategies of headache is however urgently needed (11). For disciplines that target the cervical spine in order to decrease headache, it is pivotal for clinical reasoning to understand the neuro-physiological background of headache and neck pain (12). Recently, new insights have emerged on the relation between extracranial input from the (upper) cervical spine and headache from experimental research in both animals and humans (13). This recent information can be of great value to understand and to (re)design physical approaches for different types of headache in combination with neck pain. In this review we first describe the neuro-anatomical and neuro-physiological findings from experimental studies on the trigemino-cervical complex (TCC). We then discuss neurophysiological models to explain the co-occurrence of headache and neck pain such as referred pain and generalized hyperexcitability. We further present the relation of cervical spine dysfunction and headache and research on modulation of nociception at the TCC. Finally, we describe physical treatment as an option to treat headache and neck pain.

## TRIGEMINO-CERVICAL COMPLEX, THE ANATOMICAL BASIS

Experimental research has contributed to further neuro-physiological insights in the relation of headache and neck pain. Knowledge of the neuro-anatomical structures and neural activity within the TCC seems paramount. The frequent co-occurrence of headache and neck pain is attributed to common nociceptive innervation of the head and neck in the dorsal horn C1-2, located in the trigemino-cervical complex. Animal (14, 15) and human (15) anatomical studies have shown that the TCC extends from the medulla (pars oralis and pars interpolaris) to the first and second cervical segments (pars caudalis) (**Figure 1**). In the TCC, the pars caudalis receive first order nociceptive $A^{\delta}$- and C afferent neurons of the ophthalmic nerve together with first order $A^{\delta}$- and C nociceptive afferent neurons from predominantly the dorsal root C2. These afferent neurons are directly or indirectly connected via wide dynamic range neurons to second-order neurons (16). The ophthalmic nerve delivers nociceptive input via small diameter $A^{\delta}$- and C afferent nerve fibers to nociceptive second-order neurons in the superficial and deep layers of the medullary dorsal horn C1 and 2 in the TCC (17, 18). The upper cervical root C2 represents $A^{\delta}$- and C nociceptive afferent information of vessels and dura mater of the posterior fossa, and myofascial structures of the upper cervical segments. This nociceptive input from the upper cervical nerve root C2 is well-documented and has a structural overlap with nociceptive nerve endings from the ophthalmic nerve root at the first and second cervical dorsal horn in the TCC (19–27). An extracranial origin of meningeal nociception is suggested by Schueler et al. by demonstrating *in vitro* that collaterals of trigeminal afferents form functional connections between intra- and extracranial tissues in rats and humans. So, information from pericranial muscles can reach the dura mater by ortho- and antidromic conduction through axon collaterals and possibly influence meningeal functions and the generation of headache in humans (28, 29). This finding on collateral afferent connections matches with the anatomical (30) and functional relation (31) of the dura and suboccipital muscles in the upper cervical region in humans. Therefore, the neuro-anatomical connection of ophthalmic and cervical nociceptive afferents on second order neurons at the pars caudalis of the TCC, is pivotal to understand the occurrence of headache and neck pain.

## REFERRED PAIN

The convergence of cervical ánd trigeminal nociceptive small diameter $A^{\delta}$- and C fibers on the C1 and C2 dorsal horn provides a neuro-anatomical basis for the clinical phenomenon of referred pain. The co-occurrence of headache and neck pain can be explained by referred pain: pain originating from the neck is perceived as originating from the head and vice versa.

## EVIDENCE FROM ANIMAL STUDIES

Animal-experimental neuro-physiological studies recording input of nociceptive afferent fibers at the C1-2 dorsal horn in animals contributed to the understanding of referred pain in both directions, i.e., from the neck to the head (20) and from the head to the neck (21). Vernon et al. described the increased activity in C1/C2 dorsal horns in rats after injection of inflammatory mustard oil in deep paraspinal tissues at the level of the left C1-C2 joint. Activation of trigeminal afferents of the supratentorial dura mater by mustard oil (MO) showed an enlargement of cervical cutaneous mechanoreceptive fields together with a significant ($p < 0.001$) increase in the excitability to electrical stimulation of the greater occipital nerve in C-fiber responses (21). Unilateral electric stimulation of the greater occipital nerve in cats increased metabolic activity in the dorsal horn C1 and C2. Stimulation of trigeminally-innervated structures showed a similar distribution to the trigeminal nucleus caudalis (32). Based on these findings, the well-recognized clinical phenomenon of head pain that is perceived frontal and occipital and in the upper neck may be the result of overlap of nociceptive information at the level of second order neurons.

Headache during a migraine attack seems to be primarily based on activation of the trigeminovascular pathways by increased visceral nociceptive $A^{\delta}$- and C fibers input of the dura and intracranial vessels on the TCC. This input is frequently restricted to the territory of the ophthalmic nerve, but may extend as pain to the occipital region of the head which is innervated by the greater occipital nerve C2 (33). These results indicate that headache as well as neck pain can be perceived as referred pain.

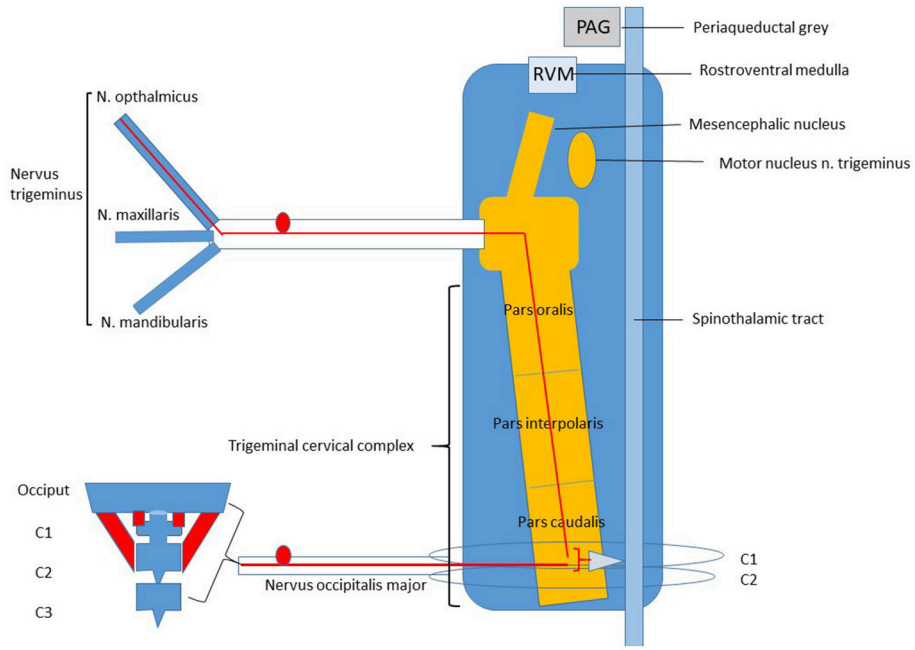


**FIGURE 1 |** Trigeminal Cervical Complex (TCC).

## EVIDENCE FROM HUMAN STUDIES

Clinical evidence of referred pain based on convergence of cervical- and ophthalmic nociceptive $A^{\delta}$- and C afferent input originating from different structures has been observed in human studies. Clinical observations have shown that intracranial nociceptive input of arteries, but also extracranial nociceptive input originating from the vertebral artery is able to provoke painful sensations in the area of the forehead (34, 35). Provocation of headache by applying experimental nociceptive stimuli to upper cervical structures has been reported in several studies. Injection of saline in the neck and suboccipital region (36), sterile water (37) and low-frequency nerve stimulation (38) over the upper cervical dorsal roots have shown to provoke headache. In a narrative review on the diagnosis and treatment of cervicogenic headache, Bogduk has described several experimental studies on humans reporting referred pain patterns on the head caused by stimulation of nociceptive afferent input from myofascial structures of the upper cervical spine (39). In 23 out of 32 patients with cervicogenic headache the pain in the head was relieved completely after a diagnostic anesthetic block at the lateral atlanto-axial joints (C1-2) (40). Mechanical nociceptive afferent stimuli -by giving a firm pressure to myofascial structures of upper cervical segments (C0-3)- also provoke the patient's typical headache in patients with cervicogenic headache (41), TTH, and migraine (42, 43). Extensive research is available on trigger points in cervical and suboccipital muscles eliciting headache (44). In summary, convergence of cervical and trigeminal nociceptive afferents on second order neurons at the TCC can cause headache as referred pain via stimulation of cervical nociceptive input of the upper cervical segments by administration of fluid-irritants or mechanical pressure.

## GENERALIZED HYPEREXCITABILITY

Hyperexcitability of second order neurons in the TCC as a result of a continuous increased peripheral somatic and vascular nociceptive activity (45–48), a decrease of supraspinal inhibition (49) or a combination of both mechanisms can cause headache (50, 51). Activation of the trigeminovascular pathways increased by vascular nociceptive $A^{\delta}$- and C fibers input of the dura and intracranial vessels on the TCC seems to be typical for migraine (47). Still, at present there is an ongoing debate what is causing the hyperexcitability of second order neurons in the TCC during migraine. Levy et al noticed that sensory innervation of the cranial meninges and immune and vascular cells may have a major role, but evidence for neurogenic inflammation during migraine and its contribution to meningeal nociception is limited (52). Prolonged or ongoing peripheral nociceptive input via trigger points in pericranial or cervical myofascial structures may contribute to hyperexcitability of second-order neurons at the C1 and C2 dorsal horn of the TCC in TTH, but evidence for this hypothesis is limited (53). Hyperexcitability of nociceptive second order neurons in the dorsal horn of C1-2 can also be caused by a decrease of endogeneous driven supraspinal descending inhibition of the periaqueductal gray (PAG), nucleus raphe magnus, or rostroventral medulla. This can lead to clinical signs such as hypersensitivity, allodynia and reduced pain thresholds in the cranio-cervical region and even in extra- cephalic regions. In patients with chronic TTH, but not

with episodic TTH, most studies report lower pressure, thermal and electrical pain thresholds in the cephalic region (54). In patients with migraine pain threshold to pressure, cold and heat stimuli in the cephalic region are found to be lower during the ictal phase than during the interictal phase of migraine or healthy controls (55). For pain pressure thresholds in the cranio-cervical region a significant decrease is described in research on patients with migraine and CTTH compared to healthy controls (56). The interaction between supraspinal descending inhibitory systems and peripheral nociceptive input in the TCC seems to be a prerequisite for the characteristics as well as in the development of episodic to chronic headache syndromes (57). Thus, trigger points or tender, painful myofascial structures at the upper cervical segments in headache patients can either emerge or be a source of hyperexcitability of second-order neurons C1-C2.

## CERVICAL MUSCULOSKELETAL DYSFUNCTIONS IN HEADACHE

Cervical musculoskeletal dysfunctions of joints and muscles have been observed in patients with migraine, TTH and cervicogenic headache (58–62). In the context of the neurophysiological interconnection between the dorsal root of C2 (greater occipital nerve) and the TCC, it may be not surprising that in participants with headache most cervical musculoskeletal dysfunctions are present in the upper cervical spine. Palpation of trigger points in suboccipital muscles and trapezius (63–66), restricted motion of the cervical segments C0-3 (43, 67), and stress on joints in the upper cervical spine (41, 42) are related to different types of headache. Although there seems to be a relation between (upper) cervical musculoskeletal dysfunctions and headache, these are documented in studies with a case–control design. Thus, no causal relation can be determined, nor solid conclusions can be drawn on this relation.

## MODULATION OF NOCICEPTION AT THE TCC: EVIDENCE FROM ANIMAL STUDIES

Evidence is emerging that addressing the cervical spine can modulate pain at the TCC. Nöbel et al. reported that injection of a nociceptive stimulant (α,β-meATP) into the temporal muscle in rats induces ongoing activity of spinal trigeminal neurons with meningeal receptive fields. In the same study local anesthesia of single neck muscles, but not of the musculus temporalis, shows a significant decrease of the provoked central trigeminal activity (68). This supports the modulation of pain in the TCC by reduction of peripheral cervical muscular nociceptive afferent input. Supraspinal diffuse noxious inhibitory control (DNIC) on convergent neurons in the trigeminal nucleus caudalis in rats can be initiated by activation of $A^{\delta}$- and C fibers. Villaneuva et al. and Bouhassira et al. demonstrated that induced activity of convergent neurons in the trigeminal nucleus caudalis was decreased up to 80% by activation of $A^{\delta}$- and C fibers (69, 70). Afferent $A^{\delta}$- and C input originating from the neck is not restricted to the TCC. Local administration of nerve growth factor into semispinal neck muscles in anesthetized mice shows not only stronger Fos immunoreactivity in the superficial layers I and II of the of cervical spinal dorsal horns C1, C2, and C3, but also in supraspinal structures such as the PAG and the medullary lateral reticular nucleus (71–76). Nearly 50% of all ventro-lateral PAG-projecting spinal neurons were found in the upper cervical segments and these segments are thereby potentially an important source to activate the ventrolateral PAG (71, 77). Activation of the ventrolateral PAG by deep somatic (deep neck muscles) and visceral pain not only leads to a resting state, but also to inhibition of trigeminal afferents (76, 78). The participation of this phenomenon in inhibition of trigeminal afferents is proposed (79, 80).

## MODULATION OF NOCICEPTION AT THE TCC: EVIDENCE FROM HUMAN STUDIES

In a clinical study, Busch et al established modulation of nociception at the TCC by detecting a decrease of R2 response areas (AUC) and significantly increased R2 latencies of the nociceptive blink reflex only at the side of an anesthetic unilateral nerve blockade of the greater occipital nerve with prilocaine in healthy persons. These findings not only confirmed previous results related to anatomical and functional convergence of trigeminal and cervical afferent pathways, but also suggested that modulation hereof could be beneficial in treatment of primary headache disorders (81). In patients with headache, blocking afferent nociceptive input by anesthesia of the GON (82, 83) or in the facet joint C1-2 (40, 84) has proven to be effective in reducing headache. Piovesan et al. described the decrease of headache in a patient with migraine after light massage of the greater occipital nerve (85). Another clinical study by Watson and Drummond (42) reported the provocation as well as the resolution of headache in migraine patients with sustained manual pressure in the suboccipital region. The referred pain during the provocation test was decreased in parallel with a change in the trigeminal nociceptive blink reflex. This finding supposes the previously proposed model that stimulation of myofascial $A^{\delta}$- and C fibers by manual pressure can activate the supraspinal DNIC system that acts specifically on spinal wide-dynamic-range (WDR) neurons and is able to modulate nociception at the TCC (69, 86).

## PHYSICAL TREATMENT OF HEADACHE AND NECK PAIN

The neuro-anatomical and—physiological relation between brainstem nuclei, the (upper) neck and trigeminal nerve has to be incorporated in development of physical treatment for headache targeted at the cervical spine, especially the upper cervical region. According to the 'gate-control' hypothesis, the relative high amount of proprioceptive afferent muscular input of upper cervical segments (87) to the central nervous system may alter nociceptive $A^{\delta}$- and C fibers afferent input. Stimulation of proprioceptive input by active exercises for neck muscles may decrease the excitability of second order neurons at the TCC (11) and activation of the supraspinal DNIC system by stimulation

of myofascial $A^{\delta}$- and C fibers by manual pressure techniques at the upper cervical spine can be of added value (42). The importance of an active treatment of neck muscles is supported by the findings of a systematic review of Varatharajan et al. stating that an active physical treatment including exercises shows promising results on reduction of headache associated with neck pain (7).

## DISCUSSION

In the last decades experimental research in both animals and humans on neuro-anatomy and neuro-physiology has contributed to understand the co-occurrence of headache and neck pain. Based on this information we further present a neuro-physiological background for physical treatment of headache and neck pain. Studies have gain new insights on the neuro-anatomical and neuro-physiological relation between headache and neck pain, but also raise questions if and how this relation can be influenced by physical treatment. Headache (migraine, tension-type headache, cervicogenic headache), neck pain, and cervical musculoskeletal dysfunctions seem to be related in case-control studies, although the strength, significance and explanation of this relation varies per type of headache.

Clinicians have to consider, by sound clinical reasoning, whether cervical musculoskeletal dysfunctions are related to the patient's headache and which neurophysiological mechanisms could be involved. Therefore, we support the recommendation to classify headache according to the ICHD III criteria and to determine cervical musculoskeletal dysfunctions in patients with migraine, tension-type headache and cervicogenic headache (88). Additionally, tests on pain sensitivity can be included to understand the underlying pathophysiological mechanism. In their clinical judgement, clinicians have to consider all collected patient data: headache symptoms and neck pain, related cervical musculoskeletal dysfunction, tests on pain sensitivity in the cervico-cephalic and extra-cervico-cephalic regions (pressure pain thresholds) and reproduction of headache by pressure or stretch on musculoskeletal structures (43). To understand underlying neurophysiological mechanisms (local nociceptive provocation, referred pain, generalized hyperexcitability) remains challenging, but is necessary to identify patients who may benefit of treatment of the neck (89). The presented neurophysiological knowledge in this paper can be helpful to guide clinicians in this clinical reasoning process.

It is a great challenge for clinicians and researchers to develop effective treatment strategies for headache targeted on modulation of cervical afferent input in order to decrease the excitability of first- to second order neurons at the level of the TCC. Experimental studies of the neurophysiological effect of physical treatment and randomized clinical trial on this topic are scarce and urgently warranted. Meanwhile, there is no standard recipe for physical treatment on the neck for different types of headache. But clinicians may be encouraged by recent evidence and new insights on headache and neck pain and may use this knowledge in clinical reasoning to provide a tailored and evidence based neuro-physiological approach for patients with headache and neck pain.

## AUTHOR CONTRIBUTIONS

RC and WD: concept development and writing of the manuscript; Both authors approved the final version.

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# Repetitive Peripheral Magnetic Stimulation (rPMS) in Subjects With Migraine—Setup Presentation and Effects on Skeletal Musculature

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**Purpose:** Repetitive peripheral magnetic stimulation (rPMS) has been successfully applied recently in migraineurs to alleviate migraine symptoms. Symptom relief has been achieved by stimulating myofascial trigger points (mTrPs) of the trapezius muscles, which are considered part of the trigemino-cervical complex (TCC). However, effects on musculature have not been assessed in detail, and the specificity of effects to muscles considered part of the TCC yet has to be elucidated. Against this background, this study presents the setup of rPMS in migraine and evaluates effects on skeletal musculature.

**Materials and Methods:** Thirty-seven adults (mean age: 25.0 ± 4.1 years, 36 females) suffering from migraine and presenting mTrPs according to physical examination underwent rPMS either to mTrPs in the trapezius muscles (considered part of the TCC; $n = 19$) or deltoid muscles (considered not part of the TCC; $n = 18$) during six sessions over the course of 2 weeks. Standardized questionnaires were filled in to assess any adverse events and experience with rPMS as well as satisfaction and benefits from stimulation. Algometry was performed to evaluate changes in pressure pain thresholds (PPTs).

**Results:** All stimulation sessions were successfully performed without adverse events, with 84.2% of subjects of the trapezius group and 94.4% of subjects of the deltoid group describing rPMS as comfortable ($p = 0.736$). Muscular pain or tension improved in 73.7% of subjects of the trapezius group and in 61.1% of subjects of the deltoid group ($p = 0.077$). PPTs of the trapezius muscles clearly increased from the first to the last stimulation sessions—regardless of the stimulated muscle (rPMS to the trapezius or deltoid muscles). However, depending on the examined muscles the increase of PPTs differed significantly (subjects with stimulation of trapezius muscles: $p = 0.021$; subjects with stimulation of deltoid muscles: $p = 0.080$).

**Conclusion:** rPMS is a comfortable method in migraineurs that can improve local muscular pain or tension. Furthermore, it is able to increase directly and indirectly the PPTs of the trapezius muscles (considered part of the TCC) when applied over mTrPs, supporting the role of the TCC in migraineurs.

**Keywords: deltoid muscle, migraine, active myofascial trigger points, repetitive peripheral magnetic stimulation, trapezius muscle, trigemino-cervical complex**

## INTRODUCTION

More than 1 billion people worldwide suffer from migraine according to a systematic analysis of the Global Burden of Disease Study of 2016 (1). Moreover, migraine has become the first cause of disability in subjects under 50 years of age (2). Although there has been a clear progress in knowledge in fields of epidemiology, etiology, acute and preventive treatment of migraine in the last decades, the distinct pathophysiology of migraine remains complex and multifactorial and is far from being entirely understood, with new aspects ranging from migraine-associated genes over specific neuropeptides to cervical afferences (3, 4).

Recent studies emphasize the association of neck pain with migraine, and there may also be a functional link between musculoskeletal dysfunction of the cranio-cervical region and migraine (5–10). Especially alterations in the trapezius muscles, semantically described as myofascial trigger points (mTrPs), seem to play a role, supporting the concept of a trigemino-cervical complex (TCC) that describes the convergence of cervical nociceptive sensory input of the radices C1-C3 with meningeal afferents in the caudal nuclei of the trigeminal nerve within the brainstem (11–17). Of note, studies have demonstrated a high occurrence of mTrPs in subjects with migraine and their associations with neck mobility (18–22).

Researchers try to modulate elements of the TCC by different invasive and non-invasive approaches in subjects with migraine to achieve symptom improvements. Neurosurgical, invasive occipital nerve stimulation (ONS) has been shown to modulate central pain processing mechanisms via inhibition of nociceptive input of cervical and meningeal afferents (23, 24). Non-invasive techniques are particularly attractive as they are well-tolerated, poor in side effects, and usually easy to apply (24, 25). Examples for centrally applied modalities are transcranial magnetic stimulation (TMS) (26–28) and transcranial direct current stimulation (tDCS) (29, 30). Non-invasive vagus nerve stimulation (VNS) (31–33) and supra-orbital nerve stimulation (SONS) (34, 35) represent further prominent interventions. Recently, repetitive peripheral magnetic stimulation (rPMS) has also been firstly applied in subjects with migraine, showing that the technique is applicable on the trapezius muscles and may successfully alleviate migraine symptoms (36). Furthermore, potential local effects of rPMS on the stimulated muscles by means of examining the pressure pain threshold (PPT) were analyzed, showing that the PPT in the trapezius muscles significantly increased during the course of six stimulation sessions, which supports the idea that rPMS has a positive, pain-reducing effect on the stimulated muscle in addition to its global effects on migraine frequency (36).

Previous studies were able to demonstrate that the PPT, which is defined as the cut-off between mere pressure and pressure-induced painful perception, tends to be decreased in the cranio-cervical region among subjects with migraine (7, 37–40). This supports the importance of muscular alterations and cranio-cervical hyperalgesia in headache disorders and provides further evidence that there might be a close link between peripheral sensitization and central nociception (7, 36, 40). However, although there is a considerable body of literature analyzing the PPT of different muscles of the cranio-cervical region in patients with migraine (e.g., trapezius, sternocleidomastoid, splenius, levator scapulae, or scalene muscles), none of the studies is examining in detail the larger shoulder girdle by comparing its muscles being involved in the TCC with those not being supposed to be part of the TCC (41, 42). Furthermore, there is a lack of evidence regarding the potential changes in PPTs in the course of modulation by techniques like rPMS considering muscles of the cranio-cervical region in comparison to muscles outside of the TCC. A potential specific effect of rPMS on muscles involved in the TCC, but not on those outside of the TCC, might further support the role of the TCC in migraine and the role of techniques like rPMS as valuable new modulatory approaches.

Against this background, the present study aims on demonstrating and evaluating the feasibility of rPMS delivered to the trapezius muscles as structures belonging to the TCC and the deltoid muscles as structures outside of the concept of the TCC among subjects with migraine. Moreover, it specifically evaluates the effects of rPMS on musculature by means of measuring the PPTs by algometry at several time points in the course of rPMS application.

**Abbreviations:** DMKG, German Migraine and Headache Society; ICHD, International Classification of Headache Disorders; MIDAS, Migraine Disability Assessment; MRI, Magnetic resonance imaging; mTrP, Myofascial trigger point; ONS, Occipital nerve stimulation; PPT, Pressure pain threshold; rPMS, Repetitive peripheral magnetic stimulation; SONS, Supra-orbital nerve stimulation; TCC, Trigemino-cervical complex; tDCS, Transcranial direct current stimulation; TMS, Transcranial magnetic stimulation; TTH, Tension-type headache; VAS, Visual analog scale; VNS, Vagus nerve stimulation.

## MATERIALS AND METHODS

### Ethics

The study was approved by the institutional review boards of both universities of Munich (TUM and LMU) and was conducted

in accordance with the Declaration of Helsinki. Written informed consent was a precondition for study enrollment.

## Participants and Experimental Protocol

Participants were recruited by announcements in the hospitals and local libraries of the two universities of Munich. The announcements informed about inclusion and exclusion criteria as well as the study plan and potential side effects of rPMS.

Inclusion criteria were (1) age between 18 and 35 years, (2) migraine (according to the German version of the headache questionnaire modified according to the International Classification of Headache Disorders [ICHD], 3rd edition and its beta version (43–45)), (3) a frequency of 15–44 days of headache during the 90 days prior to the first rPMS session (according to the headache diary of the German Migraine and Headache Society [DMKG]), (4) at least one active mTrP in one of the upper trapezius muscles (according to manual palpation by a specialized physiotherapist), (5) no metallic implants (e.g., cochlear implants), and (6) written informed consent. Exclusion criteria were (1) any neurological diseases except for migraine, (2) intake of any medication for migraine prophylaxis, (3) any changes in hormonal contraception during or shortly prior to study participation, and (4) pregnancy.

Overall, 199 subjects were screened, with 37 subjects fulfilling the inclusion criteria. Participants were randomized into two groups (randomization ratio: 1:1; participants were randomized by drawing sheets of paper with the participants' names to assign them to one or the other group) to receive rPMS either on the trapezius muscles (trapezius group; $n = 19$) or the deltoid muscles (deltoid group; $n = 18$). Overall, six sessions of rPMS were conducted per subject during 2 consecutive weeks in regular intervals (e.g., Monday/Wednesday/Friday or Tuesday/Thursday/Saturday).

## Evaluation of Migraine and Questionnaires

For this study we applied the German version of the headache questionnaire modified according to the ICHD (3rd edition and its beta version) (43–45), the headache diary of the DMKG, the Migraine Disability Assessment (MIDAS) (46, 47), a self-designed questionnaire to evaluate adverse events and experience with rPMS, and a self-designed questionnaire to evaluate the participants' satisfaction with rPMS as they were used in a previous pilot study (36).

To verify migraine diagnosis, the subjects had to initially fill in the German version of the headache questionnaire modified according to the ICHD (3rd edition and its beta version). Only those who fulfilled the criteria of migraine (migraine ± aura and/or ± tension-type headache [TTH]) were chosen for study participation. Subsequently, they were instructed to fill in the headache diary of the DMKG on a daily basis the 90 days before the period of stimulation sessions. This tool is interrogating subjects about trigger mechanisms, intensity, duration, quality, localization, concomitant symptoms, drug intake, and pain relief of each headache event. Additionally, participants were advised to evaluate the impairment in different aspects of daily life (e.g., productivity, household, social life) by headache events during the course of the 90 days prior to rPMS using the MIDAS questionnaire, which had to be completed on the first day of rPMS intervention. We used the results of the DMKG headache diary and the MIDAS questionnaire to compare the two groups (trapezius group and deltoid group) concerning their baseline characteristics regarding migraine before intervention.

Directly after each of the six individual stimulation sessions, a self-designed questionnaire assessed adverse events and experience with rPMS, covering pain perceived during stimulation (yes/no), paresthesia (yes/no, description of the uncommon sensation, assessment of the occurrence of the uncommon sensation in motion, rest, or constantly), muscle cramps (yes/no), and comfort during stimulation (yes/no/undecided). Ninety days after the intervention the participants evaluated the subjective benefit of rPMS and their satisfaction with stimulation retrospectively, using again a self-designed questionnaire assessing overall comfort (yes/no/undecided), willingness to repeat or recommend the stimulation (yes/no), and any improvements regarding the muscular situation (yes/no/undecided).

## Assessment of Myofascial Trigger Points

A certified physiotherapist specialized in mTrP palpations examined all participants within the week prior to the first scheduled rPMS session to identify two active mTrPs or, alternatively, one active and one latent mTrP in the trapezius muscles and latent mTrPs in the deltoid muscles bilaterally. To qualify as an active mTrP, palpated points had to meet the following standard criteria: (1) a taut band with a sensitive spot must be palpable, (2) its palpation must induce a referred pain at the typical localization of the subject's headache, (3) palpation of the sensitive spot must lead to a spontaneous evasive movement called "jump sign" (11, 48–50). In contrast, a latent mTrP does not show referred pain during palpation, but meets the criteria of (1) a taut band with local hypersensitivity, and (2) "jump sign" (51).

In total, we aimed to identify four points in each participant, one mTrP within the trapezius muscles bilaterally, of which at least one had to meet criteria of an active mTrP, and one latent mTrP within the deltoid muscles bilaterally. Participants showing only a unilateral active mTrP on one trapezius muscle were subsequently examined on the corresponding region of the contralateral trapezius muscle to identify a latent mTrP. In case that a subject presented more than one active or latent mTrP in one muscle, the physiotherapist chose the point that was most painful to intense palpation, with the other points not being further considered in the study.

The two mTrPs within the trapezius muscles and within the deltoid muscles were marked with a waterproof pen and documented by photos immediately after definition by the physiotherapist. Furthermore, we used a measuring tape to evaluate the distance of the mTrPs from the vertebral column, using the seventh cervical vertebra and the acromion as reference structures. The measurements were noted and further also documented by photos. Additionally, the physiotherapist documented the results meticulously in anatomical drawings of

the neck and shoulder muscles. According to randomization, we stimulated either the two mTrPs of the trapezius muscles (trapezius group) or the two mTrPs of the deltoid muscles (deltoid group).

## Determination of Pressure Pain Thresholds

Measurements of PPTs were performed by algometry three times per mTrP during each of the six rPMS sessions (7, 52). Specifically, three consecutive PPT measurements were performed separately for the two mTrPs in the trapezius muscles and the two mTrPs of the deltoid muscles immediately before and after application of rPMS. In this context, the PPT as measured by algometry was defined as the cut-off between mere pressure and pressure-induced painful perception (7, 37–40).

During algometry and stimulation, the participants were seated on a comfortable chair with armrests, headrest, and footplate in a relaxing position in order to keep neck and shoulder muscles as less activated as possible (**Figure 1**). This position was kept for the initial and post-stimulation PPT measurements and during the entire application of rPMS. The investigator performed the algometry of the mTrPs on both sides by putting the algometer with a rubber tip of 1 $cm^2$ perpendicularly to the skin whilst increasing the pressure slowly but steadily by 1 $kg/s/cm^2$ until the participant indicated that the local PPT was reached (**Figure 2**).

We initiated the PPT measurements on the mTrP planned to be stimulated first during subsequent rPMS, followed by PPT measurements of the second ipsilateral mTrP. Subsequently, PPT measurements of the remaining two contralateral points were enchained. The same order of measurement was kept for post-stimulation PPT assessments. For both pre- and post-stimulation PPT measurements, there was a short break of 30 s to relax muscles again in between the three PPT measurements per point.

## Repetitive Peripheral Magnetic Stimulation

We used the Nexstim eXimia NBS System (version 4.3; Nexstim Plc. Helsinki, Finland) with a figure-of-eight stimulation coil for rPMS. This coil induces a focal field, combined with a cooling system to prevent overheating of the coil during pulse application. Depending on initial randomization, rPMS was applied either to the mTrPs of the trapezius muscles (trapezius group) or to the mTrPs of the deltoid muscles (deltoid group). Both sides were consecutively stimulated in each session, with the starting side being subject to randomization in the first session. During the following sessions the starting side was alternatingly chosen with respect to the first session per subject.

The stimulation coil was centered and fixed above the previously identified mTrPs of the upper trapezius muscles perpendicularly to the anatomical course or above the mTrPs of the lateral deltoid muscles parallel to the anatomical course

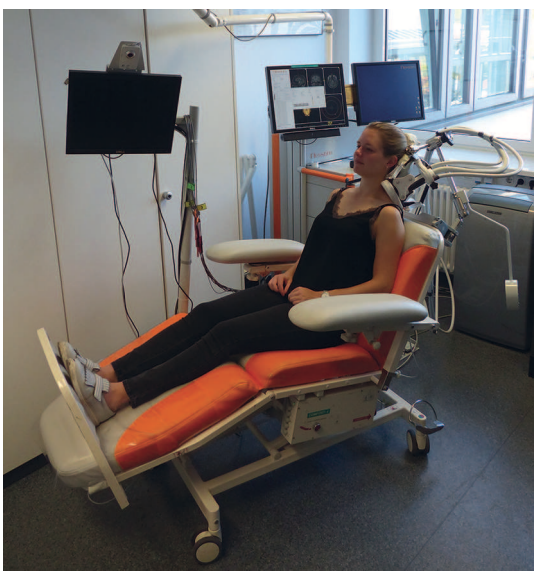

**FIGURE 1 |** Setup of repetitive peripheral magnetic stimulation (rPMS). During algometry and rPMS, the subjects sat on a comfortable chair with armrests, headrest, and footplate in a relaxing position. Application of rPMS took place either to the myofascial trigger points (mTrPs) of the trapezius muscles (as shown in this case with the stimulation coil being placed on the left trapezius muscle with the help of a static coil holder) or to the mTrPs of the deltoid muscles depending on group assignment (trapezius group or deltoid group). The subjects were advised not to move during algometry or rPMS application and to rest in a relaxing position. Written informed consent was obtained from the subject of this figure to use this photo for publication.

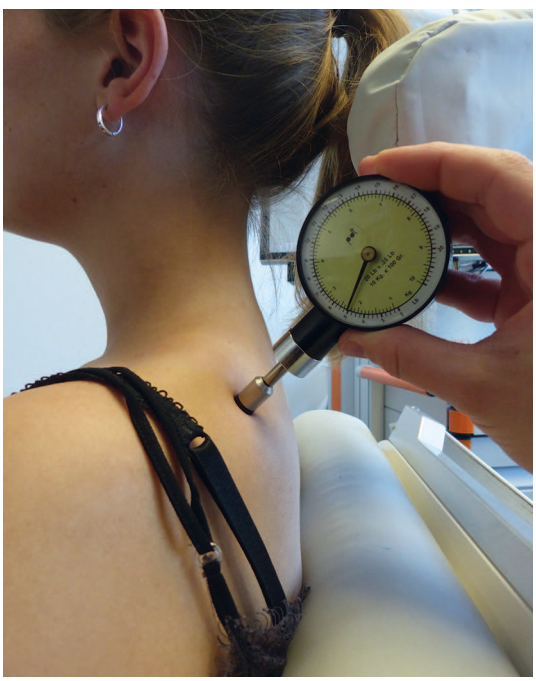

**FIGURE 2 |** Measurements of the pressure pain threshold (PPT) by algometry. Measurements of PPTs were performed with a handheld algometer, which was placed perpendicularly to the skin with increasing pressure until the subject indicated that the local PPT was reached. Algometry was carried out on all four myofascial trigger points (mTrPs) in each subject. Specifically, three consecutive PPT measurements were performed separately for the two mTrPs in the trapezius muscles and the two mTrPs of the deltoid muscles prior and subsequent to the stimulation of each session.

with direct skin contact, depending on the group assignment (**Figure 3**). The coil was fixed by a coil holder to ensure a constant and stable position. During stimulation, the shoulder or upper arm elevated to a certain degree and sank down again during relaxation time (36). Skin contact as well as the position of the coil were ensured and regularly controlled during the whole stimulation and corrected, if necessary. The approach of coil positioning was the same for both sides and all points to be stimulated in each session and participant.

In total, six individual sessions were conducted within 2 consecutive weeks in each participant. Each session consisted of stimulation of the left and right mTrP of the trapezius muscles (trapezius group) or the left and right mTrP of the deltoid muscles (deltoid group), taking 15 min per side. For each side a total of 20 bursts consisting of 6,000 stimuli with a 20-Hz frequency were applied (**Figure 3**). A single burst consisted of 300 stimuli and lasted for 15 s, followed by a 30 s relaxation time (**Figure 3**). Furthermore, there was a break of a minimum of 2 min between rPMS to either side, used for changing the coil position for stimulation of the contralateral side.

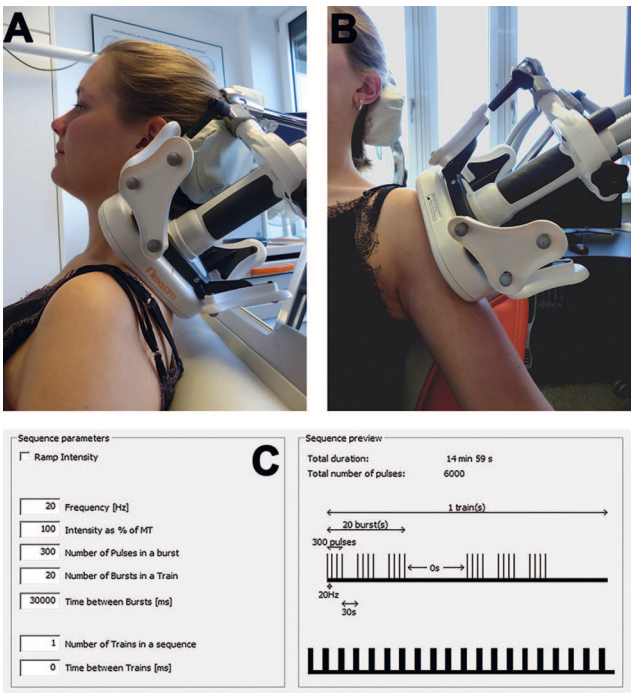


**FIGURE 3 |** Stimulation by repetitive peripheral magnetic stimulation (rPMS). A figure-of-eight stimulation coil was used for rPMS, which was applied either to the mTrPs of the trapezius muscles (trapezius group) or to the mTrPs of the deltoid muscles (deltoid group) in the context of six stimulation sessions. Direct contact between the skin and the coil surface was ensured throughout, and the coil position was fixed by a static coil holder. In subjects of the trapezius group, the coil was centered and fixed above the previously identified mTrPs of the upper trapezius muscles perpendicularly to the anatomical course **(A)**. In subjects of the deltoid group, the coil was placed above the mTrPs of the deltoid muscles parallel to the anatomical course **(B)**. The stimulation protocol was the same in both groups (20 Hz) and took 15 min per side **(C)**. Written informed consent was obtained from the subject of this figure to use this photo for publication.

Before the first stimulation session the intensity of rPMS was defined individually on the muscles to be stimulated according to assignment to the trapezius or deltoid group and was kept for the following sessions. Determination of the individual intensity was achieved in the previously described positions by starting stimulating with an intensity of 15% of the system's maximum output and increasing the intensity by steps of 5% while having the participants evaluating the comfort or discomfort/pain of each intensity on a visual analog scale (VAS) ranging from 0 to 10 (36). A score of 5 was defined as the cut-off value for painful sensation, i.e., we chose the intensity that was 5% lower than the intensity declared as 5 or higher on the VAS, thus regarded as discomfortable or painful, and used the corresponding intensity throughout for rPMS in the respective subject (36). The procedure of intensity determination was conducted on both sides for the muscles to be stimulated. In case that the results differed between sides, we chose the lower of the two intensities for stimulation of both sides.

## Data Analysis and Statistics

All statistical data analyses were performed using R software (version 3.1.0; The R Foundation for Statistical Computing, Vienna, Austria). A $p < 0.05$ was considered statistically significant.

For demographic data and headache characteristics (results of the DMKG headache calendar and MIDAS questionnaire), descriptive statistics including mean, standard deviation, median, and ranges or absolute and relative frequencies were calculated. To compare these data between subjects assigned to the trapezius or deltoid group, we used Wilcoxon-Mann-Whitney-U tests, Chi-squared, or Fisher tests. Results on experience with stimulation and adverse events and satisfaction with rPMS given as absolute and relative frequencies were compared between groups using Chi-squared or Fisher exact tests.

Regarding all analyses on PPTs as measured by algometry, we calculated the mean PPT out of the second and third measurement in each subject for each point separately (two mTrPs of the trapezius muscles and two mTrPs of the deltoid muscles), thus discarding the first measurements (53). First, for each session, differences between pre- and post-stimulation PPTs were assessed using Wilcoxon signed-rank tests, separately considering results among subjects stimulated on the trapezius or deltoid muscles and separately considering PPTs measured on the mTrPs in the right and left trapezius and deltoid muscles. Bonferroni correction for multiple testing was applied. Secondly, we compared the PPTs as measured initially before the first sessions to the corresponding values obtained after the last sessions, thus evaluating overall changes over the period of stimulations. To assess whether PPTs significantly increased, Wilcoxon signed-rank tests were used. As four tests per group were performed, Bonferroni correction for multiple testing was applied. Further, Friedman tests were used to assess whether increases in PPTs differed between examined muscles (right and left trapezius and deltoid muscles) in each group. For pairwise comparison between PPT increases in the examined muscles Nemenyi *post-hoc* tests were performed.

# RESULTS

## Demographics and Baseline Characteristics

**Table 1** shows demographics and baseline characteristics of the included subjects. We enrolled 37 young adults with an average age of 25.0 ± 4.1 years (range: 19–35 years), being randomly assigned to the trapezius group ($n = 19$) or the deltoid group ($n = 18$). Thirty-six of them were female, one was male. There were no significant differences between subjects receiving rPMS to the trapezius muscles and subjects receiving rPMS to the deltoid muscles regarding demographics or items of the headache diary of the DMKG or the MIDAS questionnaire ($p > 0.05$).

All participants presented with high-frequency episodic migraine and had one latent mTrP in each of the deltoid muscles. Moreover, all enrolled subjects showed at least one active mTrP in one of the trapezius muscles. In case that only a unilateral active mTrP was found in one of the trapezius muscles, a latent mTrP was identified on the contralateral side.

## Feasibility of rPMS and Adverse Events

Six single sessions of rPMS to either the mTrPs of the trapezius muscles or mTrPs of the deltoid muscles were feasible in all participants. There were no dropouts during the 2 weeks of application of rPMS.

**Table 2** provides a summary of the evaluation of rPMS effects for all sessions stratified by group. During the 222 conducted stimulation sessions (114 stimulation sessions in the trapezius group and 108 stimulation sessions in the deltoid group), no adverse events occurred. According to the post-interventional assessment, high fractions of 81.6% of the conducted sessions among subjects of the trapezius group and 72.2% of the sessions among the subjects assigned to the deltoid group were described as comfortable ($p = 0.220$). Overall, only 1.7% of sessions were experienced as painful according to evaluations in the trapezius group, with no sessions performed in the deltoid group being declared as painful ($p = 0.498$). Uncommon sensations in the stimulated area, evaluated in terms of sensory function, were overall equally common in both groups (trapezius group: 28.1% of sessions, deltoid group: 26.9% of sessions; $p = 0.958$), with a significant difference regarding the feeling of numbness between groups (trapezius group: 3.1% of sessions, deltoid group: 20.7% of sessions; $p = 0.046$). Other evaluated parameters were again equally distributed between the sessions of both groups ($p > 0.05$).

In a single subject of the deltoid group (female, 30 years), there was a dysesthesia occurring 48 h after the fourth stimulation session. The dysesthesia was reported to have started on the right arm, subsequently spreading to the left arm. Improvement of symptoms was achieved with intake of nonsteroidal analgesic drugs after 24 h, with symptoms disappearing 72 h after onset. No residuum was left. The subject described the dysesthesia to be similar, but slightly more prominent than her well-known sensations during migraine attacks. The participant decided to continue with the remaining rPMS sessions.

## Pressure Pain Thresholds

**Table 3** presents the PPTs of the examined muscles of both groups in the course of the six stimulation sessions. Concerning the first and second session, the PPTs did not significantly change in any of the measured muscles when considering measurements in the trapezius and deltoid group. From the third session on, significantly higher PPTs were observed when comparing pre- to post-interventional algometry for several of the points in both groups.

**Table 4** compares the first measurement of the PPT before the first stimulation with the last measured PPT after the sixth stimulation session. When measuring the PPT of the trapezius muscles, there was an increase from the first to the last measurement regardless of the stimulated muscle, i.e., increased PPT values were observed in subjects stimulated on the deltoid muscles and in subjects stimulated on the trapezius muscles (by a median value between 0.4 and 0.7, respectively). However, significantly elevated values that survived correction for multiple comparisons were found only in the left trapezius muscles (subjects with stimulation of trapezius muscles: $p = 0.005$; subjects with stimulation of deltoid muscles: $p = 0.009$). In contrast, PPTs of the deltoid muscles did not significantly change when comparing the first to the last measurements with median increases between 0.1 and 0.3, respectively. The Friedman test confirmed that depending on the examined muscles the increase of PPTs differed significantly (subjects with stimulation of trapezius muscles: $p = 0.021$; subjects with stimulation of deltoid muscles: $p = 0.080$). Pairwise comparison resulted in significantly higher PPT increases in the left trapezius muscle compared to the right deltoid muscle in subjects with stimulation of the trapezius muscles and in significantly higher PPT increases in the left trapezius muscle compared to both deltoid muscles in subjects with stimulation of the deltoid muscles.

## Participant Satisfaction With rPMS

**Table 5** gives an overview of the participants' subjective satisfaction with rPMS as evaluated 90 days after the last rPMS session. The majority of both groups retrospectively indicated rPMS to be comfortable (trapezius group: 84.2% of subjects, deltoid group: 94.4% of subjects; $p = 0.736$). More importantly, muscular pain or tension was reported to be improved in considerable fractions of 73.7% of subjects of the trapezius group and 61.1% of subjects of the deltoid group, yet with a statistical trend between groups ($p = 0.077$).

# DISCUSSION

This study evaluated the feasibility and effects of rPMS delivered to the trapezius muscles, which are considered as structures belonging to the TCC, and the deltoid muscles as structures not being part of the TCC among subjects suffering from high-frequency episodic migraine. Regarding feasibility, all stimulation sessions were successfully performed without dropouts, technical problems, or lasting adverse events, and the majority of sessions was described as comfortable

**TABLE 1 |** Demographics and headache characteristics.

| | | Trapezius group $N = 19$ | Deltoid group $N = 18$ | $p$ |
|---|---|---|---|---|
| | | Median (range) or % ($N$) | | |
| **SUBJECT CHARACTERISTICS** | | | | |
| Age (in years)[a] | | 25.0 (19–35) | 24.5 (19–32) | 0.702 |
| Female sex[b] | | 100.0 (19) | 94.4 (17) | 0.978 |
| Type of migraine[c] | Migraine without aura | 47.4 (9) | 27.8 (5) | 0.229 |
| | Migraine with aura | 36.8 (7) | 16.7 (3) | |
| | Migraine without aura and TTH | 10.5 (2) | 27.8 (5) | |
| | Migraine with aura and TTH | 5.2 (1) | 27.8 (5) | |
| **HEADACHE DIARY OF THE DMKG (DAILY OVER THE COURSE OF 90 DAYS PRIOR TO INTERVENTION)** | | | | |
| Number of days with headache[a] | | 23 (17–37) | 20 (15–40) | 0.057 |
| Cumulative duration (hours)[a] | | 194 (78–429) | 121 (60–482) | 0.448 |
| Average intensity (according to VAS)[a] | | 5.3 (3.5–6.9) | 5.2 (3.9–6.5) | 0.727 |
| **MIDAS QUESTIONNAIRE (FOR THE 90 DAYS BEFORE INTERVENTION)** | | | | |
| Missing school/work (days)[a] | | 1 (0–5) | 1 (0–12) | 0.405 |
| Productivity at school/work reduced by half (days)[a] | | 10 (2–20) | 7.5 (3–23) | 0.247 |
| Could not do household work (days)[a] | | 5 (0–11) | 4.5 (0–18) | 0.903 |
| Household work productivity reduced by half (days)[a] | | 5 (0–15) | 6 (0–14) | 0.843 |
| Missing family, social, or leisure activities (days)[a] | | 3 (0–10) | 4.5 (0–17) | 0.375 |

*This table shows cohort characteristics including details on headache (migraine with/without aura and with/without tension-type headache [TTH]) according to the headache diary of the German Migraine and Headache Society (DMKG) and the Migraine Disability Assessment (MIDAS) questionnaire. Average of headache intensity was measured with the help of a visual analog scale (VAS).*

[a] *Wilcoxon-Mann-Whitney-U test.*

[b] *Chi-squared test.*

[c] *Fisher test.*

among subjects of both groups according to immediate post-interventional assessments as well as evaluations 90 days after the last rPMS session (**Tables 2**, **5**). Concerning local effects within the muscles tested, PPTs as measured by algometry increased within the context of a single stimulation session when considering the third and later sessions (**Table 3**). More importantly, we found increases in the PPTs of the trapezius muscles from the first to the last measurements—regardless of the stimulated muscle (**Table 4**). Furthermore, depending on the examined muscles the increase of PPTs differed, with subjects stimulated on the trapezius muscles showing significant PPT differences (**Table 4**).

Various non-invasive techniques have been applied in subjects with migraine with the intention to alleviate symptoms via neuromodulation (24, 25). In this context, centrally applied modalities such as TMS (26–28) and tDCS (29, 30) as well as peripheral approaches such as VNS (31–33) and SONS (34, 35) are among the most common options. A new non-invasive technique in the field of migraine is represented by rPMS, which is an especially attractive alternative to these methods as it could induce both focal and central effects simultaneously when applied over muscles of the neck and shoulder area. On the one hand, rPMS can have influence on muscular structures, e.g. by increasing PPTs, and thus can be able to alleviate conditions like myofascial pain, neuropathic pain, or chronic pain (36, 52, 54–57). On the other hand, it was shown that rPMS—although applied peripherally—has central effects as well and is able to influence neuroplasticity, probably by increased proprioceptive inflow (58). Especially in migraine, muscular tenderness and hyperalgesia in neck and shoulder muscles are known for being linked to the incidence of migraine and the occurrence of its attacks (6, 8, 10, 59, 60). This interaction may be related to the nociceptive input of the radices C1-C3, which innervate the neck muscles and are converging with meningeal afferents in the caudal nuclei of the trigeminal nerve in the brainstem (13, 17). Central convergence and peripheral sensitization of trigemino-cervical neurons are the main aspects of the concept of the TCC, which aims to explain the complex pathogenesis of migraine associated with neck pain (13). Of note, investigations were indeed successful in triggering headache by manual palpation of mTrPs in the neck and shoulder region (19, 61). Hence, since rPMS seems to be able to approach both central and peripheral components of the TCC—as ONS is suggested to do as well—it might represent a promising and novel technique for effective interventions in subjects with migraine. Advantages over ONS are based on the non-invasive nature, ease of application, low rates of complications, and cost efficiency of the method. Importantly, the implementation of rPMS into treatment protocols is not subjected to

**TABLE 2 |** Experience with stimulation and adverse events.

| | | Trapezius group $N = 19$ | Deltoid group $N = 18$ | $p$ |
|---|---|---|---|---|
| | | % (*N*) | | |
| Did you perceive the stimulation as painful? | Yes | 1.7 (2) | 0.0 (0) | 0.498 |
| Do you feel an uncommon sensation in the stimulated area? | Yes | 28.1 (32) | 26.9 (29) | 0.958 |
| What were the characteristics of the uncommon sensation in the stimulated area? | Tingling | 40.6 (13) | 48.3 (14) | 0.732 |
| | Muscle ache | 18.8 (6) | 37.9 (11) | 0.167 |
| | Numbness | 3.1 (1) | 20.7 (6) | ***0.046*** |
| | Cold/warmth | 43.8 (14) | 17.2 (5) | 0.050 |
| | Burning sensation | 3.1 (1) | 0.0 (0) | 1 |
| | Furry feeling | 6.3 (2) | 0.0 (0) | 0.493 |
| | Post vaccination | 0.0 (0) | 3.5 (1) | 0.475 |
| | Pressure | 15.6 (5) | 0.0 (0) | 0.054 |
| If yes, does the sensation occur in motion, in rest or constantly? | In motion | 13.8 (4) | 33.3 (3) | 0.405 |
| | In rest | 31.0 (9) | 33.3 (3) | |
| | Constantly | 55.2 (16) | 33.3 (3) | |
| Did any muscular cramps occur during stimulation? | Yes | 0.0 (0) | 0.0 (0) | 1 |
| Has the treatment been comfortable? | No | 9.6 (11) | 16.7 (18) | 0.220 |
| | Yes | 81.6 (93) | 72.2 (78) | |
| | Undecided | 8.8 (10) | 11.1 (12) | |

*This table shows the results of a self-designed questionnaire to evaluate adverse events and experience with stimulation, which was assessed directly after each of the six individual stimulation sessions per subject.*
*Chi-squared test or Fisher test (for rare events with <5 observations for one of the tested groups; statistically significant p-values are printed in bold).*

refractory migraine; instead, like other neuromodulation approaches, it could be applied in different types or stages of migraine (24, 62).

To date, rPMS has been applied to active mTrPs of the trapezius muscles in subjects with migraine in one pilot study (36). This small study enrolled 20 young, predominantly female adults suffering from migraine, conducted six rPMS sessions, and evaluated acceptance and feasibility, performed algometry, and assessed potential impact on migraine (36). In both the present study as well as the previous pilot study using a similar setup and stimulation protocol, there were no dropouts or technical problems (36). Moreover, no lasting adverse events occurred during the entire study period, and single rPMS sessions were predominantly rated as comfortable (81.6% of the trapezius group and 72.2% of the deltoid group, **Table 2**). These rates are even higher than in the previous pilot trial on rPMS in migraine where rPMS was rated as pleasant regarding 55.8% of the sessions (36). Moreover, a high acceptance rate (94.7% of the trapezius group and 88.9% of the deltoid group, **Table 5**) as well as a high rate of recommendation of rPMS (89.5% of the trapezius group and 83.3% of the deltoid group, **Table 5**) were observed among participants without significant differences between the trapezius and deltoid group. Similarly, the previous pilot study reported on 100.0% of the participants willing to repeat rPMS while 90.0% would recommend it (36). Thus, rPMS appears a safe and well tolerable non-invasive technique that shows high acceptance among migraineurs who underwent stimulations, which seems a cornerstone for compliance and potential future transfer into clinics.

Previous research has shown that pressure pain sensitivity in the cranio-cervical region is generally elevated in subjects with migraine when compared to healthy controls (37, 38, 40). Consequently, subjects with migraine suffer more often from neck pain and cranio-cervical hyperalgesia, which is linked to musculoskeletal dysfunction (6, 7, 9, 10). Such hyperalgesia can be detected by measuring PPTs, and corresponding to elevated pain sensitivity, PPTs are regularly lower in the cranio-cervical region of patients with migraine than in healthy controls (7, 37, 39, 41, 53). In the present study, rPMS was indeed able to lead to a change in PPTs during the course of single rPMS sessions (**Table 3**). Increases in PPTs over the course of single rPMS sessions and particularly over the course of a 2-weeks interval of stimulation, as observed in the present study, seem to reflect improvements in hyperalgesia in migraineurs as measured by algometry. The finding that we did not observe a clear increase in PPTs in the course of the first sessions might implicate that only one session might not be able to change local conditions of neck and shoulder muscles, but repeated, thus multiple rPMS sessions seem potent enough to increase PPTs. This seems in good accordance with the previous pilot study that has also reported on increases in PPTs in the course of six rPMS sessions, but did only use stimulation of the trapezius muscles (36).

Of note, the present study did not only find increases in PPTs when comparing measurements before and after stimulation

**TABLE 3 |** Evaluation of pressure pain thresholds (PPTs) by algometry—Part I.

| Session | | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Median (range)** | ***p*** | **Median (range)** | ***p*** | **Median (range)** | ***p*** | **Median (range)** | ***p*** | **Median (range)** | ***p*** | **Median (range)** | ***p*** |
| **STIMULATION OF TRAPEZIUS MUSCLE** | | | | | | | | | | | | | |
| Trapezius muscle—right side | Pre | 2.1 (0.9–3.4) | 0.352 | 1.7 (0.6–3.6) | *0.019* | 1.8 (0.8–4.6) | *0.008* | 1.9 (0.7–4.3) | *0.003* | 1.8 (0.7–4.4) | *0.033* | 2.0 (0.7–3.8) | *0.003* |
| | Post | 2.0 (1–3.4) | | 1.8 (1.0–3.7) | | 1.9 (0.9–5.3) | | 2.1 (0.8–5.6) | | 2.0 (0.8–5.7) | | 2.5 (0.6–5.1) | |
| Trapezius muscle—left side | Pre | 1.4 (1.0–3.4) | 0.103 | 1.4 (0.6–3.6) | 0.171 | 1.6 (0.6–4.2) | *0.039* | 1.6 (0.7–3.7) | ***0.002*** | 1.8 (0.7–3.6) | *0.018* | 2.0 (0.7–5.8) | *0.010* |
| | Post | 1.8 (0.9–2.6) | | 1.7 (0.7–3.7) | | 1.8 (0.6–4.6) | | 1.9 (0.8–4.6) | | 2.0 (0.8–4.0) | | 2.5 (0.9–5.2) | |
| Deltoid muscle—right side | Pre | 1.4 (0.6–2.3) | 0.472 | 1.4 (0.6–2.2) | *0.041* | 1.4 (0.6–2.3) | *0.014* | 1.3 (0.7–3.3) | 0.184 | 1.3 (0.6–2.2) | *0.039* | 1.2 (0.5–2.2) | *0.016* |
| | Post | 1.4 (0.8–2.5) | | 1.3 (0.8–2.2) | | 1.5 (0.7–2.5) | | 1.3 (0.6–3.5) | | 1.5 (0.6–2.9) | | 1.3 (0.6–2.5) | |
| Deltoid muscle—left side | Pre | 1.3 (0.7–2.1) | 0.235 | 1.3 (0.6–2.3) | 0.258 | 1.2 (0.6–2.2) | ***0.001*** | 1.3 (0.6–2.5) | 0.117 | 1.2 (0.7–2.2) | *0.032* | 1.2 (0.6–2.4) | *0.028* |
| | Post | 1.3 (0.7–2.4) | | 1.2 (0.7–2.6) | | 1.4 (0.6–2.6) | | 1.4 (0.6–2.4) | | 1.4 (0.7–2.0) | | 1.4 (0.6–2.7) | |
| **STIMULATION OF DELTOID MUSCLE** | | | | | | | | | | | | | |
| Trapezius muscle—right side | Pre | 1.4 (0.8–5.7) | 0.053 | 1.8 (0.8–6.2) | *0.008* | 2.1 (0.8–6.6) | 0.107 | 1.7 (0.7–5.4) | ***0.0001*** | 2.0 (0.7–7.2) | ***0.002*** | 1.8 (0.6–5.8) | ***0.001*** |
| | Post | 1.9 (0.9–6.7) | | 2.2 (0.8–8.2) | | 2.2 (0.8–8.8) | | 2.5 (0.7–6.4) | | 2.5 (0.6–8.4) | | 2.2 (0.8–6.8) | |
| Trapezius muscle—left side | Pre | 1.9 (0.7–4.5) | 0.065 | 1.9 (0.6–5.7) | *0.012* | 1.9 (0.6–6.5) | *0.004* | 2.1 (0.8–6.3) | 0.850 | 1.9 (1.0–6.4) | ***0.001*** | 2.1 (0.8–7.1) | *0.012* |
| | Post | 2.0 (0.7–5.3) | | 2.0 (0.8–10.1) | | 2.2 (0.8–7.7) | | 2.2 (0.8–5.8) | | 2.2 (1.1–7.0) | | 2.3 (1.1–6.0) | |
| Deltoid muscle—right side | Pre | 1.6 (0.7–2.7) | 0.061 | 1.4 (0.7–3.0) | *0.006* | 1.5 (0.8–3.1) | *0.018* | 1.4 (0.8–4.3) | *0.012* | 1.3 (0.7–2.6) | ***0.001*** | 1.3 (0.6–3.2) | *0.003* |
| | Post | 1.7 (0.7–4.5) | | 1.5 (1.0–4.6) | | 1.6 (0.8–4.5) | | 1.6 (0.7–5.1) | | 1.6 (0.8–3.4) | | 1.5 (1.0–3.7) | |
| Deltoid muscle—left side | Pre | 1.4 (0.7–3.0) | 0.156 | 1.1 (0.6–3.5) | 0.231 | 1.2 (0.8–3.5) | ***0.002*** | 1.3 (0.7–2.8) | ***<0.0001*** | 1.2 (0.7–2.6) | *0.029* | 1.4 (0.4–2.7) | *0.011* |
| | Post | 1.5 (0.6–3.3) | | 1.4 (0.6–2.9) | | 1.4 (0.8–3.9) | | 1.4 (0.8–3.7) | | 1.4 (0.8–2.9) | | 1.5 (0.7–2.9) | |

*This table shows the results of algometry for each session, which was used to determine PPTs above the myofascial trigger points (mTrPs) of the trapezius and deltoid muscles. Three consecutive PPT measurements were performed separately for the two mTrPs in the trapezius muscles and for the two mTrPs of the deltoid muscles immediately before and after stimulation. The mean PPTs out of the second and third measurements were calculated in each subject for each point, thus discarding the first measurements.*

*Wilcoxon signed-rank test (with Bonferroni correction for multiple testing; statistically significant p-values after correction for multiple testing are printed in bold, statistically significant p-values that did not survive correction for multiple testing are printed in italics).*

**TABLE 4 |** Evaluation of pressure pain thresholds (PPTs) by algometry—Part II.

| | Trapezius muscle—right side | Trapezius muscle—left side | Deltoid muscle—right side | Deltoid muscle—left side |
|---|---|---|---|---|
| **STIMULATION OF TRAPEZIUS MUSCLE** | | | | |
| PPT pre first session median (range) | 2.1 (0.9–3.4) | 1.4 (1.0–3.4) | 1.4 (0.6–2.3) | 1.3 (0.7–2.1) |
| PPT post sixth session median (range) | 2.5 (0.6–5.1) | 2.5 (0.9–5.2) | 1.3 (0.6–2.5) | 1.4 (0.6–2.7) |
| *P*-value for comparison between first and sixth session[a] | 0.080 | ***0.005*** | 0.167 | *0.019* |
| Difference between PPTs post sixth and pre first session median (range) | 0.4 (−1.1–2.5) | 0.6 (−0.5–2.6) | 0.1 (−1.1–1.5) | 0.2 (−0.5–1.0) |
| *P*-value for comparison of PPT differences between examined muscles[b] | | ***0.021*** | | |
| *P*-values for pairwise comparison of PPT differences between examined muscles[c] | - Trapezius muscle left side and deltoid muscle right side: $p = 0.017$<br>- There were no significant differences between any other pairs | | | |
| **STIMULATION OF DELTOID MUSCLE** | | | | |
| PPT pre first session median (range) | 1.4 (0.8–5.7) | 1.9 (0.7–4.5) | 1.6 (0.7–2.7) | 1.4 (0.7–3.0) |
| PPT post sixth session median (range) | 2.2 (0.8–6.8) | 2.3 (1.1–6.0) | 1.5 (1.0–3.7) | 1.5 (0.7–2.9) |
| *P*-value for comparison between first and sixth session[a] | *0.017* | ***0.009*** | 0.327 | 0.486 |
| Difference between PPTs post sixth and pre first session median (range) | 0.7 (−1.1–3.1) | 0.7 (−0.8–1) | 0.3 (−0.8–1) | 0.2 (−1.5–1.4) |
| *P*-value for comparison of PPT differences between examined muscles[b] | | 0.080 | | |
| *P*-values for pairwise comparison of PPT differences between examined muscles[c] | - Trapezius muscle left side and deltoid muscle right side: $p = 0.04$<br>- Trapezius muscle left side and deltoid muscle left side: $p = 0.03$<br>- There were no significant differences between any other pairs | | | |

*This table shows the results of algometry of the initial measurement prior to the first stimulation session and the last measurement subsequent to the last stimulation session. The mean PPTs out of the second and third measurements were calculated in each subject for each point, thus discarding the first measurements.*

[a] *Wilcoxon singed-rank test (with Bonferroni correction for multiple testing; statistically significant p-values after correction for multiple testing are printed in bold, statistically significant p-values that did not survive correction for multiple testing are printed in italics).*

[b] *Friedman test.*

[c] *Nemenyi post-hoc test.*

**TABLE 5 |** Satisfaction with stimulation.

| | | Trapezius group $N = 19$ | Deltoid group $N = 18$ | $p$ |
|---|---|---|---|---|
| | | % ($N$) | | |
| Has the stimulation been comfortable? | No | 10.5 (2) | 0.0 (0) | 0.736 |
| | Yes | 84.2 (16) | 94.4 (17) | |
| | Undecided | 5.3 (1) | 5.6 (1) | |
| Would you repeat the stimulation? | No | 5.3 (1) | 11.1 (2) | 0.604 |
| | Yes | 94.7 (18) | 88.9 (16) | |
| Would you recommend the stimulation for migraine? | No | 10.5 (2) | 16.7 (3) | 0.660 |
| | Yes | 89.5 (17) | 83.3 (15) | |
| Did the stimulation improve the muscular situation? | No | 5.3 (1) | 33.3 (6) | |
| | Yes | 73.7 (14) | 61.1 (11) | 0.077 |
| | Undecided | 21.1 (4) | 5.6 (4) | |

*This table shows the results of a self-designed questionnaire to evaluate the subjective benefit from stimulation, which was assessed 90 days after the last stimulation session in each subject.*
*Fisher test.*

for single sessions; instead, we also found increased PPTs for the trapezius muscles when comparing the PPTs before the first stimulation with the very last measurement after the sixth rPMS session—regardless of the muscle that had been stimulated (**Table 4**). The finding that depending on the examined muscles the increase of PPTs differed (subjects with stimulation of trapezius muscles showed significant results whereas subjects with stimulation of deltoid muscles did not) might be explained within the concept of the TCC. The TCC claims that peripheral sensitization and central convergence of nociceptive afferents of C1-C3 could explain migraine pathogenesis in relation to neck pain (13). We hypothesize that the trapezius muscle that is considered part of the TCC in migraine might be more prone to improvements in hyperalgesia following rPMS than other adjacent muscles. This might be the result of central modulations probably reflected by neuroplasticity and increased proprioceptive inflow, features that have actually been observed in the course of rPMS elsewhere (58). In contrast, the deltoid muscles might not profit in the same way from rPMS, even not when stimulated directly, which might be related to missing access to the loops of the TCC that might be restricted to structures like the trapezius muscles. Hence, within the concept of the TCC in subjects with migraine, the trapezius muscles seem to be capable of responding better to both indirect and direct stimulation effects. Furthermore, the fact that the PPTs of the trapezius muscles increased even with rPMS to the deltoid muscles could be explained by a co-functional elevation of the shoulder and, thus, passive movement of the trapezius muscles during stimulation. Other explanations might be that there are connections between the trapezius and the deltoid muscles or that the afferents of both muscles converge at some point on the way to the brainstem. Thus, via measurements of effects of rPMS by algometry, this study emphasizes the importance of the trapezius muscles in the complex of the TCC and might support the assumption that the deltoid muscles are not primarily involved in the TCC (13–16).

Although this study provides new insights into rPMS and its effects on skeletal musculature in subjects with migraine, certain limitations need to be highlighted. With regards to study inclusion, the comparatively low number of participants in each group represents a shortcoming, together with the predominant enrollment of females over males. Second, the participants' narrow age range, which was between 18 and 35 years, as well as the focus on subjects with high-frequency episodic migraine might represent shortcomings as results obtained in this study might not be generalized with respect to migraineurs in different ages or with different frequency characteristics of migraine. Third, the inclusion of individuals suffering from migraine and TTH as well as individuals suffering only from migraine can be considered as a limitation as there is no evidence available regarding the issue how rPMS would influence TTH only. However, there is a high prevalence of TTH among migraineurs, similar to the prevalence among non-migraineurs (63). This shows that migraineurs suffering also from other headache disorders represent an important proportion of the population and should also be considered as participants. Fourth, the present study did not evaluate effects of rPMS applied to the trapezius or deltoid muscles on characteristics of migraine. Potential alleviating effects on the number of migraine attacks and migraine intensity, amongst other factors, have been suggested by a previous pilot study (36); however, further evidence for the positive impact of rPMS on migraine characteristics is needed.

With regards to the study's setup and design, the lack of a control condition to assess potential placebo or setting effects on PPTs reflects a potential shortcoming. Such a control condition might have been established by sham stimulation of the trapezius or deltoid muscles. A sham coil, i.e. a coil with a plastic tube to avoid direct contact between skin and coil, could be utilized to prevent actual local stimulation. In

this case the participant would still experience the device's typical noise and direct skin contact, but would not experience any muscular contractions (58, 64). Another option could be a reduction in stimulation parameters like intensity and frequency to reduce effects of rPMS so that participants could perceive a clearly less remarkable contraction of the stimulated muscles (58). However, sham-controlled studies using either of these options cannot be realized that easily in case of rPMS where a missing stimulation effect on musculature is evidently experienced by study participants (65). Second, the exact localization of stimulation was defined according to previous manual palpation performed to detect active or latent mTrPs. Manual palpation is considered the gold standard for the identification of mTrPs since decades (25, 66); however, novel techniques like qualitative magnetic resonance imaging (MRI) or quantitative MRI using T2 mapping might be capable of visualizing and determining mTrPs more objectively, thus paving the way for navigated rPMS interventions (11, 12, 67). Third, this study only involves a certain neck muscle, the trapezius muscle, as a structure being part of the TCC and only one muscle, the deltoid muscle, that is not supposed to be involved in the TCC. Particularly stimulation to other muscles outside of the concept of the TCC and more distant to musculature considered part of the TCC might provide further evidence for our suggestion that structures of the TCC might be more prone to improvements in hyperalgesia following rPMS in migraine. Future studies could make advantage of novel MRI-guided rPMS approaches and might consider control conditions and further muscle groups for stimulation in the context of more advanced study setups.

## CONCLUSION

This study applied rPMS to mTrPs of trapezius muscles (considered part of the TCC) and mTrPs of deltoid muscles (considered not part of the TCC) in migraineurs. The approach showed to be feasible and comfortable, with improvements in local muscular pain or tension being evident. Particularly the mTrPs of the trapezius muscles were responding to stimulation via application of rPMS, suggesting that the trapezius muscles might play a more complex role not only in muscular interaction but also in the concept of the TCC. Further studies are needed to explore in more detail structures in and outside of the TCC as well as modulating local and central effects of rPMS in subjects with migraine.

## DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The study was approved by the institutional review boards of both universities of Munich (Technical University of Munich, TUM, and Ludwig-Maximilians-University, LMU) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was a precondition for study enrollment.

## AUTHOR CONTRIBUTIONS

TR and NS: data acquisition, data handling, data analysis including statistics, data interpretation, literature research, drafting of the manuscript, and read and approved final version. FT-F: data acquisition, data handling, literature research, and read and approved final version. LA: data handling, data analysis including statistics, and read and approved final version. NM and MB: data interpretation, literature research, and read and approved final version. HK and BK: definition of mTrPs, data acquisition, and read and approved final version. SK: data handling, literature research, and read and approved final version. FH, LG, and ML: data acquisition, data handling, data analysis, data interpretation, literature research, drafting of the manuscript, and read and approved final version.

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REVIEW
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# Prophylactic Treatment of Pediatric Migraine: Is There Anything New in the Last Decade?

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Migraine is a frequent and very disabling disease, especially at pediatric age. Despite this, there are few controlled data on the prophylactic treatment of primary headaches in this category of age. Given that the recently introduced calcitonin gene-related peptide (CGRP) inhibitors (CGRP-r) are still limited to adulthood, there is no drug with exclusive indication for migraine treatment in pediatric age. This raises several limitations in terms of adherence and effectiveness of the therapy. Moreover, the scenario is complicated by placebo response, which is larger in children and adolescents than in adults and often leads to an improvement in the attack frequency even in absence of any active pharmacological treatment. Our aim was to investigate the real evidence concerning the prophylactic therapy of pediatric migraine by reviewing the clinical studies published between 2010 and 2019.

**Keywords: migraine, pediatric migraine, prophylactic drugs, therapy, treatment, guidelines, preventive**

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## INTRODUCTION

According to epidemiological studies, the prevalence of headache in children varies from 5.9 to 82% (1). Migraine, the most common type of primary headache in children, is highly disabling even in childhood and adolescence. The average prevalence of pediatric migraine varies according to age, going from 3% in younger children to ∼20% in adolescents (2). A noticeable social problem is represented by chronic migraine (more than 15 days with headache a month) that afflicts from 0.6 to 1.8% of children and adolescents (3).

The main reference for the diagnosis of primary headaches are the criteria of the International Headache Society (IHS) (4). These criteria have shown limitations when applied in the pediatric age (1, 5), although the last version (ICHD 3) considers some peculiarities of migraine in pediatric age, such as the shorted duration of pain and the unilateral/bilateral location of pain (1, 5).

Regarding therapies of pediatric migraine, there is a significant lack of clinical studies on acute and prophylactic therapy. This is partly due to differences between countries, where therapeutic approaches are based on cultural and political factors. Few clinical trials are available in pediatric patients and they often show conflicting findings. The paucity of data on the effectiveness of treatments in young migraineurs is also due to the power of placebo effect, in terms of reduction of both frequency and intensity of migraine attacks (6). Though representing a precious resource, the placebo effect can paradoxically represent an obstacle in controlled trials comparing the efficacy of pharmacological and non-pharmacological treatments with placebo.

Migraine prophylaxis aims at reducing the impact of migraine by improving the frequency and intensity of attacks. In children and adolescents, it should be considered when the frequency of attacks is higher than 4 attacks per month or the response to the symptomatic treatment is not satisfactory. In a previous retrospective review, Papetti et al. (7) emphasized the lack of definitive data on the possible drugs to be used.

Here, our aim is to investigate the actual evidence concerning prophylactic therapy of pediatric migraine by reviewing clinical studies published between 2010 and 2019.

# METHODS

## Literature Search Strategy

We considered studies published from January 2010 to January 2019. Medline and Cochrane library were used for the research. Search words were: "migraine and treatment or therapy," "migraine and prophylaxis," and "migraine and guidelines." The filters included clinical trials (CT), randomized control trials (RCTs), open label studies (OL), retrospective studies (RS), meta-analysis, multicenter studies, reviews and articles that were either published in the last 10 years. Our search was focused on the age group ranging from 0 to 18 years, although any article that included adult population but contained patients under the age of 18 years was also considered. Two authors (F.U. and L.P.) independently checked the studies identified by the literature search. All potentially relevant studies were reviewed by the two authors.

## Search Results

Using the above described strategy, 64 articles concerning preventive treatment of migraine in children were included in our study. Among them, there were 40 systematic reviews or meta-analysis of the literature concerning the prophylactic treatment of pediatric migraine, 21 clinical trials (CTs), and 3 retrospective studies (RSs). As for the CTs, 15 were randomized control trials (RCTs) and one was an open label study (OL) (**Figure 1**). All the included studies were published from 2010 to the present. Results of current evidence are resumed in **Table 1**.

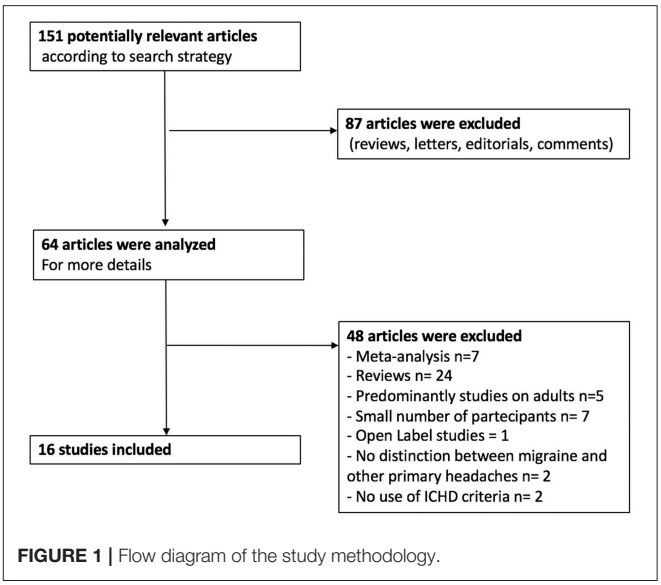


**FIGURE 1 |** Flow diagram of the study methodology.

# PHARMACOLOGICAL TREATMENT

## Calcium Channel Blockers

Flunarizine is a calcium channel blocker with properties on the cerebrovascular circulation. How flunarizine acts in preventing migraine is not yet established but it probably has both vascular and neuronal effects (8).

In an RS (2012), Basheer Peer et al. demonstrated that flunarizine (2.5–10 mg/day) shows good efficacy in children and adolescents (median age 13 years), leading to at least a 50% reduction in attack frequency in 57% of patients (41/72). Interestingly, the response rate was particularly high in patients with hemiplegic migraine (85%). The study also showed that flunarizine was well-tolerated with a reasonable safety profile. Side effects were observed in 21% of children and adolescents and included depression, weight gain and sedation (9). In a retrospective study of 475 patients, Kim et al. (10) showed that the efficacy and tolerability of flunarizine 5 mg/day were comparable to those of topiramate. The responder rate (50% reduction in headache days/month) was 80% (89/111 patients) for flunarizine (5 or 10 mg /day) and 81% (122/150 patients) for topiramate (from 25 to 100 mg/day). The frequency of adverse effects was higher in topiramate (10%) than flunarizine (6%) (10). In 2014, Topcu et al. used the PedMIDAS (the score of disability assessment in pediatric migraine) to evaluate the efficacy of different prophylactic therapies in 53 patients, recruited from a series of 88 patients suffering from migraines with an age ranging from 6 to 17 years. They found that topiramate (1–2 mg/Kg/day), propranolol (20–40 mg/day), and flunarizine (5–10 mg/day) significantly decreased PedMIDAS score. The number of days with analgesic treatment significantly decreased in the patients treated with topiramate and propranolol ($p < 0.05$), while it remained unchanged in the flunarizine ($p > 0.05$) (11). More recently, Toldo et al. (12) conducted a retrospective multicenter study among 706 patients with primary headaches. Preventive drugs were used in 19% of migraineurs and in 3% of patients with tension-type headache (12). In patients with migraine, the most used drug was flunarizine (18%), followed by antiepileptic drugs (7%) and pizotifen (6%). Flunarizine and pizotifen were the most effective drugs (72 and 82%, respectively) (12).

Flunarizine is licensed in Italy for patients over 18 years (7) and widely prescribed in Europe, while it is not licensed in the UK or the USA given the lack of published data in the development age. Placebo-controlled clinical trials in pediatric age are needed to confirm its effectiveness in pediatric migraine (13).

## Beta-Blockers

Propranolol is a non-selective beta (b) adrenoceptor antagonist that blocks the b1,2 receptors. Propranolol started to be used in the prophylaxis of migraine for more than 50 years (14). Propranolol showed efficacy and high profile of tolerability in several clinical trials on adult migraine (4). On the contrary, there

**TABLE 1 |** List of commonly used drugs for preventive treatment of pediatric migraine.

| Drug pharmacological class | Evidence level | Dosage | Side effects | When to be preferred? |
|---|---|---|---|---|
| **CALCIUM CHANNEL BLOCKERS** | | | | |
| Flunarizine | A | 5–10 mg/day | Sedation, dizziness, constipation, increased appetite, weight gain<br>Drowsiness, asthenia, weight gain, depression and extrapyramidal symptoms | Associated anxiety and insomnia<br>not overweight patients |
| **NON-SELECTIVE BETA ADRENOCEPTOR ANTAGONIST** | | | | |
| Propranolol | C | 3 mg/kg/day | Fatigue, reduction of mood, nightmares. Less frequent adverse events: bradycardia, orthostatic hypotension, impotence, hallucinations, weight gain | History of hypertension<br>No history of asthma or allergy<br>No history of bradyarrhythmia |
| **TRICYCLIC ANTIDEPRESSANT** | | | | |
| Amitriptyline | B | 1 mg/Kg/day | Sedation, dizziness, constipation, increased appetite, weight gain | Not obese patients<br>history of depression or insomnia<br>chronic migraine |
| **ANTIEPILEPTIC DRUGS** | | | | |
| Sodium Valproate | B | 30 mg/kg/day | Somnolence, nausea/vomiting, thrombocytopenia,<br>tremor, alopecia, increased appetite, emotional lability | History of psychosis<br>Male patients |
| Topiramate | A | 2–3 mg/Kg/day | Paresthesia, somnolence, dizziness, anorexia, metabolic acidosis, cognitive/memory dysfunction | Overweight<br>No history of cognitive impairment |
| **SEROTONIN MODULATORS** | | | | |
| Pizotifen | C | 1.5 mg/day | Increased appetite, weight gain, drowsiness, sleepiness, dizziness, dry mouth, tiredness, constipation | No obese patients<br>history of depression or insomnia |
| Cyproheptadine | C | 0.2–0.4 mg/kg/day | Drowsiness, fatigue, increased appetite, weight gain, dizziness | No history of asthma |
| **NUTRACEUTICS** | | | | |
| Hydroxytryptophan | C | 100 mg Kg/day | Nausea, bloating<br>Flatulence, loose stools or diarrhea | Mild intensity of the attack<br>Low frequency<br>Refusal of pharmacological drugs<br>Very young children (<6 year) |
| Magnesium | C | 400–600 mg/day | Nausea, abdominal pain | |
| Butterbur(petasites hybridus) | C | 100–150 mg | Burping or belching<br>Itchy eyes, diarrhea, difficulty breathing, drowsiness, liver toxicity | |
| Riboflavin | C | 400 mg/day | Diarrhea, increased urine | |
| Coenzyme Q10 | C | 150–300 mg/day | Nausea and/or vomiting<br>upset stomach, diarrhea<br>heartburn, loss of appetite, abdominal pain or discomfort | |
| Tenacetum parthenium –Feverfew (MIG99) | C | 6.25 mg<br>18.75 mg TID/day | Abdominal pain, mouth ulcers, bloating, diarrhea, nausea | |

*RS, Retrospective Study; RMS, Retrospective Multicenter Study; RCT, Randomized Controlled Trial; TPM, topiramate; PZT, pizotifen; VPA, valproic acid; AMI, amitriptyline; PGB, pregabalin; PPL, propranolol; FNZ, flunarizine; CNZ, cinnarizine.*

are only a few studies supporting the efficacy of propranolol in pediatric age (15–17).

In 2010, Bidabadi et al. compared the efficacy and safety of propranolol (started at a dosage of 3 mg/kg/day) and valproate (30 mg/Kg/day) for migraine prophylaxis in childhood. In this study, 60 patients were enrolled (30 in the group A that received propranolol 3 mg/kg/day and 30 in the group B treated by sodium valproate 30 mg/kg/day). The mean age of

the patients was 9.85 ± 2.63 years. Headache frequency was significantly reduced by more than 50% in 83% of patients treated with propranolol and in 63% of patients treated with sodium valproate without significant differences between the drugs. Furthermore, no significant difference in side effects between the two groups was found (18). Eidlitz-Markus et al. (19) compared the efficacy of a low dose of propranolol (the initial dose was 0.47 ± 0.17 mg/kg/day) with a low dose of amitriptyline (mean initial dose, 0.26 ± 0.1 mg/kg/day) in children and adolescent suffering from severe migraine. Although the study was not blinded and placebo controlled, it included a large number of patients (118 with a mean age of 12.54 ± 3.14 years). Both propranolol and amitriptyline, when combined with non-pharmacologic treatments, showed efficacy in reducing the frequency of migraine attacks in children (reduction of attack frequency >50% per month in 80% of patients). Propranolol group showed less frequent side effects (19). In 2012, Fallah et al. compared efficacy and safety of propranolol (1 mg/kg/day) and topiramate (3 mg/kg/day) in a parallel single-blinded randomized clinical trial. Authors enrolled 100 patients that were divided in two groups (50 patients treated with propranolol and 50 patients treated with topiramate). After 3 months of treatment, 62% of patients treated with propranolol and 82% of patients treated with topiramate showed more than a 50% reduction in monthly headache frequency ($p < 0.05$). No serious adverse events were seen in both groups and, in particular, the main side effects after treatment with propranolol were mild hypotension and drowsiness (20). In a RCT (2013), Bakhshandeh Bali et al. compared effectiveness, safety and tolerability of propranolol (10 to 20 mg/day divided in two doses; group b) and pregabalin (50 to 75 mg/day; group a). After 4 and 8 weeks of pregabalin administration, headache frequency was reduced by 81.8 and 85.45%, respectively. Using the same treatment intervals, propranolol reduced monthly headache frequency by 64.54 and 68.25%, respectively. The difference between drugs was statistically significant ($p = 0.04$) (21).

Recent data showed that beta-blockers are rarely used in Italy, probably because their tolerability profile is not excellent and they are licensed over 18 years (4).

## Tricyclic Antidepressant

Amitriptyline is one of the most used drugs for preventive treatment of pediatric migraine (22). It is also recommended in cases of tension-type headache associated with anxiety, insomnia and depression (22). Efficacy of amitriptyline prophylaxis is achieved with much lower doses than those required for anti-depressive therapy (10–20 mg/day up to 25–75 mg/day) (7). It is advisable to use increasing doses before reaching the maintenance dose in order to reduce the side effects and improve tolerability. Contraindications are cardiac, hepatic, renal, prostatic and thyroid diseases; glaucoma, hypotension, epilepsy, use of anti-MAO. Amitriptyline also should be used with caution for its anticholinergic effects. The most frequent adverse events are dry mouth, constipation, sedation, and increase in appetite, increased weight, occasionally orthostatic hypotension and cardiotoxicity (22).

As reported above, it was shown that low-dose propranolol and low-dose amitriptyline, if combined with non-pharmacological measures, were both effective in reducing migraine attacks frequency (19). Between July 2012 and November 2014, Hershey et al. conducted a double-blinded, placebo-controlled study with the aim to determine the most effective prophylactic treatment in children and adolescents (CHAMP study). Authors compared the efficacy of amitriptyline, topiramate, and placebo in 361 subjects (from 8 to 17 years of age). In a period of 6 months, 52% of patients receiving amitriptyline (dose 1 mg/kg per day), 55% of patients receiving topiramate (dose 2 mg/kg per day), and 61% of patients receiving placebo had a reduction in headache days of at least 50%, without any significant difference between groups. Furthermore, the patients treated with amitriptyline or topiramate presented higher rates of adverse events compared to placebo control group (23). In conclusion, considering the negative outcome of this study in terms of efficacy and the increased risk of undesirable effects from amitriptyline or topiramate in this sensitive category of patients, the benefit / risk ratio of these drugs is considered unfavorable. In an Iranian parallel, single-blinded randomized clinical trial, the efficacy of amitriptyline (1 mg/kg/day) was compared to melatonin (0.3 mg/kg/day) in a population of migraineurs ranging from 5 to 15 years. A reduction of more than 50% in monthly headache frequency was seen in 82.5 and 62%.5 of patients treated with amitriptyline and melatonin, respectively. Amitriptyline was significantly more effective ($P = 0.04$) (24). Amitriptyline showed a good efficacy for treatment of chronic headaches in association with cognitive behavioral therapy (25–28).

## Antiepileptic Drugs

Sodium Valproate (500–1,500 mg/day) and topiramate (50–100 mg/day) were evaluated for prophylactic therapy of pediatric migraine in some controlled studies (7).

In the last 8 years, one RCT compared the efficacy of valproate and propranolol for the preventive treatment of migraine in the pediatric age. Sixty children (aged 5–15 years) with migraine without aura were included. Patients received propranolol (3 mg/kg/day) or sodium valproate (30 mg/kg/day) for at least 6 months. The main endpoint (reduction of more than 50% in monthly headache frequency) was observed in 83% of the propranolol group and in 63% of sodium valproate group without statistical significance. The global reduction of baseline headache frequency was better in the group of propranolol ($p < 0.05$) (18).

Topiramate is a first-line strategy for the treatment of migraine in adults. In 2014, the U.S. Food and Drug Administration (FDA) approved topiramate for migraine treatment in the pediatric patients aged 12 to 17 years (29). In adults, topiramate proved efficacious in the preventive treatment of migraine with and without aura in episodic and chronic form, and excessive use of symptomatic drugs (24, 30). In a parallel single-blinded randomized clinical pediatric trial, the efficacy and safety of topiramate (3 mg/Kg/day) and propranolol (1 mg/Kg/day) were compared, and the results showed that topiramate was more effective in reducing the monthly frequency, severity, duration and disability of the headache. Topiramate was superior to

propranolol in reducing the frequency of the attacks by at least 50% (respectively 82 vs. 62% of patients) (31). In another study by the same authors, recruiting a population of 100 pediatric patients (mean age of 10.46 ± 2.11 years) treated with topiramate (3 mg/kg/day), the frequency and duration of headache attacks reduced from 15.34 ± 7.28 to 6.07 ± 3.16 attacks and from 2.28 ± 1.55 to 0.94 ± 0.35 h, respectively. The pediatric migraine disability assessment score was reduced from 32.4 ± 9.3 to 15.5 ± 6. Side-effects were seen in 21% of the patients, including hyperthermia, anorexia and weight loss, and drowsiness (32). Authors concluded that topiramate could be considered a safe and effective drug for migraine therapy in pediatric patients (32). As reported above, Kim et al. showed that the response rate, retention rate and the rate of side effects were not significantly different between flunarizine and topiramate (10). In a randomized, double-blind clinical study of 44 migraineurs (aged 4–15 years), Ashrafi et al. compared the efficacy and safety of cinnarizine and topiramate in the prevention of pediatric migraine. The primary endpoint was the monthly frequency of migraine. Measures of secondary efficacy were the intensity of monthly migraine and a response rate higher than 50%. During the double-blind phase of the study (week 8), both patients treated with cinnarizine and topiramate showed a statistically significant 50% responder rate (cinnarizine: 55%, $p = 0.004$; topiramate: 50%, $p = 0.001$). Also monthly migraine intensity reduced in both groups ($p < 0.001$) (33). After 12 weeks of treatment, a significant reduction of monthly migraine frequency was observed for both cinnarizine and topiramate ($p < 0.05$) with no significant differences between groups (33).

The CHAMP study failed in showing any superiority of treatment with amitriptyline or topiramate, as compared to placebo (23).

Verapamil, levetiracetam and zonisamide have also been studied for treatment of migraine, but there is a lack of evidence supporting their use in the pediatric population (34).

## Serotonin Modulators

Pizotifen was studied in a placebo controlled trial conducted on 37 subjects (6–15 years), at a dosage of 1.5 mg/day, with a significant reduction in attack frequency and mild side effects (35). In a subsequent controlled study, the dose of 1–1.5 mg, administered for 6 months in 47 migraine subjects (7–14 years), was not more effective than placebo. Side effects consisted of sedation, increase in appetite and weight (36). In the last decade, no trials have been conducted on pizotifen from which definitive efficacy data can be drawn.

Cyproheptadine was first evaluated in an open study at a dosage of 0.2–0.4 mg/kg/day for 3–6 months, achieving a good improvement (68%) and a remission (21%) of the headache (37). This substance, usually used in younger patients, can have the same side effects as pizotifen, that is drowsiness, weight gain and tenderness. Contraindications consist of asthma, glaucoma and peptic ulcer.

Despite the lack of definitive data, Pizotifen is the only licensed drug in Italy for prophylaxis in migraineurs children (7, 38).

A recent survey on treatments for primary headaches, in 13 specialized juvenile Italian headache centers, reported that pizotifen (1 mg/kg/day) was one of the most efficacious (82% perceived by patients) and tolerated treatments for migraineurs children (12).

# NON-PHARMACOLOGICAL APPROACH

## Nutraceutics and Herbals

The term Nutraceutical refers to all those compounds that derive from "nutrition" and "pharmaceutical." It refers to the study of active ingredients of food origin that are supposed to have a beneficial function on human health. More active ingredients can be combined with each other to enhance their effects. The term "herbal" refers to all those compounds, such as plants or derivatives of medicinal plants. In general, nutraceutics are chosen to have fewer side effects and a more "natural" approach to the treatment of the disease. These products are generally marked in the absence of validative studies (efficacy and safety) (39).

Data on the use of nutraceuticals and herbals are available for the following molecules: magnesium, riboflavin, coenzyme Q10, butterbur, feverfew and hydroxytryptophan (40).

The rationale of the use of nutraceutics in the treatment of migraine is based on the involvement of these substances in anti-inflammatory or antioxidant molecular pathways or in the mitochondrial energy activity (39).

Despite the widespread use in clinical practice, there are few RCTs available for these substances. Thus, the level of evidence remains low (level b or c), as well as the recommendation (class III).

The few RCTs on magnesium, riboflavin, feverfew, and hydroxytryptophan are prior to 2010 and have not shown conclusive results (41–43).

A more recent RCT investigated the effect of coenzyme Q10 (100 mg/day) in the prophylaxis of pediatric migraine (44). A significant reduction in migraine frequency ($p < 0.001$), severity ($p < 0.05$), and duration ($p < 0.05$) was equally found in the placebo and CoQ10 groups (44).

Ginkolide B, in combination with other nutraceutics, was studied in pediatric open label studies. It is a platelet-activating factor (PAF) receptor antagonist, and would modulate pro-inflammatory mechanisms (42). One open-label trial verified the efficacy of a complex of ginkgolide B, coenzyme Q10, riboflavin and magnesium (doses not specified) in pediatric patients with migraine. After 3 months of treatment, the number of attacks in a month was significantly lower (45). Another open label study compared the efficacy of a combination of ginkgolide B (80 mg/day), coenzyme Q10 (20 mg/day), riboflavin (1.6 mg/day), and magnesium (300 mg/day) with a complex of L-tryptophan (250 mg/day), 5-hydroxytryptophan (50 mg/day), vitamin PP (9 mg/day), and vitamin B6 (1 mg/day) for a treatment period of 6 months. Both combinations were associated with a significant reduction of frequency of headache attacks with a major effect for the complex including ginkgolide B (39, 40).

## Onabotulinumtoxin A

The use of botulinum toxin proved promising in adult patients with migraine, and in particular, its efficacy has been recognized

in adults with chronic migraine. However, there are few retrospective data regarding the pediatric experience. This treatment is particularly useful in patients that present side effects of oral drugs or in drug resistant migraine (46). In a retrospective case series study, Ahmed et al evaluated tolerability and efficacy of botulinum toxin type A in the treatment of pediatric chronic headache (47). The study included 10 patients with age ranging from 11 to 17 years who received a standard 100-unit dose of onabotulinumtoxin A. The patients had attempted an average of 8.0 ± 2.40 SD therapies prior to botulinum toxin. A decrease in headache intensity was observed in 40% of patients and 20% noted a decrease in headache frequency with global improvement in quality of life (47). In 2012, Kabbouche et al. reviewed the data of pediatric patients who had received Onabotulinumtoxin A (average dose of 188.5 units±32 with a minimum dose of 75 units and maximum of 200) for chronic migraine in a pediatric headache center from 2004 to 2010. A significant reduction in the frequency of the headache attacks was observed (from 27.4 headache per month±5.2 to 21.3 ± 10.3; $p < 0.05$), while there was no significant change in the severity of pain (48).

## Complementary Therapies

Non-pharmacological treatment for pediatric migraine includes cognitive behavioral therapy, acupuncture, and biofeedback.

As stated above, cognitive behavioral therapy (CBT) proved effective in treating chronic forms of migraine, although the best results were observed when this therapy was combined with pharmacological therapy, in particular amitriptyline (25–28).

A randomized study conducted on 135 patients (mean age 14.4 ± 2) with chronic migraine evaluated the efficacy at 20 weeks of the combined treatment with CBT plus amitriptyline vs. headache education plus amitriptyline. The authors found that 47% of patients in the CBT plus amitriptyline group had less than four headache days per month compared to 20% in the headache education plus amitriptyline group ($p < 0.005$). At 12 months post treatment, 72% of patients in the CBT plus amitriptyline group had less than four headache days per month compared to 52% in the headache education plus amitriptyline group ($p < 0.05$) (27).

In a recent RCT, two different training programs [multimodal cognitive-behavioral training (CBT) and applied relaxation (AR)] were compared with an educational intervention (EDU). Sixty-five children and adolescents with at least 2 attacks of headache per month were assigned to one of the three group. The main outcome endpoints included changes in headache frequency, intensity and duration, responder rate (50% reduction of headache frequency), and number of the attacks needed to treat (NNT). All three groups presented a significant reduction in headache frequency and duration, while no significant differences were observed in the intensity of pain. The group of CBT showed the highest responder rates (50% reduction of headache frequency) after 4 weeks of treatment (63 vs. 32% of AR and 19% of EDU). However, at follow-up after six months, no significant differences were found in the NNTs (CBT: 63%, AR: 56%, EDU: 55%). At follow-up assessment, the effects of the headache frequency remained stable in all groups (49).

There is only limited data on the use of acupuncture for the treatment of pediatric migraine. While efficacy of acupuncture in reducing the frequency of the attacks of migraine was shown in earlier studies (50, 51), no further result has been published in the last 10 years.

Although there are no studies in the last decade on the efficacy of biofeedback for the treatment of pediatric migraine, a recent meta-analysis resumes the main findings on this topic (52). It concludes that biofeedback showed efficacy in reducing attack frequency ($p < 0.001$) and duration ($p < 0.001$), and intensity of pain ($p < 0.001$). However, biofeedback demonstrated no adjuvant effect when combined with other behavioral and no more benefits than pharmacological treatment (52). It is worth to be underlined that data on biofeedback comes only from retrospective studies or pilot studies (53–55).

Overall, non-pharmacological treatment for migraine can be a valid alternative for selected patients.

The choice of a non-pharmacological therapy should be reserved for patients who have failed drug therapies or, as a first line treatment, in patients who cannot tolerate the side effects of drugs. However, most published studies on non-pharmacological treatments have been carried out in adults, while definite results in children and adolescents are still lacking. Therefore, further confirmation with rigorous randomized controlled trials is mandatory for the majority of these approaches (56).

# FURTHER CONSIDERATIONS AND FUTURE PROSPECTIVES

The main novelty of the last decade in the prophylaxis of pediatric migraine comes from the results of the CHAMP study. This study showed that pharmacological treatments, such as amitriptyline and topiramate, do not differ from placebo. Three main issues are raised by this study:

- *First, placebo effect proves very powerful in pediatric age (about 60% of patients), thus it should be considered as a fundamental therapeutic resource.* Placebo response rate is known to be high in pediatric migraine studies (25). The high therapeutic efficacy of placebo should not be considered only as a threat to the success of clinical studies, but it represents a therapeutic possibility in the treatment of pediatric migraine. Research should be addressed to further investigate the exact mechanisms connected with high placebo response rate in children with migraine. A higher knowledge in this field could allow us to use placebo as a non-harmful and effective treatment.
- *The CHAMP study get us to wonder whether the use of pharmacological treatment is still allowed.* Although the CHAMP results must be taken into account, we cannot forget the results of other RCTs reviewed in the present study and supporting the efficacy of some pharmacological treatments. Moreover, CHAMP trial did not consider some dynamics that may influence the course of migraine independently of drug therapy, such as psychological factors mostly linked to school attendance. It is known that untreated young migraineurs have a lower frequency of attacks in summer months, while

they suffer more after the start of the school (57, 58). This means that whether the efficacy of placebo is measured in a favorable (e.g., from February to August), or unfavorable (e.g., from August to February) period can influence the response to therapy. In conclusion, we believe that CHAMP study should induce us to be even more rigorous in the treatment selection, considering the evidence-based data of efficacy and safety as being crucial for the therapeutic choice.

- *Lastly, we must underline that there is no drug available in pediatric age with exclusive indication for migraine treatment* (59). From this point of view, there is high expectation for the use of calcitonin gene-related peptide (CGRP) inhibitors (CGRP-r). The large trials conducted in the adult population (60, 61) have led Food and Drug Administration (FDA) to give the green light to commercialization of these drugs (Erenumab; Galcanezumab; Fremanezumab) in USA. The same drugs have been recently approved from European Medicines Agency (Erenumab; Galcanezumab). Although results from trials in children and adolescents are not available yet, the Pediatric and Adolescent Headache special interest group of the American Headache Society proposed recommendations on the use of these agents for pediatric headache disorders (62). The authors suggested that the use of CGRP receptor antagonists could be considered in postpubertal adolescent patients with frequent migraine attacks ($\geq$8 headache days/month), who have moderate to severe disability associated with migraine (PedMIDAS score $\geq$30) and have failed $\geq$2 preventive therapies. For younger patients, who are refractory to multiple preventive therapies, CGRP receptor antagonists may also be considered with proper monitoring (e.g., bone health, linear growth, weight/BMI, infections) (62).

## AUTHOR CONTRIBUTIONS

LP and FU took care of the selection of the articles and wrote the manuscript. RM and ST contributed to the selection of articles. MF and GS contributed to the methodology. FV supervised the final manuscript. MV designed and supervised the work.

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# Gender Differences in the Clinical Presentation of Cluster Headache: A Role for Sexual Hormones?

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**Introduction:** Cluster Headache (CH) is a well-characterized primary headache that mostly affects men, although a progressive decrease in the male-to-female ratio has occurred over time. Available, but partly discordant, data on gender-related differences in CH suggest a more marked overlapping with migraine features in female subjects. The aim of this study is to carefully evaluate the female/male distribution of the typical migraine-associated symptoms and of other features of the disease in a large and well-characterized clinical population of CH subjects.

**Materials and Methods:** We enrolled consecutive CH patients regularly followed at the tertiary Headache Science Center of the IRCCS Mondino Foundation of Pavia (Italy) who attended the Center for a CH bout between September 2016 and October 2018. The subjects were requested to fill in a semi-structured questionnaire focused on the presence of migraine-associated symptoms, familiarity for migraine and, for women, the relationship of CH onset with the reproductive events of their life. These data were compared and integrated with those recorded over time in our clinical database, including demographics and clinical characteristics. The primary outcome was the gender distribution of subjects who satisfied ICHD-III criterion D for migraine-associated symptoms. The secondary outcomes were represented by the gender distribution of individual migraine-associated symptoms and of other disease features included in the questionnaire and/or in the clinical database.

**Results:** Data from 163 males (mean age 41.46 ± 10.37) and 87 females suffering of CH (mean age 42.24 ± 11.95) were analyzed. We did not find a different distribution between sexes as regards the primary outcome measure (F 73.6%, M 65.6%, $p = 0.200$). However, when we analyzed the occurrence of individual symptoms, nausea and osmophobia were reported more frequently by women ($p = 0.048$, $p = 0.037$, respectively). Ptosis and nasal congestion were predominant in females ($p = 0.017$ and $p = 0.01$, respectively), while enlarged temporal artery was more frequently reported by men ($p = 0.001$). Distribution of pain across the head tended to be larger in women, extending more frequently to the zygomatic ($p = 0.050$), parietal ($p = 0.049$), and frontal ($p = 0.037$) regions. Women had a longer mean attack duration ($p = 0.004$) than men. In CH women the onset of disease often corresponded with moments of important changes

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in the levels of sexual hormones (menarche, post-partum, menopause). Concomitant thyroid diseases and psychiatric disorders were observed more frequently in women than in men, while snoring and smoking habit was reported by a higher percentage of men than women.

**Conclusion:** We confirmed the presence of distinct gender-related differences in CH and added some novel information that lends credibility to the hypothesis of a closer phenotypical similarity between CH and migraine in the female sex. These observations are relevant for advancing our knowledge on CH pathophysiology, as well as for a more refined diagnostic framing and improved management of the disease.

**Keywords: cluster headache, female, sex-differences, gender-related variables, migraine**

## INTRODUCTION

Cluster Headache (CH) is a rare but phenotypically well-characterized primary headache disorder. According to the diagnostic criteria defined by the International Classification of Headache Disorders (ICHD-III) (1) CH is a strictly unilateral headache occurring in attacks lasting 15–180 min and characterized by very severe pain commonly localized in the orbital or sovraorbital area, associated to ipsilateral autonomic symptom (ptosis or miosis, lacrimation, eyelid oedema, sweating, conjunctival injection, lacrimation, nasal congestion, rhinorrhea) or a sense of restlessness, or both. CH exists in two forms: the episodic one being the most prevalent, and the chronic one, more rare, which may evolve from the episodic or less frequently start *de novo*.

Originally considered a male disorder, CH has been described more and more frequently in women. The data from the literature have indeed pointed to a progressive reduction in the male-to-female ratio over the years, with a transition from the initial 5–7:1 reported 40 years ago (2, 3), to the more recent 2–3:1 (4, 5). The reasons behind the ratio modification are not clear but several factors have been proposed. *In primis,* an improvement in the diagnostic accuracy, which has led to the correct diagnosis of CH in women previously misdiagnosed as migraine sufferers (4). Another possible explanation is represented by the profound changes occurred in our society in the last decades leading to the redistribution among sexes of environmental and life habit factors likely to play an etiological role in CH, e.g., stress, alcohol and smoking habit, etc. (6).

Although CH attacks are very clear-cut, studies over the years have revealed gender differences (7). In a retrospective study, Rozen et al. (8) reported an increased occurrence of nausea and vomiting in CH women, a finding that has been recently confirmed in an large internet survey (9). Manzoni et al. reported an increased occurrence of nausea but not of vomiting in CH females (10). On the contrary, Dong et al. failed to detect any difference between sexes in a relatively quite large clinical population of CH subjects, which however included a small number of women (11). CH men seem more likely to have cranial autonomic symptoms (9, 12), although these seem to be less pronounced in the subjects who experience a late onset of the disease (12). In contrast with these findings, a larger Danish survey has reported an increased occurrence of ptosis, eyelid edema in CH women when compared to men (4). Interestingly, episodic CH shows a bimodal distribution of age onset in women, with the second peak occurring around the menopause (13, 14). Other studies have suggested an association between cluster headache and hormonal fluctuations, with the report of more severe CH attacks during the menstrual period, a tendency toward the improvement during pregnancy and a possible negative effect of oral contraception and hormonal replacement therapy (5, 15, 16). Finally, CH women tend to have a positive family history of migraine more frequently than CH men (2, 10).

Though intriguing, all these findings remain so far inconclusive, hence the need to further investigate gender-related differences in CH. The primary aim of this study was to focus on the occurrence during CH attacks of migraine-associated symptoms—strictly defined according to ICHD-III criterion D for migraine without aura—in a representative population of CH subjects regularly followed at our Headache Center.

## MATERIALS AND METHODS

We conducted a cross-sectional evaluation of the consecutive CH subjects regularly followed at the tertiary Headache Science Center of the IRCSS Mondino Foundation of Pavia (Italy) who attended the Center for a CH bout in the period between September 2016 and October 2018. The study was evaluated and approved by our local Ethics Committee (which in 2016 was held jointly with San Raffaele Scientific Institute—Milan, Italy).

During the visit, which was performed by a neurologist with a long expertise in headache, the patients' diagnosis was confirmed against the ICHD-III criteria for CH. After signing the informed consent for the study, patients were asked to fill in a semi-structured questionnaire specifically devised for the study. The questionnaire focused on the presence of migraine-associated symptoms (nausea, vomiting, phonofobia, photophobia, and osmophobia), familiarity for migraine and, for women, relationship of CH onset with reproductive events (menarche, menstrual cycle, duration of periods, use of contraceptive pills, number of pregnancies, menopause).

During the visit we also collected data regarding the characteristics of the attacks (frequency, duration, severity,

associated symptoms, response to acute treatment) and of the most recent bouts (frequency, duration, response to preventive treatments). These latter pieces of information were compared with the data available from the same patients in our clinical database in order to minimize recall biases. Our clinical database indeed is continuously updated at each patient visit and contains general demographics (age, sex, occupation, lifestyle factors), information regarding cluster headache type, characteristics and recurrence of attacks (location, severity, duration, and frequency of pain, associated autonomic symptoms, associated migraine-like symptoms, circadian and circannual frequency, duration), acute and preventive treatments and their effect, and documentation of concomitant diseases. In case of a >10% discrepancy between the data collected during the visit—with the questionnaire and/or the direct interview—and the data reported in the database, the issue was discussed with the patient, who was then invited to consider the additional information before elaborating the final answer.

In this way, we used a hybrid methodology that combines cross-sectional data collected with the standardized questionnaire and during the actual study visit, with the review of data stored in our clinical database.

Our primary outcome was the difference in the number of female and male CH patients who satisfied ICHD-III criterion D for migraine-associated symptoms during their attacks. More specifically the criterion D was satisfied when "nausea and/or vomiting" or "photophobia and phonophobia" were present during CH attacks. Secondary analyses evaluated the difference in gender distribution of individual associated symptoms and as well as of all the other items included in the questionnaire and collected during the visit (see above).

## Statistical Analysis

The sample size was calculated with the Open Source Epidemiologic Statistics for Public Health (www.openepi.com). For the primary outcome we considered meaningful a difference between groups of at least a 20% based on previous reports and our clinical experience. The following parameters were used: two-sided confidence level: 95%; power 80%; ratio of sample size: 2; expected percent of male with outcome: 55%; expected percent of female with outcome: 75%; odds ratio: 2.43; risk/prevalence ratio: 1.36; risk/prevalence difference: 19.80. According to Fleiss method, the minimum suggested sample size was 228 (152 for male patients, and 76 for female patients).

For the statistical analysis, we used SPSS (Statistical Package for the Social Sciences) for Windows, version 21.0.

For quantitative variables the Kolmogorov-Smirnov test showed a normal distribution.

For quantitative variables, differences between females and males were tested with Student's *t*-test for unpaired samples. For categorical data, differences between females and males were examined with $\chi 2$ tests, or Fisher exact test where appropriate. Quantitative variables are presented as: mean ± standard deviation (95% confidence interval for mean). An alpha of 0.05 was used for all statistical tests.

# RESULTS

We collected and analyzed data from 250 CH patients, 163 males (mean age 41.46 ± 10.37) and 87 females (mean age 42.24 ± 11.95), with a male to female ratio of 1.9:1. Most of our patients suffered from episodic CH (90.4 %) (**Table 1**).

We did not find statistically significant difference between male and female subjects in terms of satisfaction of ICHD-III criterion D. Indeed the criterion was satisfied by a quite high percentage of subjects in both sexes: F 73.6%, M 65.6%, $p = 0.200$. When we analyzed gender-related distribution of individual migraine-associated symptoms, we observed that nausea and osmophobia were reported more frequently by females than males: nausea F 55.2 vs. M 40.6%, $p < 0.05$; osmophobia F 21.8 vs. M 12.3%, $p < 0.037$. Vomiting, photo and phonofobia, were numerically more frequent in female patients, but the difference did not reach a statistically significant level (**Table 2** and **Figure 1**).

As regards local autonomic symptoms, most of them were equally distributed in women and men, with the exception of ptosis and nasal congestion, which were more frequently reported in female sufferers: ptosis F 90.8 vs. M 79.8%, $p = 0.017$; nasal congestion F 65.5 vs. 47.9%, $p = 0.005$), and enlarged temporal artery, which was instead more frequently reported in males (F 12.6 vs. M 30.1%, $p = 0.001$) (**Table 2** and **Figure 1**).

Pain location was typically orbital/retro-orbital in both sexes, without significant difference ($p = 0.337$), but women experienced a more widespread distribution of pain, as demonstrated by the higher percentage of female CH subjects who reported pain also in the zygomatic (F 25.3 vs. M 16%, $p = 0.050$), parietal (F 14.9 vs. M 7.4%, $p = 0.049$), and frontal (F 49.9 vs. M 36.8%, $p = 0.037$) areas.

CH women had a longer mean duration of untreated attacks than men (79.5 ± 48.9 vs. 64.5 ± 32.6 min, $p = 0.004$). We also detected a pattern toward a higher number of attacks/24 h in the female sex, which however did not reach a statistical significance (F 2.28 ± 1.06 vs. M 2.00 ± 0.98, $p = 0.053$).

The bout frequency was similar between sexes, with the majority of patients reporting only one per year. No gender differences were detected in the duration of bouts, which lasted 45.7 ± 29.6 days in men and 43.4 ± 23.8 days in women ($p = 0.553$) (**Table 2**).

A family history of migraine was quite frequent in both sexes, numerically more prevalent in women as compared to men (68.6

**TABLE 1** | Demographic variables: comparison between sexes.

| | | Male (M) | Female (F) | *p*-value |
|---|---|---|---|---|
| N | | 163 | 87 | – |
| Age (years) | | 41.46 ± 10.37 (39.9–43.1) | 42.24 ± 11.95 (39.7–44.8) | 0.594 |
| Type of CH (%) | Episodic | 90.8% | 89.7% | 0.466 |
| | Chronic | 9.2% | 10.3% | |

*CH, Cluster Headache; M, Male; F, Female.*

**TABLE 2 |** Clinical variables: comparison between sexes.

| | | Female (F) | Male (M) | *p*-value |
|---|---|---|---|---|
| *N* | | 87 | 163 | |
| CH onset (years) | Total | 26.3 ± 12.7 (23.6–29.0) | 27.9 ± 9.9 (26.4–29.4) | 0.282 |
| | Episodic | 25.6 ± 12.7 (22.8–28.5) | 27.3 ± 9.5 (25.8–28.9) | 0.265 |
| | Chronic | 32.1 ± 11.8 (26.3–41.2) | 33.5 ± 12.7 (26.5–40.5) | 0.793 |
| Family history of migraine (%) | | 68.6% | 58.5% | 0.119 |
| Family history of cluster headache (%) | | 4.7% | 9.1% | 0.203 |
| Bout frequency/year | | 1.03 ± 0.8 (0.9–1.2) | 1.03 ± 0.7 (0.9–1.1) | 0.957 |
| Mean Duration of active phase (days) | | 43.4 ± 23.8 (37.9–48.8) | 45.7 ± 29.6 (41.1–50.7) | 0.553 |
| Duration of attacks (min) | | 79.5 ± 48.9 (69.0–91.9) | 64.5 ± 32.6 (60.9–71.6) | **0.004** |
| Attack frequency / day | | 2.28 ± 1.06 (2.0–2.5) | 1.78 ± 0.98 (1.8–2.2) | 0.053 |
| **Distribution of migraine-associated symptoms** | | | | |
| ICHD-III criterion satisfied | | 73.6% | 65.6% | 0.200 |
| **Individual migraine-associated symptoms** | | | | |
| Nausea | | 55.2% | 40.6% | **0.048** |
| Vomiting | | 26.4% | 18.2% | 0.095 |
| Photophobia | | 71.3% | 66.3% | 0.254 |
| Phonophobia | | 58.6% | 51.5% | 0.174 |
| Osmophobia | | 21.8% | 12.3% | **0.037** |
| **Cranial parasympathetic autonomic features** | | | | |
| Lacrimation | | 94.3% | 95.7% | 0.410 |
| Miosis | | 5.7% | 10.4% | 0.156 |
| Ptosis | | 90.8% | 79.8% | **0.017** |
| Conjuntival injection | | 89.7% | 86.5% | 0.306 |
| Rhinorrea | | 67.8% | 58.3% | 0.090 |
| Nasal Congestion | | 65.5% | 47.9% | **0.005** |
| Prominent temporal artery | | 12.6 % | 30.1% | **0.001** |

*CH, Cluster Headache; M, Male; F, Female.*
*In bold: significant p-values.*

vs. 58.5%, $p = 0.119$). By contrast, the family history of CH was reported more frequently by male patients than females, but again the difference did not reach a statistically significant level (9.1 vs. 4.7%, $p = 0.203$). The mean age at CH onset was 27.9 ± 9.9 in men and 26.3 ± 12.7 in women ($p = 0.282$). Patients with episodic CH had a mean age at onset of 26.8 ±10 (27.3 in men and 25.7 in women), while those with the chronic form had a mean age at onset of 33.0 ± 12.1 (33.5 in men and 32.1 in women) (**Table 1**).

Interestingly, 61% of female patients reported occurrence of the onset of disease during periods of abrupt fluctuations of sexual hormones: 16 reported their onset of disease at menarche, 8 during the post-partum, 23 at the menopause, and 6 during the intake of birth control pills.

Concomitant thyroid diseases (F 23 vs. M 1.8%, $p = 0.001$) and psychiatric disorders, namely depression and anxiety (F 17.2 vs. M 9.2%, $p = 0.04$) were more frequent in women than men, while snoring and smoking habit were more frequent in men: M 53.4 vs. F 19.5% ($p = 0.00$) and M 67.5 vs. F 49.4% ($p = 0.005$), respectively.

# DISCUSSION

CH is considered a predominant male disease, although several studies have pointed to a progressive decrease of the male-to-female ratio over time (2–5). This observation has stimulated, in recent years, speculations and investigations on the possible factors involved in this phenomenon and on the possible occurrence of differences in CH presentation between the sexes.

Available data on gender-related differences in CH are interesting but limited and partly discordant. This study provides additional information that overall suggests a relevant overlap of symptoms between migraine and CH, which is more marked in the female sex.

As regards our primary outcome, we did not find a significant difference in gender-related distribution of migraine-associated symptoms, as evaluated with the ICHD-III D criterion for migraine without aura. Indeed, the difference between sexes (8%) was lower than the value that we considered clinically meaningful defined (20%), but it seems worth noting that the criterion was satisfied in the large majority of CH subjects. Interesting findings were derived from our secondary analyses, which confirmed some previous data on the clinical presentation of CH and its gender differences, but also provided new pieces of information that are relevant for an improved understanding of CH pathophysiology.

## Associated Symptoms

In our study, women more frequently experienced nausea and osmophobia during cluster attacks. The presence of migraine-associated symptoms has already been reported in CH patients (17, 18), although in a lower percentage of patients than our population, but only a few studies have looked into gender differences. A previous Italian study noted an increased occurrence of nausea in CH women (10), Rozen et al. (8, 9) and Bahra et al. (5) reported an increased occurrence of nausea and vomiting in women with CH. The findings were not confirmed by Dong et al., whose population, however, included a very limited number of women (11).

Here, in a large and well-characterized clinical CH population followed at a tertiary referral center, we confirm the presence of nausea as a distinctive gender-related sign in female CH. In addition, we report a higher incidence of osmophobia in female CH subjects, which, to the best of our knowledge, has never been investigated in this detail so far. Osmophobia has a high specificity for migraine (19) and has been proposed as an additional feature for migraine diagnosis. Our finding regarding osmophobia may thus reinforce the hypothesis that CH and migraine shares some pathophysiological mechanisms, especially in the female sex.

In our population, ptosis and nasal congestion were more frequently reported in women, while an enlarged temporal artery was predominant in males. Published data on a gender-related differential expression of autonomic symptoms are inconclusive.

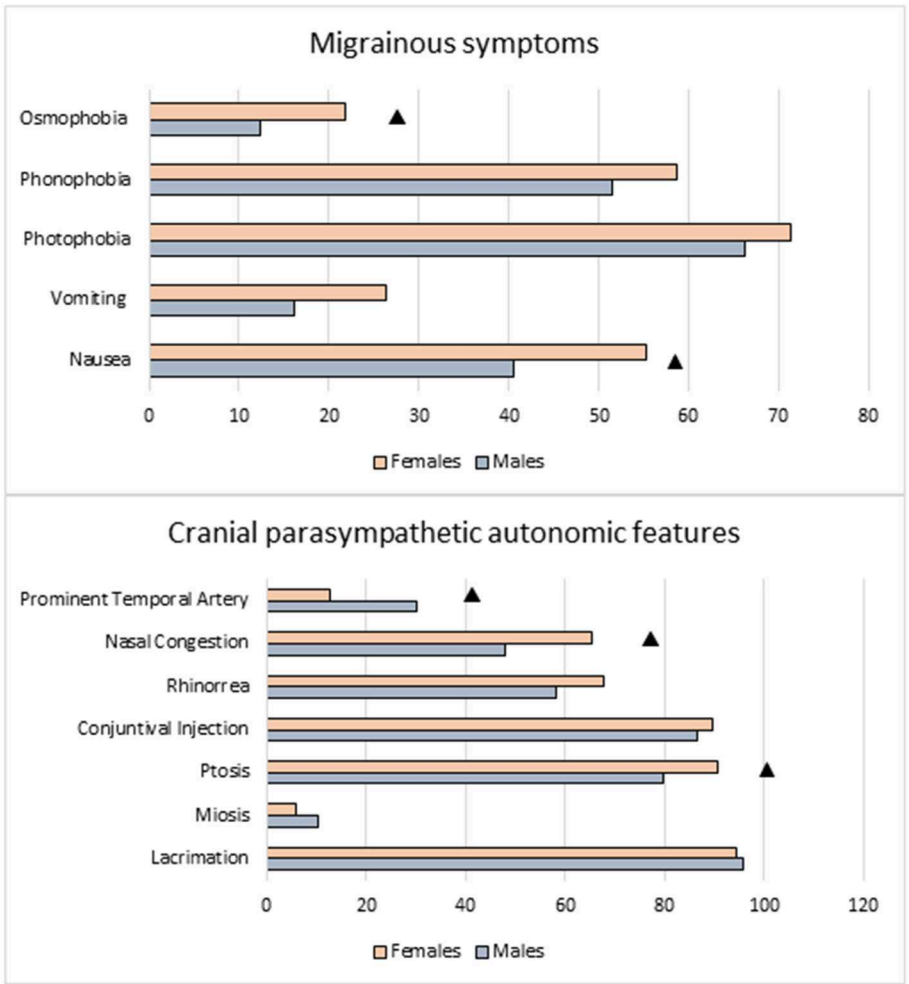


**FIGURE 1 |** Migraine-like and trigeminal autonomic symptoms: comparison between sexes. ▲ Females vs. Males: $p < 0.050$.

Rozen et al. (8) reported a tendency toward a higher prevalence of ptosis and miosis in CH women. In a more recent study, other Authors confirmed the increased occurrence of ptosis in CH women, together with a higher occurrence of eyelid edema (4). Male CH subjects seem to experience more frequently than women lacrimation and facial sweating (9, 20). In partial agreement with our findings, another Italian group noted a lower occurrence of ptosis, tearing and nasal congestion in a subgroup of males with late onset of CH (12), to suggest a possible role of age on the differential expression of associated symptoms.

## Duration of CH Attacks

We confirmed that women had a significantly longer duration of untreated CH attacks than men, as previously noted by Kudrow (21). This is partially in contrast with others studies (8–10) that reported a tendency toward a shorter attack duration in females together with a similar daily attack frequency. These contradictory findings may reflect recall biases, even more so in retrospective studies using questionnaires mailed to patients. In line with this, a recent Danish study that compared retrospective and prospective descriptions of attack features found that, when compared to men, women often report longer and more severe attacks with more severe migrainous symptoms (22). In our study, we collected cross-sectional data from an ongoing bout, that were matched with the data recorded over time in our hospital database from patients that were regularly followed at our headache center and were used to fill in a headache diary during their active bouts. The weekly reports of these diaries are recorded and stored in our clinical database. Altogether, we believe that our hybrid methodology provides a considerable degree of robustness to the data collected, while minimizing as much as possible the occurrence of recall biases and the variability between different bouts.

## Pain Location and Extension

In our study both sexes reported the classic pain location within the distribution territory of trigeminal V1 (orbital or retro-orbital areas), but we noted that women more frequently reported a higher widespread distribution of pain that extended over the zygomatic, parietal and frontal regions. This is consistent

with previous reports of a frequent location of pain outside V1 trigeminal area in CH women (5–9). Furthermore, in line with our findings, in a very recent Korean study, focused on the assessment of clinical gender characteristics in subjects with CH in a prospective registry, women more frequently experienced pain in the forehead, compared to men (46.3 vs. 30.1%, $P = 0.043$) (20).

### CH Onset

The mean age at CH onset was similar in both sexes, even though we observed a trend toward an earlier occurrence in female subjects, as reported in literature (8, 23–25). More importantly, we report that a non-negligible percentage of CH women associate the onset of their disease with reproductive events of their life, such as menopause, menarche, pregnancy, or post-partum and hormonal contraceptives (in order of prevalence), thus suggesting a possible role for important hormonal shifts in the pathogenesis of CH.

Previous studies looked at the fluctuations in the prevalence of the sex distribution across ages: Kudrow reported an increased frequency of CH in women when they reached the age of fifty or sixty (2), and Ebkom and Mosek confirmed an initial onset of CH after the menopause (14, 26). This finding has been recently confirmed, mostly for the chronic form of CH, by Manzoni et al. (27), who also noted an increased occurrence of CH in women before the age of 14. These observations fit well with our findings regarding the role of hormones in CH women when considering that several studies have reported a tendency toward a bimodal distribution of age at onset of CH in women (2nd−3rd decade and 5th−6th decade) (8, 25), while CH onset in men manifests peaks during the 3rd decade (8).

In a large population of CH patients compared with migraine females, van Vliet et al. (15) found that menstruation, use of oral contraceptive, pregnancy, and menopause had a much smaller influence on CH attacks than on migraine, as reported by other earlier studies (2, 10). Therefore, unlike migraine, no definitive relationship between CH and female reproductive phases of life could be established in a recent review of the literature (16). Hence, the importance of our present findings to lend further evidence on the existence of a hormonal link between CH female population and disease onset, could stimulate further studies, possibly prospective, to better evaluate the role of hormonal changes in CH pathophysiology.

### Comorbidities—Associated Conditions

A body of literature has connected psychiatric comorbidities, especially depression, anxiety, and aggressive behavior to CH patients, without any gender differences (28, 29). Whether psychiatric comorbidities in CH is the consequence of the psychological effect of the extreme intensity of the attacks or it represents a manifestation of a common pathophysiological process is still a matter for debate. The increased prevalence of depression and anxiety observed in our female population is in line with a previous large internet American survey (9) and with a very recent Korean study (20), although we cannot rule out the possibility that the higher incidence may be simply related to the higher epidemiological impact of psychiatric conditions in the female sex. More disease-specific seems the increased prevalence of thyroid disease in our female population, when considering that the prevalence of thyroid disorders in the Italian population is lower: 10% according to the official data from www.portaledellasalute.it. It is interesting to observe that thyroid disease is associated to poorer response to standard treatments for mood disorders (30). To the best of our knowledge, our study is the first to ever report this triple connection CH-depression-thyroid disease in CH females. Though available evidence does not warrant any pathophysiological speculations at this moment, it seems nonetheless important to consider both these comorbidities when deciding the choice of the preventative treatment in women suffering from CH.

The higher occurrence of snoring and smoking in men is in line with previous results (7, 31–33). Smoking prevalence has been consistently reported to be significantly higher in CH patients, compared to general populations (48–68%), and also when stratifying by sex (34); this close relation between smoking habit and cluster headache has been identified as a contributing factor of the disease in predisposed individuals.

## CONCLUSION

We confirmed the presence of distinct gender-related differences in CH and added some novel information that may be relevant to advance our knowledge of the pathophysiological mechanisms underlying the disease, to improve the diagnostic process and possibly lead to an improved management of CH.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of IRCCS San Raffaele Scientific Institute, Milan, Italy. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MA and CT designed the project. MA wrote, reviewed, and edited the article. LA and AP collected data from the questionnaire and the database. MA, RD, EP, and GS enrolled patients. RD and RG performed statistical analysis. CT reviewed and revised the manuscript. All authors contributed to the planning and development of the study, supervised by MA. All authors read and approved the final manuscript.

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REVIEW
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# Caffeine and Primary (Migraine) Headaches—Friend or Foe?

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**Background:** The actions of caffeine as an antagonist of adenosine receptors have been extensively studied, and there is no doubt that both daily and sporadic dietary consumption of caffeine has substantial biological effects on the nervous system. Caffeine influences headaches, the migraine syndrome in particular, but how is unclear.

**Materials and Methods:** This is a narrative review based on selected articles from an extensive literature search. The aim of this study is to elucidate and discuss how caffeine may affect the migraine syndrome and discuss the potential pathophysiological pathways involved.

**Results:** Whether caffeine has any significant analgesic and/or prophylactic effect in migraine remains elusive. Neither is it clear whether caffeine withdrawal is an important trigger for migraine. However, withdrawal after chronic exposure of caffeine may cause migraine-like headache and a syndrome similar to that experienced in the prodromal phase of migraine. Sensory hypersensitivity however, does not seem to be a part of the caffeine withdrawal syndrome. Whether it is among migraineurs is unknown. From a modern viewpoint, the traditional vascular explanation of the withdrawal headache is too simplistic and partly not conceivable. Peripheral mechanisms can hardly explain prodromal symptoms and non-headache withdrawal symptoms. Several lines of evidence point at the hypothalamus as a locus where pivotal actions take place.

**Conclusion:** In general, chronic consumption of caffeine seems to increase the burden of migraine, but a protective effect as an acute treatment or in severely affected patients cannot be excluded. Future clinical trials should explore the relationship between caffeine withdrawal and migraine, and investigate the effects of long-term elimination.

**Keywords: headache, caffeine, adenosine, dopaminergic, histaminergic, circadian, yawning, withdrawal**

> *"I am not acquainted with any agents which equal these substances* (coffee and tea, aa), *in the power of removing headache without leaving inconvenient results. And as their physiological action is so purely cerebral, restoring the intellectual faculties, and ministering to the sensations of well-being, as well as lessening any sad emotions, we have here an adequate presumption, were any required, that this headache is seated in the nerves, which are immediately related with the molecular action of the brain."*
>
> John Addington Symonds, the Goulstonian lecture for 1858 (1)

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## INTRODUCTION

It is well-know that caffeine can stimulate wakefulness, increase concentration and decrease the sensation of fatigue (2), but how does it affect one of the most common human agonies (3), headaches? Caffeine is commonly used as analgesic adjuvant for the acute treatment of pain. However, despite the flattering description of the efficacy above, the general analgesic effect of caffeine seems at best modest (4). Besides, chronic consumption of it may have a flip side, withdrawal may cause caffeine withdrawal (5, 6), a syndrome including symptoms such as drowsiness, headache, mood-changes, difficulty focusing, nausea and muscle pain/stiffness (**Box 1**). Even small amounts of caffeine have been shown to suppress this (5). Headache can occur independently of the other symptoms (7), and *Caffeine-withdrawal headache* (**Box 2**), properly described in the 1940s (8, 9), is recognized as an own diagnostic entity by the International Classification of Headache Disorders (ICHD-3) (10). Results from both experimental and clinical studies indicate a high rate of caffeine withdrawal in the modern society, that may even be underestimated (5). The real world extent and clinical (physiological and psychological) importance are not well-known (11). The dual effects of caffeine in headaches, relieving on one side and triggering on the other side, make caffeine a very interesting substance in headache pathophysiology research. Still, the prevailing theory of the withdrawal headache is basically a rebound vasodilation due to caffeine's vasoconstrictive effect (12), at large a too simplistic theory that is not in conformity with modern views of headache pathophysiology (13). The caffeine withdrawal syndrome, which includes symptoms suggestive of the prodromal phase of migraine, is hardly of peripheral origin. Based on the current established knowledge on migraine pathophysiology, this narrative review aims to explore how caffeine, which has profound biological effect as an adenosine receptor antagonist (14), may influence pathways involved in headaches, with a particular focus in migraine.

**BOX 1** | Diagnostic criteria for *Caffeine-withdrawal* according to the DSM-5.

A. Prolonged daily use of caffeine.
B. Abrupt cessation of caffeine use, or reduction in the amount of caffeine used, followed within 24 h by 3 or more of the following symptoms:
   a) Headache.
   b) Marked fatigue or drowsiness.
   c) Dysphoric or depressed mood, or irritability.
   d) Difficulty concentrating.
   e) Symptoms of nausea, vomiting, or muscle pain/stiffness.
C. Clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. Not due to the direct physiological effects of a general medical condition and are not better accounted for by another mental disorder.

**BOX 2** | Diagnostic criteria for *Caffeine-withdrawal headache* according to the ICHD-3.

A. Headache fulfilling criterion C.
B. Caffeine consumption of >200 mg/d for > 2 weeks, which has been interrupted or delayed.
C. Evidence of causation demonstrated by both of the following:
   1. Headache has developed within 24 h after last caffeine intake
   2. Either or both of the following:
      a) Headache is relieved within 1 h by intake of caffeine 100 mg.
      b) Headache has resolved within 7 days after caffeine withdrawal.
D. Not better accounted for by another ICHD-3 diagnosis.

## MATERIALS AND METHODS

The article is based on unsystematic searches in PubMed with terms like "caffeine and headache," "caffeine withdrawal," "adenosine and headache," with more, and on own knowledge of older and recent literature on migraine. A discretionary selection of publications was made.

## RESULTS AND DISCUSSION

### Caffeine and Adenosine

Caffeine is a major constituent of coffee and tea, but also naturally occur in guarana, cola nuts, cocoa, and several other plants (2). Soft drinks, energy drinks, and dietary supplements are also important sources, in particular among the younger population (15). The typical level in an ordinary cup of coffee varies between 50 and 100 mg (2). After oral ingestion, caffeine is rapidly and completely absorbed (99%), with peak plasma concentration reached usually within an hour (16, 17). Caffeine passes through all biological membranes, including the blood-brain barrier, and is distributed in all body fluids (18). It is metabolized by the cytochrome P450 system, the isoenzyme CYP1A2 responsible for 90% of caffeine clearance, and in adults it has a typical half-life of 5 h (19). Numerous factors, including a broad and variable genetic basis (20, 21), modify caffeine clearance.

The actions of caffeine in doses relevant to human consumption (50 to several 100 milligrams) are through antagonism of G protein-coupled purinergic (P1) receptors, more specifically the adenosine receptors (ARs), preferentially the $A_1R$ and $A_{2A}R$ (18, 22, 23). The human genes encoding for these two receptors are $ADORA_1$ and $ADORA_2$, respectively. Single nucleotide polymorphisms (SNPs) in $ADORA_2$ appear to play a role in an individual's subjective response to caffeine (24–26).

Adenosine is found in every cell in the form of adenosine 5′-diphosphate (ADP) or adenosine 5′-triphosphate (ATP). It is continuously formed by breakdown of ATP and the physiological effects of adenosine are directly related to the metabolic activity (27). It modulates the activity of numerous cells, including mast cells, smooth muscle cells, platelets, and neurons (28). In the nervous system, adenosine appears to play an important role in

modulating brain neurotransmitter release, locomotion, reward, sleep/wakefulness, cognition, and analgesia (14). Adenosine is neither stored nor released as a classical neurotransmitter, but may exert marked effects on neuronal excitability through G protein-coupled adenosine receptors (AR) $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$ in both the peripheral and the central nervous system. The $A_1R$ is virtually found everywhere in the brain. In general it mediates tonic inhibition, especially through inhibition of glutamate release from presynaptic nerve endings (27). The $A_{2A}R$ is concentrated in dopamine-rich regions (18), especially on striato-pallidal GABAergic neurons (23), where it exerts excitatory effects on neurons and contributes to inhibition of motor activity (29). The $A_{2A}R$ actions are complicated by the fact that it co-localize and form heteromeres with dopamine-, cannabinoid-, and glutamate receptors (23). The roles of $A_{2B}R$ and $A_3R$ are not as well understood, but it appears that adenosine has a lower affinity for these receptors compared to $A_1R$ and $A_{2A}R$ receptors. Their activation is more likely to happen under conditions of hypoxia during which there is increased adenosine availability (30, 31).

## The Caffeine's Effects Are in General Opposite to the Effects of Adenosine

The brain levels of adenosine in cats and rodents in resting physiological condition have been estimated to 30–200 nM/L, concentrations sufficient to activate $A_1$, $A_{2A}$ and possibly $A_3$ receptors if numerous on the cells (30, 31), but in most tissues the adenosine signaling is not very prominent (14). Even low concentrations of caffeine, such as 1–10 μM achieved after consumption of a single cup of coffee, result in significant antagonism of adenosine $A_1$ and $A_{2A}$ receptors and may result in increased alertness (32).

### Sleep and Arousal

An important function of adenosine in the CNS is its involvement in the sleep/arousal system. Adenosine has sleep-promoting effects (33). During sustained and prolonged wakefulness the extracellular adenosine accumulates in the basal forebrain cholinergic region, and it declines slowly during recovery sleep (34). This rise of adenosine reduces the cortical activity by direct $A_1R$ modulation of the corticopetal system, the major extrathalamic relay of the reticular ascending system (RAS) to the cortex, and indirectly via $A_{2A}R$-modulation of the hypothalamus (35). It has been shown, for instance, that infusion of a specific $A_{2A}R$ agonist into the subarachnoidal space, inducing NREM sleep, will cause increased activity in the ventrolateral-preoptic (VLPO) area of the anterior hypothalamus and a reduced activity of the tuberomammilary nuclei (TMN) in the posterior hypothalamus as seen by increased number of Fos-positive neurons (36). Caffeine-induced wakefulness depends on adenosine $A_{2A}$ receptors (37). It seems that blocking of $A_{2A}R$ in nucleus accumbens inhibits the GABAergic output to the lateral hypothalamus, the TMN and the locus coeruleus (LC), causing activation and the major arousal effect of caffeine (38). Genetic knockout models have shown that both $A_1$ and $A_{2A}$ receptors are involved in mediating the sleep-promoting properties of adenosine in the brain (39). Moreover, the arousal effects of caffeine seen in wild-type animals are blunted in *ADORA*$_{2A}$-knockout mice (38). It is therefore conceivable that adenosine receptor ligands could be used as normal cognitive enhancers or sleep promoters.

### Pain

Experimental data indicate that caffeine at doses between 25 and 100 mg/kg have intrinsic antinociceptive effects (40). To extrapolate data derived from animal experiments to humans, it is generally assumed that giving 10 mg/kg caffeine to a rat corresponds to giving 3.5 mg/kg (about two to three cups of coffee) to a 70 kg human (18), although such an assumption may be premature given the higher metabolic rate of rodents and hence the shorter half-life of caffeine in their system. Based on this assumption, caffeine at doses around 600–1,200 mg may be needed to achieve anti-nociception in caffeine-naive humans. As an adjuvant caffeine (≥65 mg) can potentiate the analgesic properties of other medications (4, 41) by 40% (42), and there is a possibility that caffeine alone in such low doses might have intrinsic analgesic properties for some types of pain, such as headache. Ward et al. employed a double-blind placebo-controlled crossover design to assess whether caffeine alone (60 and 130 mg) has independent analgesic effects on non-migrainous headaches, and found equivalent effects to acetaminophen (43). Caffeine, and combination analgesics with caffeine may be used in tension-type headache, but frequent use is not recommended due to the risk of developing medication-overuse headache (41). It is also used in hypnic headache (44) and post-lumbar puncture headache (45), but probably not to the analgesic effect *per se*. In hypnic headache the effect of caffeine is claimed to go "beyond the usual analgesic effects observed in other headache disorders" (44). Hypothalamic effects, as described in the next section, may play a role. The effect on post-lumbar puncture headache, which has "not conclusive evidence" according to a Cochrane report from 2013 (45), has been attributed non-analgesic mechanisms, including adenosine-mediated vasoconstriction (46, 47).

Analgesic properties of caffeine may be hard to reconcile with analgesic effects of adenosine. When the concentrations of adenosine increase during stressful conditions, including noxious stimulation, it may reduce pain (48), and adenosine receptor agonists produce antinociception in a variety of pain models (49). Mice lacking $A_1R$ show signs of increased anxiety and hyperalgesia, and the antinociceptive effects of adenosine seen in wild-type mice (50) cannot be shown (48). $A_1R$ is present on peripheral sensory nerve terminals and in lamina II of the spinal cord, and it has been suggested that peripheral anti-nociception achieved by activation of $A_1R$ occurs via blocked release of endogenous calciton gene-related peptide (CGRP) (51) and substance P (52). Under inflammatory conditions, experimental data indicate that the analgesic effect is by reducing hypersensitivity through a central mechanism (49, 53). This is in accordance with human studies, showing that intrathecal injection of adenosine does not cause antinociception to acute thermal or chemical stimuli, but reduce allodynia from intradermal capsaicin injection (53). Adenosine may also increase pain mediated by $A_{2A}$ receptors (28). Experimental data

indicate that there are pro-nociceptive $A_{2A}$Rs on the peripheral nerve terminals (28, 54), and that blocking of these may cause antinociception (40). Caffeine in doses normally consumed by humans can probably act as an analgesic, partly through blockade of $A_{2A}$ receptor (40). Central dopaminergic mechanisms may also be involved. Like other analgesics (55), caffeine increases dopamine release (18), probably via inhibition of $A_{2A}$R (56). Notably, $A_{2A}$ receptor antagonists did not affect dural meningeal vasodilatation caused by CGRP in a rat model (57). The recent marketing of CGRP receptor antibodies and the development of CGRP antagonists has been considered a major breakthrough in the migraine field (58). Despite the fact that $A_{2A}$R does not appear to be located in the spinal cord, a specific inhibition of the activity of the intermediolateral cell column (the sympathetic system) was shown by Brooks et al., indicating that the $A_{2A}$R may be located on presynaptic inhibitory terminals of descending fibers from higher brain centers (59).

It is clear that both adenosine and blockade of adenosine by caffeine may cause anti-nociception. Since the nanomolar affinities of adenosine for $A_1$R and $A_{2A}$R are almost the same, this indicates a fine balanced modulation of the pain processing (30), making it very difficult to predict the net effects of caffeine on nociception in humans.

### Caffeine Overuse and Withdrawal

Caffeine causes increased well-being in small to moderate doses and its overuse has the potential to cause physical dependence (60). The caffeine dependence syndrome has been recognized by the World Health Organization as a behavioral disorders due to frequent use of caffeine (61). Considerable evidence suggests that this is due to enhanced dopaminergic activity, especially via blocking of $A_{2A}$R causing increased dopamine release in the ventral striatum (nucleus accumbens) (26). However, there is a compensatory up-regulation of the adenosine system, causing increased functional sensitivity to adenosine during withdrawal (5, 10). These molecular changes appear to increase functional sensitivity to adenosine during caffeine abstinence, and play an important role in the behavioral and physiological effects produced by caffeine withdrawal (5, 10). In humans, caffeine withdrawal following chronic consumption may give rise to a time-limited syndrome comprising of headache, drowsiness, mood-changes, difficulty focusing, nausea, and muscle pain/stiffness (**Box 1**) (5, 6, 62). Consequently, caffeine consumption may be maintained to avoid withdrawal symptoms. Caffeine-withdrawal headache is a headache developing within 24 h after regular consumption of caffeine in excess of 200 mg/day for more than 2 weeks, which has been interrupted. According to the ICHD3 classification, this type of headache resolves spontaneously within 7 days in the absence of further consumption (10).

Further, repeated exposure to caffeine may lead to rapid development of tolerance, preferentially to the $A_1$-blocking effect, and in some cases it even may result in opposite effects than expected (14). By drinking three to four cups of coffee regularly around 50% $A_1$ and $A_{2A}$ receptor occupancy can be achieved for several hours, and many of the actions of caffeine are due to this AR blockade (18).

**TABLE 1 |** Caffeine withdrawal symptoms and migraine prodromal symptoms.

| Frequent symptoms reported in different studies (underlined are the major criteria in the withdrawal syndrome) | Juliano (7) Caffeine withdrawal symptom, % (*) | Quintela (64) Migraine prodromal symptom, % ($n$ = 100) | Schoonman (65) Migraine prodromal symptom, % ($n$ = 461) |
|---|---|---|---|
| Tiredness/fatigue/asthenia | 21–56 | 31–38 | 47 |
| Drowsiness/sleepiness | 18–59 | 35 ("somnolence") | NA |
| Difficulty concentrating | 27–50 | 36 | 28 |
| *Mood change* | | | |
| Depression/sadness | 16* | 39 | 18 |
| Irritability | 21 | 42 | 28 |
| Yawning | 21–43** | 40 | 36 |
| Nausea | 3–33*** | 24 | 29 |
| *Sensory hypersensitivity* | | | |
| Phonophobia | NR | 37 | 36 |
| Photophobia | 14 (*blurred vision*****) | 44 | ****** |
| Anxiety | 10–29 | 46 | NA |
| Craving | 28–43******* | 15 | 17 |
| Thirst | NR | 17 | NR |
| Muscle pain/stiffness | 43 | NA | 35 (stiff neck) |

*Data were collected from 57 experimental and nine survey studies. **21% reported in one survey and 43% in one experimental study. According to Juliano et al. (7) further research is needed to determine the validity of yawning as a withdrawal symptom. ***3–21% in surveys and 10–33% in experimental studies. ****Blurred vision was demonstrated in only 2 of 11 experimental studies. *****Photophobia was excluded in this study. ******Reported in 2 of 2 experiments. According to Juliano et al. (7) further research is needed to determine the validity of craving as a withdrawal symptom. NA, not assessed, NR, Not reported.*

## The Migraine Syndrome

Migraine is a disorder characterized by recurrent attacks of head pain associated with hypersensitivity to sensory stimuli (10) and when full-blown it involves different phases (63). (a) A *prodromal or premonitory phase* hours prior to the onset of the headache with a broad range of symptoms (**Table 1**), which patients can reliably recognize, and thus predict the occurrence of a headache, (b) Transient neurological symptoms, known as *migraine aura* (typically visual alterations), just before the actual headache starts (in migraine with aura patients), (c) An intense *headache*, typically involving only one site of the head, accompanied by nausea, sensitivity to light, noise and smells, (d) The *postdrome phase* following the resolution of the headache and characterized mainly by fatigue and inability to concentrate (66). Understanding the mechanisms involved in the transition from a headache-free to the headache state is crucial in understanding the underlying cause of headaches and the development abortive drugs. In many primary headache disorders, but especially migraine (67, 68), several external factors have been reported to trigger this transition; stress, bright light and lack of sleep are probably the most commonly reported (69). The periodicity of migraine attacks strongly indicates involvement of internal clock mechanisms in its pathophysiology (70).

## Does the Migraine Prodromal Syndrome and Caffeine-Withdrawal Syndrome Share the Same Symptoms?

The prodromal, or premonitory, phase of migraine is usually defined as the period 2–48 h prior to aura or migraine headache with symptoms (**Table 1**) indicating an attack. Thirty to 90% of migraine patients report such a phase (71). In a prospective electronic diary study, Giffin et al. found that yawning, increased emotionality and concentration difficulties (difficulty reading and speaking) were the most reliable predictors (72). In another study by Schoonman et al., where patients had to choose among 12 specific premonitory symptoms, the most frequently reported were fatigue, phonophobia and yawning. Increased emotionality and concentration difficulties were reported by almost one third (10). Kelman found that tiredness, mood change and gastrointestinal symptoms (nausea) were the most frequent reported symptoms, and that yawning was rarely reported (69). However, there were specific questions about the former categories, but none about the latter symptom. In a prospective survey of 100 unselected patients, Quintela et al. (64) found that anxiety, phonophobia, irritability, unhappiness and yawning were the most common reported prodromal symptoms, whereas asthenia, tiredness, somnolence and concentration difficulties were the most common symptoms reported in the postdromal phase. Due to different methodologies used to identify symptoms, it may be difficult to compare results from different studies, but interestingly, the most prevalent symptoms reported are much the same as the symptoms of the caffeine-withdrawal syndrome. In **Table 1** findings from the very good and comprehensive review about caffeine withdrawal symptoms made by Juliano et al. (7) are compared with findings from two of the mentioned surveys. These data strongly suggest that the same or similar pathophysiological pathways may be involved in both the prodromal phase of migraine and the caffeine withdrawal syndrome. However, sensory hypersensitivity, a cardinal migraineous feature (10), does not seem to be part of the caffeine withdrawal syndrome. This may nevertheless be due to an underlying thalamocortical dysrhythmia (73), that appears to be specific for migraine. The overlap of symptoms may also be due to the fact that caffeine withdrawal may act as a trigger of a migraine attack in migraine patients?

## Is the Caffeine Withdrawal Headache Similar to Migraine?

Headache as a caffeine withdrawal symptom has been frequently studied (7), and in some case reports and experimental studies it has been characterized. However, premorbid primary headache syndromes, even in otherwise solid papers (74), are seldom reported. It seems though that subjects with a history of frequent headaches (75) are at increased risk, and that migraineurs and subjects who experience withdrawal headache share some comorbidity such as major depression and anxiety (5). To "produce experimental headaches which would be more physiological than experimental histamine and nitrite headaches," Dreisbach in 1940 gave a number of non-habitual coffee drinkers capsules of 10–12 grains (650–780 mg) of caffeine daily for 1 week and then withdrew the treatment. On the day of withdrawal, almost all developed a moderate to severe headache. In migraineurs, "typical migraine syndromes" ensued (8). Unfortunately, the report does not give sufficient data for valid interpretation. Three years later, however, he and a colleague reported 38 similar trials in 24 persons of whom 5 had migraine. In 21 of the trials the subjects experienced their worst headache ever, in 11 it was definite but not severe, and in 6 there was slight or no headache. All of the migraineours experienced caffeine withdrawal headache "quite different from the migraine syndrome." It is reason to question this statement. The headache was accompanied by nausea in 4 and vomiting in 1. In 4 subjects the headache was consistently accompanied by serous rhinorrhea. This may indicate cranial autonomic symptoms, frequently seen in migraine (76). No information about other accompanying symptoms was given. It was argued that 2 subjects had headache localized to the opposite side of the head from their usual migraine. In one subject, who used to have left-sided frontal migraine, it occurred bilaterally and was localized in the occipital region. Our clinical experience, however, confirms that is not unlikely for migraine to switch sides or to be bilateral rather than unilateral. Scotomas, regularly experienced by 3 migraine patients, did not occur. Scotoma, is a symptom usually described in migraine with aura patients and to date no headache-induced substance has been found to consistently trigger migraine aura. Further, two of the migraineurs had migraine attacks on the height of the caffeine stimulation, and in one of these subjects this reoccurred in a second trial. In these trials, and in later studies the headache is described to typically evolve gradually (60, 77, 78), being diffuse (79), throbbing (9), severe (60, 80), intensified with exercise (77), and Valsalva manoeuver (9) and having a mean duration for 2–3 days (81).

Despite being claimed that caffeine-related headache has a non-migrainous clinical presentation (82), the description of caffeine withdrawal headache given in the literature is not very different from migraine. With the high prevalence of migraine (83), and the lack of information on pre-existing headache in many studies taken into consideration, there seems to be a clear shortcoming in the knowledge when it comes to separating caffeine withdrawal as a migraine trigger from caffeine withdrawal headache *per se*.

## Does Caffeine Cause Headaches?

Caffeine itself is rarely reported as a trigger of migraine (68), but as noticed by Driesbach it probably has the potential (9). As an important cause of *medication-overuse headache* (84) caffeine has been strongly incriminated, partly due to the withdrawal syndrome encouraging patients to continue their overuse (85–87). In a double blinded, randomized, placebo-controlled, 12 week crossover study of 45 healthy subjects who habitually consumed 4 to 6 cups of coffee a day (81),withdrawal caused headaches during the first or second day in 19 (42%) (81). The ratio of subjects reporting headaches during caffeine weeks and during non-caffeine weeks was 1. However, what is obvious, but not commented by the authors, is that when the withdrawal weeks (week 1 and 7) are removed the ratio increases to 7.7. Subjects also reported improved sleep during the non-caffeine weeks.

Caffeine-overuse may even cause chronic headache in children (15). Hering-Hanit and Gadoth reported 36 children with chronic headache, none with a prior history of migraine, who consumed excessive amounts of caffeine in the form of cola drinks (in average ∼190 mg caffeine/d), and of whom 33 completely recovered after gradual withdrawal. Three children continued to have infrequent migraine without aura after withdrawal (15). In general, most chronic daily headaches in children appear to be migraine related (88). Caffeine has also been a suspected risk factor for episodic migraine evolving into *chronic migraine*, which in essence is defined as headache on ≥15 d/month for >3 months (66). A strong positive correlation between caffeine consumption and both episodic (89) and chronic migraine (90) has been found. In a retrospective population-based study, Scher et al. found that dietary and medicinal caffeine consumption appears to be only a modest risk factor for developing chronic daily headache, including chronic migraine (91). Overall, no relationship between current caffeine consumption and headache was found, neither was that found in two further studies (92, 93). However, in the cross-sectional population-based study by Boardman et al., headache sufferers were more than twice as likely to be heavy caffeine consumers compared to non-sufferers (92). In a Norwegian large-scale cross-sectional population-based study only a small association between high consumption of caffeine (>540 mg/d) and infrequent migraine was found (94). In this study chronic headache was more prevalent among individuals with low caffeine consumption (mean of 125 mg/d).

In general, chronic consumption of caffeine seems to be associated with increased migraine burden. Either chronic caffeine increases the risk of migraine *per se*, or in contrast, has beneficial effects in patients severely affected by migraine. Whether long-term elimination of caffeine diet will reduce the migraine burden has not been studied previously.

## Pathophysiological Aspects

In 1990, Welch et al. substantiated the concept of migraine as a state of central neuronal hyperexcitability (95). Later it has become clear that some sort of cortical dysexcitability may even be present between attack (73). The mechanisms underlying the abnormal regulation of cortical function and the cyclic features of migraine remain largely unknown, but older, largely intuition based theories of hypothalamic dysfunction as the cause of periodicity of attacks have in recent years had a renaissance, especially after brain imaging evidence of hypothalamic activity both in the prodromal (96) and the pain phase (97) of migraine. There is accumulating indirect evidence for a pivotal role of hypothalamus in many primary headache disorders (98–102). The discovery of a mutation in a clock-gene (CK1δ) causing so called familiar advanced sleep phase syndrome was strongly linked to migraine both clinically and experimentally (103). Mice engineered to carry the mutation exhibit lower threshold for cortical spreading depression (CSD), the phenomenon underlying aura (see beneath), and increased sensitivity to noxious stimuli after nitro-glycerine treatment. A clear relationship between sleep and migraine exists (104), and caffeine can certainly disrupt sleep (105). Disrupted sleep-patterns predispose, and sleep *per se* protects against migraine (100). The risk of getting a migraine attack is low during sleep, but spikes in the morning, especially when associated with insomnia (106), and peaks in the afternoon probably due to work-related stress (107). Menstrual migraine and weekend headaches are also clear examples of the periodicity. The higher prevalence of migraine on weekend mornings reported was attributed to caffeine withdrawal by Couturier et al. (108).

### Adenosine Can Cause Headache

It is now accepted that the pain during a migraine attack is perceived to be felt on intracranial structures, such as, the dura mater and intracranial vasculature (109, 110). Activation of the ophthalmic division (V1) of the trigeminal nerve is regarded primarily responsible for causing the pain in primary headache disorders (102). Upon activation of the trigeminal fibers, several neuropeptides such as substance P, neurokinin A, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase activating peptide (PACAP) and nitric oxide (NO) are released into the innervated tissue (dura mater and meningeal vessels) with the potential to cause neurogenic inflammation. Migraine has been attributed to such a local sterile meningeal inflammation (111), possibly involving release of histamine from mast cells (112). Activation of the trigeminal fibers is referred to as "trigeminovascular activation" and is considered the key event in causing headache. Accumulating data support a pivotal role of CGRP in migraine (58), and when given intravenously a delayed migraine-like headache will be induced in a large fraction of migraineurs but not in controls (113). CGRP causes only a modest, around 10%, vasodilation which is unlikely to activate perivascular trigeminal afferents (114). In general, the former "vascular theory" of migraine has been abandoned by several experiments showing that vasodilatation of neither extracranial- or intracranial/meningeal arteries is neither necessary nor sufficient to cause migraine headache (113). However, vasodilatation may worsen pain in an already sensitized pain network. The trigeminal fibers, that carry the sensory information from the intracranial structures, project on second-order neurons within the trigeminocervical complex (TCC; trigeminal nucleus caudalis, C1 and C2 spinal levels). These neurons give rise to the main ascending trigeminothalamic pathway that carries sensory information to third order neurons in the thalamus, before processing the information to higher cortical areas (115).

As with other recognized experimental triggers of migraine (116), such as CGRP, it is hard to conceive how adenosine itself, not passing the blood-brain barrier readily (14), could act centrally to elicit a migraine cascade. Further, adenosine has been ascribed peripheral anti-nociceptive effects by blocking the release of CGRP (51). Nevertheless, increased levels of adenosine in the blood during migraine attacks have been reported (117), and headaches are often reported when adenosine is used intravenously in cardiology (118). The $A_{2A}$ agonist regadenoson does also induce headache frequently (119). The drug dipyramidole, which increases the level of adenosine by inhibiting adenosine re-uptake, can cause headache as an adverse

effect in one third of the patients. It has been also reported to increase the migraine frequency in migraine patients (120) and to elicit migraine in an experimental setting (121). In addition, intravenous application of adenosine can trigger migraine attacks (122). Based on this, antagonizing adenosine by caffeine may theoretically have an abortive effect in migraine. The problem is, as mentioned earlier, that chronic caffeine consumption in humans seems to increase the migraine burden. Supported by experimental findings (123, 124), an increased vascular tone due to up-regulation of adenosine receptors and compensatory increased levels of plasma adenosine have been suggested mechanisms underlying this risk (125, 126). Increased cerebral blood velocities have been measured after caffeine withdrawal (12), and there is no doubt that caffeine has the opposite effect causing a decrease in cerebral blood flow due to central vasoconstriction. However, the neuronal-vascular coupling is complex and in a functional magnetic resonance imaging study (fMRI), reduced cerebral perfusion induced by caffeine was independent of previous caffeine consumption (127). In a study of the rat middle meningeal artery, caffeine was found to reverse the relaxing effect of adenosine, mainly mediated by blocking of $A_{2A}$R (128). Whether vasoconstriction significantly contributes to the effects of caffeine in withdrawal headache remains unclear since vasodilation hardly is a primary cause of the headache. As mentioned earlier, blocking of $A_{2A}$R does not seem to affect neurogenic vasodilation (57). Further, discrepancy between different studies has been observed. In an experimental cat migraine model, the $A_1$R agonist GR79236 had a dose-dependent inhibitory effect on trigeminovascular nociceptive transmission (129). This effect was explored in humans. In 12 healthy female volunteers the adenosine $A_1$ receptor agonist GR79236 was shown to inhibit trigeminal nociception, as measured by the blink reflex (130). Further studies in pigs did not show any effect on capsaicin-induced CGRP release (131), and in a multicenter evaluation of the adenosine agonist GR79236X in patients with dental pain after third molar extraction, no efficacy was shown when compared to placebo (132).

## Caffeine Has the Ability to Induce Cortical Excitability, and May Even Predispose for CSD?

Traditionally, the migraine aura has been considered a distinctive phase, but probably it is a consequence of the same or parallel mechanisms that triggers the pain (133, 134). It is believed that the migraine aura itself is caused by so called cortical spreading depression (CSD) (135). CSD is a wave of neuronal depolarisation linked with depressed neuronal activity and blood flow changes (136). In animals, CSD can quite readily be induced by focal cortical stimulation for example by applying $K^+$ (137). Despite being accepted by most experts as a plausible mechanism of migraine aura and even headache in migraine without aura ("silent spreading depression") it has been difficult to prove that CSD actually is the underlying mechanism in humans. It also remains enigmatic how CSD could be triggered in patients during migraine. So called calcium waves in astrocyte networks is a speculative (138), but alluring mechanism that could offer an alternative explanation to the classical CSD. Recent advances support the idea that astrocytes could play an important role in spreading depression initiation (139). ATP-receptors (P2 receptors) are both necessary and sufficient for propagation of calcium waves (140), and thus has the potential to initiate and sustain a heighten state of neuronal excitability. Caffeine may possibly modulate this susceptibility (141). An $A_{2A}$ receptor gene haplotype has been reported to be associated with migraine with aura (142), but the findings should be reproduced. There appears to be only one published case where intravenous adenosine precipitated migraine aura (122). Activation of $A_1$R has been shown to increase $K^+$ conductance and thus hyperpolarize CNS neurons (50). It is thus more plausible that acute caffeine could increase the susceptibility to CSD, and pre-published reports supported that (143, 144). However, caffeine exposure did not affect the susceptibility to CSD in a recent study of mice (82). Curiously, CSD can induce yawning in rats (145).

## Yawning Indicates Hypothalamic Alterations

It has been demonstrated that activating the $A_1$R on TMN-neurons increases NREM sleep (146), and that blocking them on hypocretinergic neurons of the lateral hypothalamus increases wakefulness (147). Both neurotransmitter systems have been suggested to play an important role in migraine (148, 149). The TMN of the posterior hypothalamus has been suggested to play a role in the initial phases of a migraine attack and to be responsible for the morning occurring migraine attacks (148, 150). During drowsiness and normal recovery sleep the firing from the histaminergic neurons are reduced or absent, but during wakening and arousal they fire, allegedly the most wake-selective firing pattern identified to date (151). Adenosine may well have a protective effect against migraine during sleep, but during non-recovery sleep and wakefulness disrupted homeostasis may cause increased histaminergic firing predisposing for headaches. It has been postulated that yawning is the manifestation of a switch in brain states from "default mode" to an "attentional mode" by increasing clearance of adenosine (152). It remains to be proven in experimental models that increased histaminergic firing sensitizes the TCC.

Yawning may also be indicative of an individual's inability to properly maintain thermal brain homeostasis (153). If yawning occurs without being associated with tiredness, it may perhaps indicate a thermoregulatory dysfunction. In the study of Schoonman et al. of the premonitory symptoms of migraine there was no correlation between "sleep problems" and yawning (Spearman's rank correlation of 0.024) (65). Further, Jacome described 3 migraineurs with compulsive yawning as a prodromal symptom, independent of fatigue and drowsiness (154). In a recent cross-sectional study, 45.4% of 339 migraineurs reported repetitive yawning during migraine attacks (155). Sleepiness was significantly more often reported in patients with yawning compared to those who did not yawn during their migraine attacks.

Thermoregulation and sleep are interrelated. It is well-known that yawning has a clear circadian pattern parallel to the rise in body and brain temperature, normally occurring most often before sleep onset and after waking (153). A hypothesis that migraine attacks serve to restore the brain temperature has recently been put forward (156). In general, the neurons of

the brain are very sensitive to variations in the temperature (157). Short visual stimulation of the rat invokes a rise in temperature over the visual cortex (158), and during prolonged (4 min) visual stimulation in man, an increase in regional cerebral blood flow caused an average decrease in temperature by 0.2°C (159). Histamine has been shown to mainly excite heat-sensitive neurons in the anterior hypothalamus, causing hypothermia. In contrast to adenosine (160), caffeine increase body temperature parallel to arousal during circadian misalignment in humans (161). Injecting neuropeptide orexin-A into the rat PVN elicits a cortical arousal response followed by yawning (162), and injecting it into the ventromedial hypothalamus it induces hyperthermic reactions (163).

Based on the fact that migraineurs show a lower threshold for central dopamine receptor activation than normal subjects (164), and that exogenously administered dopamine receptor agonists may produce some symptoms experienced in the prodromal phase of migraine such as drowsiness and yawning, dopamine may play an important role in migraine pathophysiology. This theory is consistent with the idea that caffeine withdrawal symptoms are due to increased sensitivity of adenosine, causing increased drowsiness (due to increased disinhibition of VLPO sleep-active neurons reducing histaminergic tone) and excessive yawning due to increased dopaminergic tone. It has been shown that injecting dopamine (D2) agonists into the paraventricular nucleus of the hypothalamus (PVN) of rats, increases local nitric oxide (NO) production and thereby activates central oxytocinergic neurotransmission, inducing yawning (165). However, microinjection of other substances into the PVN, such as histamine (166) and nitroglycerine (167) also induces yawning. As distinct from dopamine agonists, that seldom induces headache (168), both donors of NO and histamine are established triggers in pharmacological models of migraine (116). Glyceryl trinitrate has even been shown to both induce prodromal symptoms of migraine (169) and activate the hypothalamus (96).

### Caffeine Can Alter the Circadian System and Neuronal Excitability

It has been proposed that the hypersensitivity to light during migraine may be exerted by intrinsically photosensitive retinal ganglion cells (ipRGCs) through a pathway that modulates the activity of dura-sensitive thalamocortical neurons (170). The ipRGCs entrain the circadian rhythms and influence sleep/wakefulness (171). Adenosine, through $A_1R$ inhibition of glutamate release, seems to fine-tune the circadian system through gating of both photic and non-photic input to the superior biological clock, the suprachiasmatic nucleus (27). Giving an $A_1R$ agonist during midday, phase-shift mimicking the effect of a 3 h sleep deprivation procedure may be achieved in hamsters (172). Caffeine increases light responsiveness of the mouse circadian pacemaker (173), and it has been shown that chronic exposure to caffeine interferes with the ability of the SCN to entrain normally to light, and that it potentiates phase-delays (174). Further, it has been claimed that glasses that filter out blue light can reduce the frequency of migraine attacks with short periods of usage (175), and in an experimental study light stimulation with the peak wavelength of ipRGC induced migraine attacks more frequently than extensive-wavelength (176). Based on this, it may be speculated that caffeine interferes with the ability of the biological clock to entrain to light, causing increased excitability in pathways involved in migraine headache, including the dura-sensitive thalamocortical neurons.

The pharmacology of both the TCC and the thalamus provides interesting insights into migraine pathophysiology, as they are prominent sites of action of migraine specific medication-triptans (177), of clinically active preventives (178, 179) and of other potential anti-migraine compounds (180). The modulation of sensory transmission in the thalamus, assumes further significance as it has been shown not only to be a pivotal area for the development of sensory hypersensitivity to light during migraine (170), but could also participate in the development of hypersensitivity to noise (181), and non-cranial allodynia that is frequently seen in migraine patients (182). Experimental data show that presynaptic adenosine $A_1$ receptors on thalamocortical neurons can mediate reduced cortical excitability directly (183). When interacting with serotonin, adenosine may also modulate thalamic sensory gating during sleep (184). If the caffeine withdrawal syndrome is due to increased sensitivity to adenosine, this may explain why sensory hypersensitivity is not a symptom of caffeine withdrawal. It is tempting to speculate that caffeine can increase the sensory hypersensitivity that accompanies migraine headache.

Both the TCC and the thalamus have reciprocal direct or indirect connections with multiple brainstem, midbrain and cortical nuclei that control the excitability of the ascending trigeminothalamic pathway (185). These brain nuclei make up the descending pain modulatory system (115), which is a powerful regulator of pain-related activity along the ascending trigeminothalamic pathway. Disruption of normal endogenous descending modulatory tone may play a critical role in primary headache disorders, but what really alters the excitability of the ascending trigeminothalamic pathway in a manner that a migraine attack develops in susceptible individuals, remains to be revealed. As mentioned earlier, central dopaminergic mechanisms (via $A_{2A}R$) may be involved. In an experimental headache model, stimulation of the dopaminergic A11 significantly inhibited peri-MMA dural and noxious pinch evoked firing of neurons in the TCC, an effect that was blocked by a D2 receptor antagonist (186). Whether the A11 neurons have adenosine receptors, and whether caffeine induces release of dopamine from the A11 nucleus, is not known.

## CONCLUSION

The current opinion is that caffeine both can relieve and trigger headaches. It has to be clarified whether caffeine withdrawal triggers or merely resembles the migraine syndrome. The nature of the caffeine withdrawal syndrome needs to be better understood. In assessing the clinical effects of caffeine withdrawal, there is a chance that a triggered migraine syndrome is interpreted as part of the caffeine withdrawal syndrome, explaining an overlap between these two. If it triggers migraine it

offers a good human migraine model. A clinical trial thoroughly evaluating the withdrawal syndrome specifically in subjects with migraine should be performed. Furthermore, whether long-term elimination of caffeine diet will reduce or increase the burden of migraine should also be evaluated.

There is compelling evidence that adenosine may trigger headaches, but how this poor blood-brain-barrier penetrating substance can trigger central mechanisms when given intravenously remains enigmatic. Chronically blocking adenosine receptors by habitually drinking coffee seems to increase the burden of migraine, and it is tempting to believe that this causes an increased sensitivity to adenosine, evident when caffeine is withdrawn. Caffeine withdrawal and migraine prodromal symptoms are definitely caused by alterations in the CNS. Looking beyond the peripheral effects, central adenosine mechanisms should be explored in experimental headache models. The link between adenosine, the circadian system, sleep, and pain points at the posterior hypothalamus as a locus in quo. The effects of caffeine on the TMN and the A11 may offer novel insight, and the $A_{2A}R$ seems to be of particular interest. Two positron emission tomography (PET) $A_{2A}R$-ligands have been developed, and this may render human *in vivo* imaging studies possible (14). Future research should also confirm and investigate a role of receptor genes like ADORA2A in migraine and caffeine withdrawal.

## AUTHOR CONTRIBUTIONS

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# Inhibition of Trigeminal Nociception by Non-invasive Vagus Nerve Stimulation: Investigating the Role of GABAergic and Serotonergic Pathways in a Model of Episodic Migraine

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Migraine is a prevalent neurological disease that is characterized by unpredictable episodic attacks of intense head pain. The underlying pathology involves sensitization and activation of the trigeminal system. Although non-invasive vagus nerve stimulation (nVNS) is recommended for the treatment of migraine, the abortive mechanism of action is not well-understood. The goal of this study was to compare the ability of nVNS and sumatriptan to inhibit trigeminal activation in two animal models of episodic migraine and to investigate the receptor mechanism of action of nVNS. Nocifensive head withdrawal response was investigated in adult male Sprague Dawley rats using von Frey filaments. To induce trigeminal nociceptor sensitization, complete Freund's adjuvant was injected in the trapezius muscle and trigeminal neurons were activated by exposure to a pungent odor or injection of the nitric oxide donor sodium nitroprusside. Some animals received nVNS or sumatriptan as treatment. Some animals were injected intracisternally with antagonists of $GABA_A$, 5-HT3 or 5-HT7 receptors prior to nVNS since these receptors are implicated in descending modulation. While unsensitized animals exposed to the pungent odor or nitric oxide alone did not exhibit enhanced mechanical nociception, sensitized animals with neck muscle inflammation displayed increased trigeminal nocifensive responses. The enhanced nociceptive response to both stimuli was attenuated by nVNS and sumatriptan. Administration of antagonists of $GABA_A$, 5-HT3, and 5-HT7 receptors in the upper spinal cord suppressed the anti-nocifensive effect of nVNS. Our findings suggest that nVNS inhibits trigeminal activation to a similar degree as sumatriptan in episodic migraine models via involvement of GABAergic and serotonergic signaling to enhance central descending pain modulation.

**Keywords: neck inflammation, pain, sensitization, sumatriptan, nitric oxide, vagus nerve**

## HIGHLIGHTS

- Neck muscle inflammation mediated sensitization of the trigeminal system to a pungent odor or nitric oxide that promoted mechanical nociception.
- nVNS inhibited trigeminal nociception in two models of episodic migraine.
- The inhibitory effects of nVNS involve GABAergic and serotonergic pathways.

## INTRODUCTION

Migraine is a prevalent neurological disease characterized by unpredictable episodic attacks of severe head pain that is accompanied by autonomic symptoms including photophobia, phonophobia, and nausea (1). The disease burden of migraine is significant since it disproportionally affects women of childbearing age and negatively impacts performance at school and work, and interferes with family and social activities (2–4). Migraine pathology involves sensitization and activation of the trigeminal system, which provides sensory innervation to much of the head and face including the meninges (5). Recently, non-invasive electrical stimulation of the vagus nerve has been reported to be beneficial in the treatment of migraine and cluster headache (6–9). The pathological pain associated with migraine involves activation of trigeminal ganglion nerves, which provide sensory innervation of the head and face and relay nociceptive signals to the spinal trigeminal nucleus (STN) (10). The use of a non-invasive vagus nerve stimulator (nVNS, gammaCore$^{TM}$) is FDA approved for the acute (episodic) and preventive (episodic and chronic) treatment of cluster headache and the acute treatment of migraine in adult patients. Additionally, results from clinical trials have provided evidence that nVNS is a safe and well-tolerated therapeutic option (6, 9). Importantly, the reported 2-h pain-free rate for nVNS in treating episodic migraine is similar to that of the triptans (11). Thus, nVNS is proposed as a novel non-pharmacological therapeutic alternative or complement to the triptan class of abortive migraine drugs. Although similarly effective to triptans, nVNS likely functions via different physiological and cellular mechanisms to modulate pain signaling in response to trigeminal nerve activation. The mechanism by which triptans function to block trigeminal pain is thought to involve inhibiting the release of calcitonin-gene related peptide (CGRP) and other pro-inflammatory molecules from peripheral and central terminals of the trigeminal nerve as well from the cell body within the ganglion (12). In contrast, the inhibitory effect of nVNS as an acute migraine treatment is proposed to promote multiple distinct cellular changes and pathways within the brain and spinal cord to facilitate descending pain modulation (13). The descending inhibitory pathway is known to involve activation of 5-HT3 and 5-HT7 receptors on inhibitory interneurons that stimulates release of glycine and GABA, which act as inhibitory neurotransmitters of primary or secondary trigeminal nociceptors (14). Thus, the reported efficacy of nVNS may involve modulation of GABAergic and serotonergic signaling but this pathway has not been demonstrated in episodic migraine models.

Migraineurs are genetically predisposed to development of a hyperexcitable nervous system that is susceptible to multiple risk factors, which function to promote peripheral and central sensitization or can act as triggers to initiate a migraine attack (15). Premonitory symptoms may include increased sensitivity to physical stimuli such as flickering lights, loud, or irregular sounds, or even pungent odors such as those from the California bay laurel (CBL) or headache tree (16, 17). Similar to other complex neurological diseases, stress and anxiety are reported migraine risk factors that can significantly influence disease onset, progression, and maintenance of the clinical phenotype (18) and can manifest as increased tension and pain in neck and shoulder muscles (19). Chronic muscle tension and inflammation in the neck and shoulders can mediate persistent muscle fiber contraction, local ischemia, and the release of pro-inflammatory mediators that facilitate sensitization of primary and secondary nociceptors (20). The convergence in the upper spinal cord of nerves providing sensory innervation of neck/shoulder muscles and those emanating from the trigeminal ganglion may explain why neck/shoulder pathology is often cited as a risk factor for orofacial pain conditions including migraine (21, 22). In support of this notion, neck muscle inflammation has been reported to promote sensitization of primary trigeminal neurons so that exposure to a known migraine trigger, the pungent odor from a CBL leaf extract, was sufficient to cause an increase in trigeminal nociception in response to mechanical stimulation (23). One of the main active molecules in CBL trees leaves is umbellulone, which has been shown to cause activation of TRPA1, the subsequent release of CGRP, and to increase trigeminal nociception (17). Another factor known to promote activation of trigeminal nociceptors in animal models of migraine is nitric oxide (24). Using nitric oxide donors to mimic migraine pathophysiology is supported by human data that infusion of a nitric oxide donor in migraine susceptible individuals will trigger a migraine attack (25). Thus, a goal of this study was to compare the efficacy of nVNS to sumatriptan in two animal models of episodic migraine involving trigeminal sensitization mediated by neck muscle inflammation and trigeminal activation via either a pungent odor or nitric oxide. Another goal was to investigate the mechanism of action of nVNS to inhibit trigeminal nociception.

## METHODS

### Animals

One hundred and ninety-five adult (d45-d56) Sprague Dawley male rats (200–300 g), were purchased from Missouri State University's Central Management Breeding Colony (Springfield, MO) and allowed to acclimate for 1 week to facility conditions prior to use. Animals were housed individually in plastic rat cages with aspen chip bedding and unrestricted access to both food and water in a room with 12 h light/dark cycles. All protocols were approved by Missouri State University's Institutional Animal Care and Use Committee and conducted in compliance with the Animal Welfare Act, National Institutes of Health, and ARRIVE Guidelines. Concerted efforts were made to minimize suffering, as well as the number of animals. The attending veterinarian provided guidance on appropriate dosing of all compounds and

also determined if animals were to be removed from the study due to excessive suffering. One hundred eighty-two animals were used for final analysis, due to exclusion of outliers that were defined as average values more than 2 standard deviations from the mean of that group at one or more timepoints. No animals were removed from the study due to ill health.

## Sensitization and Activation of Trigeminal Nociceptive Neurons

The experimental design for the first episodic migraine model was based on a prior study and involves activation of sensitized trigeminal neurons in response to exposure to a pungent odor (23). Animals were placed under 3% isoflurane and received 10 injections of 10 μl of complete Freund's adjuvant (CFA, Sigma-Aldrich, St. Louis, MO; 1:1 in 0.9% sterile saline) into the upper trapezius. Animals were monitored for normal behaviors for a total of 8 days. To cause activation of trigeminal nociceptors, animals were exposed for 10 min to the volatile compounds from an oil extract obtained from California bay laurel tree leaves (CBL, World Spice, Seattle, WA) that was prepared as described previously (23).

In the second episodic migraine model, nitric oxide was used to mediate trigeminal nociceptor activation in sensitized animals 8 days post trapezius CFA injection. Animals were lightly anesthetized using 3% isoflurane and injected intraperitoneally at a dose of 0.01 mg/kg with sodium nitroprusside (SNP, Sigma-Aldrich) dissolved in sterile 0.9% saline. This dose was chosen since it did not cause increased nociception in naïve animals and hence was determined to be subthreshold. In control animals, an equal volume of sterile saline was injected.

## nVNS and Sumatriptan Treatments

The procedure for nVNS was performed essentially as described previously (23). Animals were lightly anesthetized under 3% isoflurane and the stimulator electrodes placed on a shaved area over the vagus nerve. Initially, a 1 ms pulse of 5 kHz sine waves, repeated at 25 Hz, for 2 min was administered that was followed 5 min later by a second 2 min stimulation. Animals receiving sumatriptan were given a dose of 0.3 mg/kg subcutaneously, which was shown previously to effectively inhibit trigeminal activation (26).

## Inhibitor Injections

Animals were lightly anesthetized using 3% isoflurane prior to intracisternal injection of antagonists to $GABA_A$ and the 5-HT3 and 5-HT7 receptors. Bicuculline ($GABA_A$ inhibitor, Tocris Bioscience, Minneapolis, MN) was dissolved in DMSO, then diluted to 20 μM in sterile 0.9% saline, while Ondansetron Hydrochloride (5-HT3 inhibitor, Tocris) and SB 269970 (5-HT7 inhibitor, Tocris) were dissolved in 0.9% sterile saline to a final concentration of 100 nM. In addition, a mixture of 100 nM Ondansetron and 100 nM SB 269970 was prepared in sterile saline. All inhibitors were administered via injection of 20 μl between the occipital bone and C1 vertebrae to naïve animals or delivered immediately prior to nVNS (2 h post odor exposure). Bicuculline was also administered to sensitized animals that received CBL exposure with no nVNS treatment.

## Nocifensive Behavior Testing

Behavioral changes were the primary outcome measured in this study. Changes in nocifensive response to mechanical stimulation of trigeminal neurons were determined essentially as described (23). Prior to nociception testing, animals were allowed to acclimate to the Durham Animal Holder (UGO Basile, Gemonio, Italy) in the designated procedure room for 5 min on 3 consecutive days. To minimize reflexive or startle responses, animals were conditioned to a mechanical stimulus by gently rubbing the hair in the facial region with a pipette tip. This method measures deep musculoskeletal pain responses rather than cutaneous, reflexive defensive responses and hence higher weight filaments were required to test nociception. Following acclimations, animals were allowed to rest for 48 h prior to baseline assessments.

Mechanical nocifensive thresholds were determined in response to a series of calibrated von Frey filaments (Stoelting, Wood Dale, IL) between 8 a.m. and 12 p.m. Nocifensive withdrawal reactions, defined as a head withdrawal observed prior to the bending of the filament, were verified by two scientists blinded to the experimental conditions. Each filament was applied 5 times over both the right and left areas of each animal and reported as an average number of reactions. Animals were randomly sorted into groups, and baseline measurements were established prior to any treatments. Animals that responded on average more than 2.5 times to the 100 g filament during baseline measurements were not included in the study. Additional measurements were taken 8 days post-muscle injections, 2 h post odor exposure or SNP injections, 1 h post nVNS or sumatriptan treatments, and 24 h post treatment. Animals were euthanized following testing via $CO_2$ asphyxiation and decapitation.

## Statistical Design and Analysis

An a priori power analysis using G*Power Software (Dusseldorf, Germany), allowing for comparison between groups at 5 time points, resulted in a recommended minimum of 5 animals per group to detect effects of treatments. Following collection, data were evaluated for normality using a Shapiro–Wilk test. Behavioral data were found to be non-normal ($P < 0.05$), so non-parametric statistical tests were applied. To determine if nociception was different across all groups, a Kruskal–Wallis test was performed. Upon reaching a significant result, a Mann–Whitney *U*-test with a Wilcoxon's W *post-hoc* test was performed to determine if there were pairwise differences in nociception between groups at each evaluated time point. Statistical analysis was performed using SPSS Statistical Software 24 (IBM), and changes were considered significant if $P < 0.05$.

# RESULTS

Initially, the level of trigeminal nociception to mechanical stimulation was determined with the use of von Frey filaments in a model of episodic migraine (**Figure 1**). The average number of nocifensive head withdrawals to mechanical stimulation was <1 response out of 5 applications at the basal time point for all experimental conditions. At day 8, the nociceptive response for

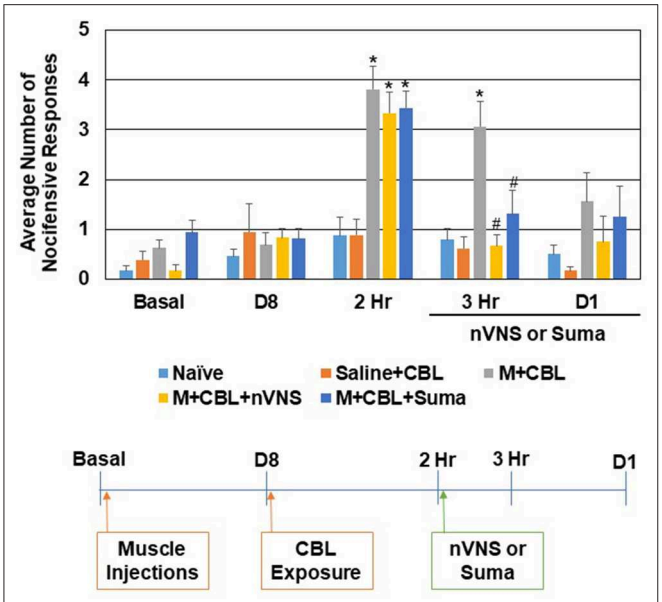


**FIGURE 1 |** nVNS and sumatriptan inhibit trigeminal nociception mediated by a pungent odor in sensitized animals. The average nocifensive head withdrawal response ±SEM of 5 applications to each side to mechanical stimuli are reported. Some animals were left untreated (Naïve), some were injected with saline in the trapezius (Saline) and exposed to the pungent extract from California Bay Laurel leaves (CBL), while others were injected with complete Freund's adjuvant 8 days prior to exposure to CBL (M+CBL) and nociceptive responses determined at 2 h, 3 h, and 1 day post CBL exposure. Some of the M+CBL animals were treated with nVNS or sumatriptan and nociception measured 1 h and 1 day post treatment. *$P < 0.05$ when compared to Naïve while #$P < 0.05$ compared to M+CBL.

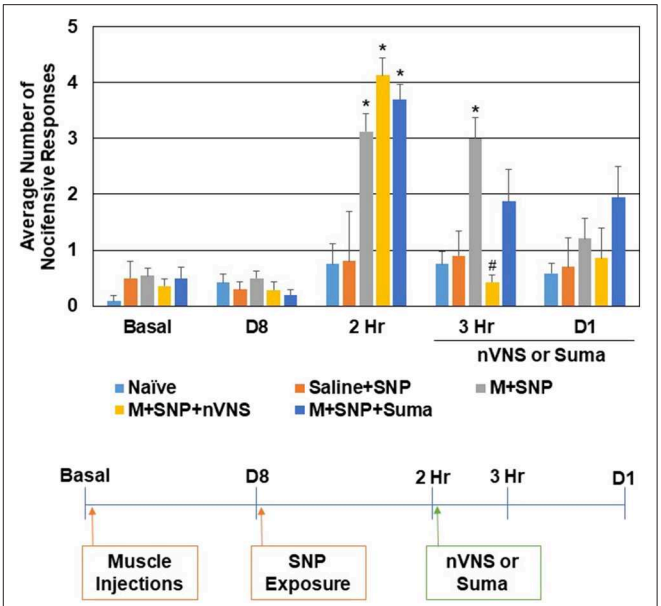


**FIGURE 2 |** nVNS and sumatriptan inhibit trigeminal nociception mediated by nitric oxide in sensitized animals. The average nocifensive head withdrawal response ±SEM of 5 applications to each side to mechanical stimuli are reported. Some animals were left untreated (Naïve), some were injected with saline in the trapezius (Saline) and exposed to the nitric oxide donor sodium nitroprusside (SNP), while others were injected with complete Freund's adjuvant 8 days prior to exposure to SNP (M+SNP) and nociceptive responses determined at 2 h, 3 h, and 1 day post SNP exposure. Some of the M+SNP animals were treated with nVNS or sumatriptan and nociception measured 1 h and 1 day post treatment. *$P < 0.05$ when compared to Naïve while #$P < 0.05$ compared to M+SNP.

all conditions including animals that received upper trapezius injection of CFA were similar to basal levels. In sensitized animals mediated by neck muscle inflammation however ($n = 8$), the average number of nocifensive responses was significantly ($P < 0.05$) elevated over naïve ($n = 12$) levels 2 h after exposure to the pungent odor from a CBL extract ($P < 0.001$) but not in animals injected with saline ($n = 9$) in the upper trapezius ($P = 0.39$). One hour after treatment with nVNS ($n = 7$) or sumatriptan ($n = 8$) (3 h after odor exposure) a significant decrease ($P = 0.001$, $P = 0.028$) in nociception was observed when compared to untreated sensitized animals, which were still elevated at this time point ($P < 0.001$). The average number of nocifensive responses was no longer significantly different between any groups 1 day post odor exposure or treatment with nVNS or sumatriptan ($P = 0.071$). No change in nociception was observed in animals receiving only saline at 3 h and day 1 ($P = 0.62$, $P = 0.89$).

The effect of nVNS and sumatriptan were also compared in a second animal model of episodic migraine. In this model, sensitization of trigeminal nociceptive neurons was mediated by injection of CFA in the upper trapezius 8 days prior to injection of the nitric oxide donor sodium nitroprusside (SNP), which was used to trigger activation and a nocifensive response (**Figure 2**). Consistent with the CBL data, in sensitized animals mediated by neck muscle inflammation, the average number of nocifensive responses was significantly ($P < 0.05$) elevated over naive levels 2 h after injection of SNP ($n = 12$, $P < 0.001$) but not in animals injected with saline in the upper trapezius prior to SNP injection ($n = 6$, $P = 0.61$). One hour after treatment with nVNS (3 h after CBL) a significant decrease ($n = 7$, $P < 0.001$) in nociception was observed when compared to untreated sensitized animals, which were still significantly elevated over naive ($P < 0.001$). Sumatriptan also caused a decrease in the average number of withdrawal responses such that the response was not significantly different from SNP-stimulated animals or naive levels ($n = 8$, $P = 0.13$, $P = 0.15$). The average number of nocifensive responses was no longer significantly different between groups 1 day post SNP or treatment with nVNS or sumatriptan ($P = 0.15$). No change in nociception was observed in animals receiving only saline at 3 h and day 1 ($P = 0.89$, $P = 0.96$).

To determine if intracisternal administration of inhibitors of the $GABA_A$, 5-HT3, and 5-HT7 receptors would cause a change in the basal level of trigeminal nociception to mechanical stimulation, unsensitized animals received injections of selective antagonists and nocifensive responses were measured at the same time points as the episodic migraine models. Administration of the $GABA_A$ inhibitor Bicuculline (20 μM) or a mixture of antagonists of 5-HT3 (Ondansetron, 100 nM) and 5-HT7 (SB-269970, 100 nM) did not mediate a significant difference in the average number of nocifensive responses at any of the time points (data not shown). To test if the inhibitory effect of nVNS on trigeminal nociception observed in the CBL odor-induced episodic migraine model involved $GABA_A$

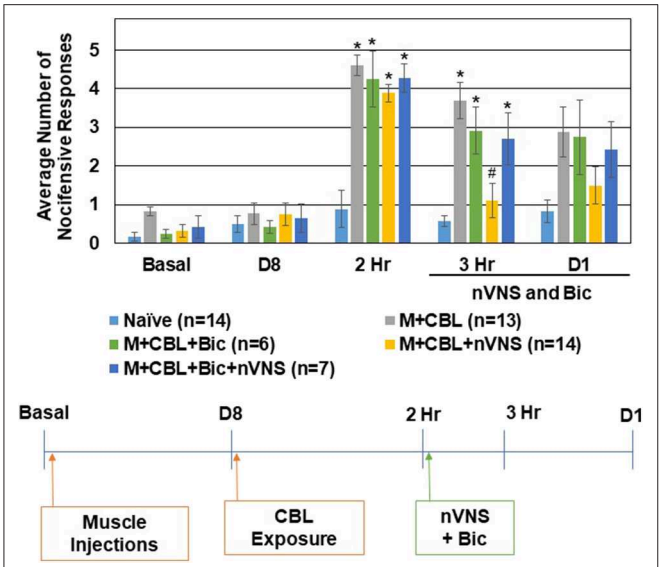


**FIGURE 3 |** Inhibitory effect of nVNS on trigeminal nociception involves $GABA_A$. The average nocifensive head withdrawal response ±SEM of 5 applications to each side to mechanical stimuli are reported. Some animals were left untreated (Naïve), some were injected with complete Freund's adjuvant 8 days prior to exposure to a pungent extract from California Bay Laurel leaves (M+CBL) and nociceptive responses determined at 2 h, 3 h, and 1 day post CBL exposure. Some of the M+CBL animals were treated with Bicuculline and/or nVNS 2 h after CBL exposure and nociception measured 1 h and 1 day post treatment. *$P < 0.05$ when compared to Naïve while #$P < 0.05$ compared to M+CBL.

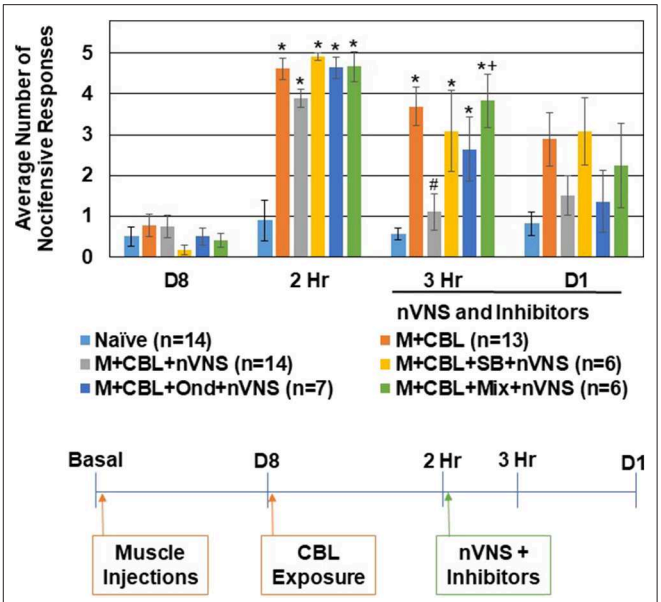


**FIGURE 4 |** Anti-nociceptive effect of nVNS involves 5-HT3 and 5-HT7 receptors. The average nocifensive head withdrawal response ±SEM of 5 applications to each side to mechanical stimuli are reported. Some animals were left untreated (Naïve), some were injected with complete Freund's adjuvant 8 days prior to exposure to a pungent extract from California Bay Laurel leaves (M+CBL) and nociceptive responses determined at 2 h, 3 h, and 1 day post CBL exposure. Some of the M+CBL animals were treated with Ondansetron, SB 269970, or a mixture (Mix) prior to nVNS and nociception measured 1 h and 1 day post treatment. *$P < 0.05$ when compared to Naïve while #$P < 0.05$ compared to M+CBL. +$P < 0.05$ when compared to M + CBL + nVNS.

signaling, the $GABA_A$ receptor antagonist was administered just prior to nVNS. All of the animals exhibited a similar level of nocifensive response to mechanical stimulation at the day 8 time point prior to CBL exposure (**Figure 3**). As before, sensitized animals exposed to CBL ($n = 13$) exhibited elevated nocifensive responses at 2 h when compared to naïve animals ($n = 14$) (M + CBL, $P < 0.001$; M + CBL + nVNS, $P = 0.001$; M + CBL + Bic + nVNS, $P = 0.003$). As expected, nVNS ($n = 14$) significantly inhibited ($P < 0.05$) the level of nociception mediated by CBL in sensitized animals 1 h post treatment ($P = 0.002$). Administration of the $GABA_A$ receptor antagonist Bicuculline (20 μM) prior to nVNS, however, suppressed the inhibitory effect of nVNS, which resulted in the average number of nocifensive responses being significantly different from Naïve levels ($n = 7$, $P = 0.004$). However, animals treated with Bicuculline prior to nVNS were not significantly elevated compared to animals receiving nVNS alone ($P = 0.067$). As a control, Bicuculline administered to sensitized animals immediately following CBL exposure did not potentiate or inhibit the nocifensive response and was significantly elevated when compared to Naïve levels ($n = 6$, $P = 0.001$). At day 1 post treatments, no significant differences in trigeminal nociception were observed although the trends were similar to the 3 h time point.

To determine if the inhibitory effect of nVNS on trigeminal nociception observed in the CBL odor-induced episodic migraine model also involved activation of 5-HT receptors, selective 5-HT3 and 5-HT7 antagonists were injected intracisternally prior to nVNS. All of the animals exhibited a similar level of nocifensive response to mechanical stimulation at the day 8 time point prior to CBL odor exposure (**Figure 4**). In this experiment, all sensitized animals exhibited a robust increase ($P < 0.05$) in the average number of nocifensive responses following pungent odor exposure for each experimental condition. While nVNS significantly inhibited ($P = 0.002$) the level of nociception mediated by CBL odor in sensitized animals 1 h post treatment, administration of the 5-HT3 antagonist Ondansetron (100 nM) ($n = 7$), 5-HT7 antagonist SB 269970 (100 nM) ($n = 6$), or a mixture (100 nM of each) ($n = 6$), prior to nVNS suppressed the inhibitory effect of nVNS. The average number of nocifensive responses for animals treated with Ondansetron, SB 269970, or the mixture was significantly different from naïve levels ($P = 0.011$, $P = 0.05$, $P < 0.001$, respectively). Animals treated with Ondansetron or SB 269970 prior to nVNS were not significantly elevated compared to animals receiving nVNS alone ($P = 0.064$, $P = 0.108$, respectively). However, animals treated with the mixture were significantly elevated from M + CBL + nVNS animals ($P = 0.007$). At day 1 post treatments, no significant differences in trigeminal nociception were observed when compared to naïve levels.

## DISCUSSION

The major finding from our study was that nVNS was as effective as sumatriptan in inhibiting trigeminal nociception in two different rodent models of episodic migraine. In both models, sensitization of trigeminal neurons was mediated by neck muscle inflammation, which is a reported migraine risk factor (27, 28). In this primed state, exposure of the animals to the pungent odor from a CBL extract or a nitric oxide donor was sufficient to cause a significant transient increase in trigeminal nociception to mechanical stimulation. Exposure to either triggering agent in unsensitized animals, however, did not result in an enhanced state of trigeminal nociception. In this way, these models are designed to mimic pathophysiological events associated with episodic migraine in humans. Importantly, nVNS and sumatriptan were both effective in inhibiting the increased level of trigeminal nociception mediated by CBL odor and nitric oxide in sensitized animals. This finding is consistent with human studies that have reported nVNS provides a therapeutic benefit that is similar to that of sumatriptan for the acute treatment of episodic migraine (11). Our finding that nVNS inhibits the average number of nocifensive responses to mechanical stimulation mediated by a pungent odor is also consistent with results from an earlier study (23) and with results from other animal studies that mimic aspects of migraine pathology (24, 29, 30) and other types of orofacial pain (31, 32). While previous studies have utilized nitric oxide donors to directly cause trigeminal nociception (24, 33, 34), in our model, a subthreshold concentration of sodium nitroprusside promoted activation of trigeminal nocifensive response in sensitized animals. In this way our model is designed to mimic human studies in which nitric oxide infusion causes a migraine attack in migraine susceptible individuals (25). An interesting feature of our model is that trigeminal nociception is not elevated by upper trapezius inflammation but rather a sensitized or primed state of nociceptors is promoted. This pathological condition mimics a commonly cited risk factor since neck muscle pain and tenderness are reported during the prodrome and attack phases of migraine (27, 28). Neck muscle inflammation is likely to mediate central sensitization of the trigeminal system via increased peripheral signaling since afferent projections from these muscles terminate in the upper spinal cord and subsequently converge with the trigeminal system (22, 35). This supports the notion that neck muscle inflammation could promote central sensitization by activating ascending nociceptive second order neurons or by facilitating downregulation or dysregulation of the inhibitory descending pain modulation pathway. These events would result in an increase in the allostatic load and promote development of a hypersensitive or hyperexcitable state of the trigeminal system that would be more responsive to inflammatory stimuli, which is characteristic of migraine pathophysiology (36).

Although nVNS and sumatriptan are reported to have similar efficacy in treating episodic migraine, the pathways by which each of these abortive therapies function to inhibit trigeminal pain signaling are likely to be mediated via different cellular and molecular mechanisms. Based on animal studies, the inhibitory effects of sumatriptan are thought to be primarily mediated via direct modulation of primary trigeminal neurons and involve blocking the release of CGRP and the excitatory neurotransmitter glutamate (12). Hence, sumatriptan's mechanism of action would inhibit neurogenic inflammation in the dura, inhibit neuron-glia communication in the ganglion, and also inhibit activation of second order neurons and glia cells within the spinal cord to decrease peripheral and central sensitization of the trigeminal system. In contrast, the primary effects of nVNS are likely to be multimodal and would involve modulation of central cellular activities that regulate descending pain inhibition pathways (37). The findings from our study provide evidence for the involvement of $GABA_A$ receptors and 5-HT3 and 5-HT7 receptors in mediating the inhibitory effect of nVNS in an episodic migraine model. Specifically, intracisternal injection of the $GABA_A$ receptor antagonist Bicuculline or administration of the 5-$HT_7$ receptor antagonist SB 269970 and the 5-$HT_3$ receptor antagonist Ondansetron, or a mixture of the two antagonists, significantly inhibited nVNS repression of trigeminal nociception. The inhibitory effect of nVNS is likely to be mediated by activation of $GABA_A$ receptors on primary and second order neurons (32, 38, 39), which would result in neuronal hyperpolarization via an influx of chloride to inhibit neurotransmitter release. Although not a focus of this study, the source of 5-HT is likely from activation of descending projections from the rostroventromedial medulla (RVM), which functions as a final relay in the control of descending pain facilitation. The activation of 5-$HT_3$ and 5-$HT_7$ receptors on inhibitory neurons by nVNS would enhance the descending inhibitory pain pathway via activation of spinal interneurons and release of the inhibitory neurotransmitters, GABA and glycine, to suppress ascending pain transmission. This mechanism is supported by other orofacial pain studies involving trigeminal nerve activation in which direct stimulation of the vagus nerve was shown to exhibit anti-nociceptive effects, to facilitate the serotonergic descending inhibition pathway, and to modulate inhibition of GABAergic neurons (14, 40, 41). Other mechanisms may also be involved in nVNS inhibition of trigeminal pain signaling. In a previous study (23), nVNS treatment of sensitized animals inhibited CBL odor-stimulated nuclear expression of the signaling protein P-ERK in trigeminal ganglia. In the same model of episodic migraine utilized in this study, nVNS also inhibited stimulated expression of GFAP and Iba1, which are biomarkers of activated astrocytes and microglia, respectively (42). These findings are suggestive that nVNS can inhibit cellular changes implicated in peripheral and central sensitization. nVNS has also been reported to inhibit the nitroglycerin-mediated increase in glutamate levels in cerebral spinal fluid in a model of trigeminal allodynia (24). Another possible mechanism of nVNS involves the direct regulation of pain signaling in the upper spinal cord based on data from a recent human imaging study that provided evidence of the trigeminal and vagus systems being interconnected at the level of the spinal trigeminal nucleus (43). Taken together, the inhibitory effect of nVNS in migraine is facilitated via multiple mechanisms that function to suppress peripheral

and central sensitization of the trigeminal system and inhibit pain signaling.

In summary, exposure to a pungent odor or administration of nitric oxide, which are both reported migraine triggers in humans, resulted in an enhanced nocifensive state in response to mechanical stimulation of trigeminal neurons in animals with ongoing neck muscle inflammation, another reported risk factor associated with migraine pathology. nVNS was as effective in inhibited trigeminal nociception as sumatriptan in two rodent models of episodic migraine. We propose that the inhibitory effect of nVNS is mediated, in part, via activation of 5-HT3 and 5-HT7 receptors on inhibitory neurons within the spinal trigeminal nucleus that results in release of GABA and subsequent activation of GABAA receptors on sensory neurons. However, 5-HT released from the RVM could also directly modulate sensory neurons via activation of other serotonergic receptors. Given its central mechanism of action involving GABAergic and serotonergic pathways associated with descending pain modulation, nVNS offers a non-pharmacological alternative or adjunctive therapy to triptans.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The animal study was reviewed and approved by IACUC Missouri State University.

## AUTHOR CONTRIBUTIONS

LC was primarily responsible for the collection and analysis of the behavioral results and assisted in the writing and editing of the final manuscript. SW was primarily responsible for the inhibitor studies and assisted in drafting the original manuscript and editing of final version. PD was responsible for the study design, directing research efforts, and final analysis of the results as well as writing and editing of the manuscript.

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# Baseline Brain Gray Matter Volume as a Predictor of Acupuncture Outcome in Treating Migraine

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**Background:** The present study aimed to investigate the use of imaging biomarkers to predict the outcome of acupuncture in patients with migraine without aura (MwoA).

**Methods:** Forty-one patients with MwoA received 4 weeks of acupuncture treatment and two brain imaging sessions at the Beijing Traditional Chinese Medicine Hospital affiliated with Capital Medical University. Patients kept a headache diary for 4 weeks before treatment and during acupuncture treatment. Responders were defined as those with at least a 50% reduction in the number of migraine days. The machine learning method was used to distinguish responders from non-responders based on pre-treatment brain gray matter (GM) volume. Longitudinal changes in GM predictive regions were also analyzed.

**Results:** After 4 weeks of acupuncture, 19 patients were classified as responders. Based on 10-fold cross-validation for the selection of GM features, the linear support vector machine produced a classification model with 73% sensitivity, 85% specificity, and 83% accuracy. The area under the receiver operating characteristic curve was 0.7871. This classification model included 10 GM areas that were mainly distributed in the frontal, temporal, parietal, precuneus, and cuneus gyri. The reduction in the number of migraine days was correlated with baseline GM volume in the cuneus, parietal, and frontal gyri in all patients. Moreover, the left cuneus showed a longitudinal increase in GM volume in responders.

**Conclusion:** The results suggest that pre-treatment brain structure could be a novel predictor of the outcome of acupuncture in the treatment of MwoA. Imaging features could be a useful tool for the prediction of acupuncture efficacy, which would enable the development of a personalized medicine strategy.

**Keywords: migraine, acupuncture, prediction, gray matter, machine learning**

# INTRODUCTION

Migraine is characterized by recurrent episodes of severe headaches that are often unilateral and are accompanied by symptoms of autonomic nervous system dysfunction, such as nausea, vomiting, photophobia, and phonophobia (1). Migraine ranks second among the global level-4 causes of disability and is the most common cause of disability in those aged 15–49 years (2, 3). Migraine was reportedly experienced by as many as 1.04 billion people in 2016 (2). Thus, there is a pressing need to improve the clinical care of migraine.

Acupuncture is used for migraine treatment in many countries (4–11), although its superiority compared with sham acupuncture and medication remains controversial (7, 9, 10). However, about 50% of patients do not achieve substantial improvement after acupuncture (10, 11). The ability to predict the efficacy of acupuncture would prevent non-responders from enduring a long period of unsuccessful treatment. In one previous study, the outcome of acupuncture in patients with migraine was predicted by the presence of throbbing symptoms and expectations for a cure (12); however, an objective prognostic biomarker is still lacking.

Two recent studies that used baseline brain structure to predict the placebo response of sham acupuncture in patients with migraine found that the baseline prefrontal cortex volume and the fibers of the prefrontal-amygdala region predicts the placebo outcome after 8 weeks and discriminate responders from non-responders (13, 14). This suggests the potential of neuroimaging markers as predictors of migraine acupuncture treatment outcomes. In addition, previous studies have found that patients with migraine have brain gray matter (GM) abnormalities. Patients with migraine without aura (MwoA) have increased GM in the thalamus, parahippocampal gyrus, and frontal gyrus regions (15–17), and have decreased GM in the brainstem region (18). These findings indicate that brain GM might be useful in predicting the response of MwoA to acupuncture treatment.

The machine learning classification method has been increasingly used to classify subtypes of patients or to predict remission and non-remission with certain treatments (19–21), thus providing a new strategy for the development of personalized treatment. The present study aimed to use machine learning technology to predict the responders to acupuncture treatment for MwoA based on pre-treatment brain GM volume. The longitudinal changes in the GM regions were also examined.

# METHODS

## Participants

Chinese patients with MwoA were recruited from the outpatient acupuncture departments of the Beijing Hospital of Traditional Chinese Medicine, Capital Medical University between 2017 and 2019. The trial protocol was registered (ISRCTN11800433) and ethics approval was obtained from the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine (ref: 2016BL-081-02) prior to trial commencement. The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent for study inclusion. One experienced neurologist assessed the eligibility of all potential participants following pre-defined inclusion/exclusion criteria and provided a detailed explanation of the study design. The inclusion criteria were MwoA diagnosed in accordance with the International Classification of Headache Disorders (versions III beta) (1); age 18–65 years; history of migraine for at least 1 year; migraine frequency attacks of more than twice a month; no prophylactic treatments with acupuncture or pharmacological medicine administered in the past 3 months; right-handedness.

The exclusion criteria were as follows: (1) chronic migraine, tension-type headache, cluster headaches, or another primary headache; (2) secondary headache or other neurological diseases, such as headache caused by otorhinolaryngology diseases or intracranial pathological changes, and a history of depression, Parkinson's disease, or other extrapyramidal diseases; (3) relatively severe systemic diseases (cardiovascular disease, acute infectious disease, hematopathy, endocrinopathy, allergy or methysis); (4) pregnancy or lactation; (5) use of prophylactic migraine medication in the last 3 months; (6) magnetic resonance imaging (MRI) contraindications such as cardiac pacemakers or other metallic implants; or (7) alcohol or drug abuse.

Participants were randomly divided into the acupuncture group and the sham acupuncture groups. This present study consisted of two phases: a baseline period after enrollment (week 1 to week 4) and a treatment period (week 5 to week 8). The experimental design is shown in **Figure 1**. Participants were required to keep a headache diary from the baseline period to the end of treatment. Imaging and clinical data were collected at the end of week 4 and week 8.

## Clinical Assessment

In the headache diaries, the participants recorded the details of their migraine attacks, including migraine days, intensity, locations, cause of the headache, concomitant symptoms (nausea, vomiting, photophobia, and phonophobia), and acute medications (if any) taken for each migraine attack. Headache intensity was assessed by the visual analog scale (VAS, 0 to 10). Participants who achieved at least a 50% reduction in the number of migraine days were defined as responders (10, 11, 14). Repeated-measures analysis of variance was used to analyze the changes in clinical data in responders vs. non-responders.

## Acupuncture Treatment

All participants received three acupuncture sessions each week for 4 weeks. Each session lasted for 30 min. Participants were allowed to take acute headache medication during this study and were required to record the details. The acupuncture points were selected based in accordance with information collected from a vast number of Chinese medicine reference books and the consensus of acupuncture experts based on their clinical experiences, and comprised GV20 (Baihui), GV24 (Shenting), bilateral GB13 (Benshen), GB8 (Shuaigu), and GB20 (Fengchi) (**Figure 1**). The sham acupuncture points are shown in the

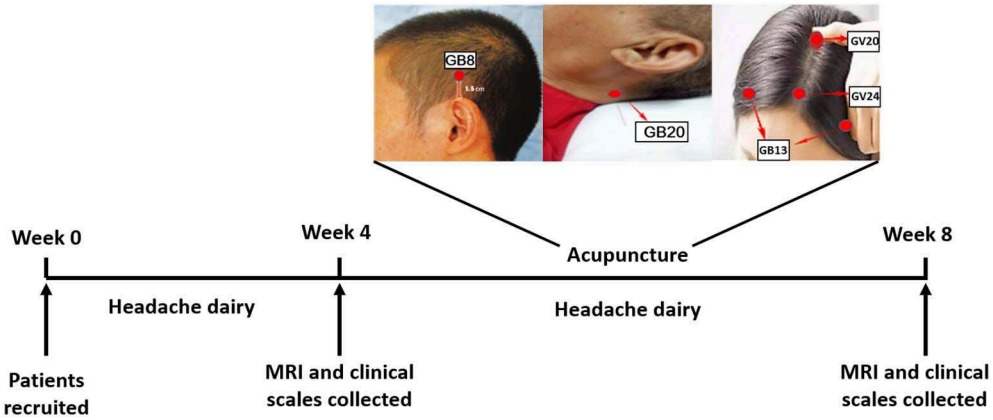


**FIGURE 1 |** Experimental flow chart. The stimulation points were GV20 (Baihui), GV24 (Shenting), and bilateral GB13 (Benshen), GB8 (Shuaigu), and GB20 (Fengchi).

Methods in **Supplementary Materials**. Eight sterile disposable steel needles (gauge and size: 0.25 mm × 25 mm; Hwato Needles, Suzhou, China) were used in each acupuncture session. To ensure treatment consistency, all treatments were performed by one acupuncturist, who was registered with the Ministry of Health of the People's Republic of China and had more than 20 years of clinical experience.

## Imaging Data Acquisition

MRI was performed during the interictal headache phase, at least 3 days from last attack. Images were obtained using a 3-T Siemens MRI system (Skyra, Siemens Medical System, Erlangen, Germany) at the Beijing Hospital of Traditional Chinese Medicine, Capital Medical University. The parameters were as follows: voxel size 2.3 × 2.3 × 3.0 $mm^3$, 40 continuous slices with a slice thickness of 3.0 mm, repetition time = 3,000 ms, echo time = 30 ms, flip angle = 90°, field of view = 220 × 220 mm, matrix = 94 × 94.

## Data Preprocessing

The structural image preprocessing and analysis were performed using Statistical Parametric Mapping12 (www.fil.ion.ucl.ac.uk), while the voxel-based morphometry analysis was performed using the Computational Anatomy Toolbox (CAT12) toolbox in the MatLab environment (www.mathworks.com). The CAT12 is an advanced and powerful qualitative MRI program that automatically evaluates the differences between regions with different GM volume without prior information to define the anatomical borders (22, 23). The Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm normalization program included in the CAT12 toolbox was used to transform the structural magnetic resonance image of the native space into the 152 standard space template of the Montreal Neurological Institute. The images were segmented into white matter, GM, and cerebrospinal fluid to extract a GM region of 1.5 × 1.5 × 1.5 $mm^3$ voxels. In the last step of the Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm normalization program, the GM tissues were modulated by a non-linear deformation method to compare the relative GM volume after adjusting for individual brain size. After preprocessing, the CAT12 toolbox was used to perform a quality inspection to evaluate the homogeneity of the GM tissues. The normalized and modulated structure magnetic resonance images were then spatially smoothed with an 8-mm full-width at half-maximum Gaussian smoothing kernel.

## Feature Selection

Two-sample *t*-testing was first performed to identify brain voxels that had a significant difference in GM volume between responders and non-responders. Voxels with a *P*-value less than a specific number were selected. Considering the huge number of voxels in the GM template (1 × 1 × 1 mm), this number was set using the grid-search method from 0.0025 to 0.05 with a step of 0.0025. Clusters of at least 50 significant voxels were identified, and the average GM volume across the voxels in each cluster was extracted as the initial feature.

The 10-fold cross-validation-based least absolute shrinkage and selection operator (LASSO) method was then used to further shrink the initial features into fewer more important features. Briefly, datasets were randomly split into 10 groups. Each group was then excluded in turn, and the LASSO method with the mean squared error as the cost function was performed on the remaining nine groups (24). This step was repeated 10 times, resulting in 10 different sets of selected features. Finally, those features that occurred 10 times were selected as LASSO features for classification model construction.

## Model Construction

The linear support vector machine (SVM) method was used to construct the classification model based on the LASSO features. The accuracy, sensitivity, specificity, and dice similarity coefficient (DSC) were used as indices to assess the performance of the classification model. These four indices were defined as shown below:

$$\text{accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$\text{sensitivity} = \frac{TP}{TP + FN} \quad (2)$$

$$\text{specificity} = \frac{TN}{TN + FP} \quad (3)$$

$$DSC = \frac{2TP}{2TP + FP + FN} \quad (4)$$

where TP represents true positive, TN represents true negative, FP represents false positive, and FN represents false negative. Ten-fold cross-validation was used to estimate the reliability of the model. Briefly, subjects were randomly divided into 10 groups. Each group was used in turn for testing, while the remaining nine groups were used for training. The feature selection and classification model construction steps were performed only for the training group, while the testing group was used to test the performance of the model. Finally, the mean standard difference of each index across 10 performances was calculated.

## Correlation Analysis and Longitudinal Changes

After performing the 10-fold cross-validation, all GM masks that contained the clusters corresponding to the selected LASSO features in each training group were added, the number of times that each voxel occurred in these masks was counted, and those voxels that occurred at least five times were reserved, as those voxels that occurred less than five times were considered to be reliant only on the specific splitting training group. Next, the average GM volume across the selected voxels in each cluster was extracted as the GM predictive regions. To further investigate the relationship of these predictive regions with acupuncture outcome, Pearson correlation testing was performed to assess the correlations between Δmigraine days (pre-treatment number of migraine days—post-treatment number of migraine days) and baseline GM volume of the predictive regions. The two-sample *t* test was used to compare the differences between the 10 predictive regions in responders vs. non-responders at baseline. Repeated-measures analysis of variance was performed to detect the longitudinal changes in GM volume in the predictive regions. For GM with an interaction effect of group × time, *post-hoc* analysis was used to detect the GM volume changes in different groups and at different time points. SPSS for Windows (version 18) was used to analyze the abovementioned comparisons with Bonferroni correction for multiple comparisons.

# RESULTS

## Clinical and Demographic Information

Forty-one patients who underwent acupuncture treatment were included in the final clinical analyses. Details of the sham acupuncture group were provided in the **Supplementary Materials** (Results, **Table S1**). The responder rate in the acupuncture group was significantly higher than that in the sham acupuncture group ($P = 0.007$, **Table S2**).

**TABLE 1 |** Baseline demographics and clinical information of acupuncture responders and non-responders.

| | Responders (*n* = 19) | Non-responders (*n* = 22) | *P* |
|---|---|---|---|
| Age, years (SD) | 35.0 (10.4) | 37.5 (11.87) | 0.481[a] |
| Women, *n* (%) | 13 (68.4) | 20 (90.9) | 0.157[b] |
| Duration of illness, year (SD) | 15.3 (8.4) | 14.7 (9.9) | 0.854[a] |
| Days of migraine (SD) | 6.9 (5.0) | 9.0 (7.6) | 0.310[a] |
| **LOCATION OF HEADACHE, *N* (%)** | | | |
| Unilateral | 7 (36.8) | 6 (27.3) | 0.511[b] |
| Bilateral | 12 (63.2) | 16 (72.7) | |
| **CAUSE OF HEADACHE, *N* (%)** | | | |
| Tiredness | 6 (31.6) | 10 (45.5) | 0.364[b] |
| Sleep problems | 12 (63.2) | 12 (54.5) | 0.577[b] |
| Mental stress | 13 (68.4) | 13 (59.1) | 0.536[b] |
| Other | 15 (78.9) | 13 (59.1) | 0.173[b] |
| **ACCOMPANYING SYMPTOMS, *N* (%)** | | | |
| Nause or vomting | 16 (84.2) | 17 (77.3) | 0.87[b] |
| Photophobia or audiaphobia | 14 (73.7) | 13 (59.1) | 0.326[b] |
| Other | 10 (52.6) | 10 (45.5) | 0.647[b] |

*Data were presented as mean ± standard deviation (SD), number (percentage).*
[a] *P-values based on the independent two sample t-test.*
[b] *P-values based on the chi-squared test.*

In the acupuncture group, 19 responders (46%) achieved a 50% reduction in the number of migraine days, which was close to the incidences of responders reported in our previous study and the study by Diener et al. (10, 11). The baseline information did not significantly differ between responders and non-responders (**Table 1**). After acupuncture treatment, the responders had significantly fewer migraine days and a significantly lower VAS scale than non-responders (**Table 2**). The number of patients using acute headache medication, such as aminopyrine phenacetin or ibuprofen, did not significantly differ between responders and non-responders after acupuncture treatment (**Table 2**).

## Classification Results

The classification of responders and non-responders showed a high degree of precision (sensitivity 73%, specificity 85%, accuracy 83%, and DSC 75%). Fourteen participants were classified as responders (true value was 19) and 20 were classified as non-responders (true value was 22). **Figure 2B** displays the receiver operating characteristic curve of the classification model. The area under the curve was 0.7871. Together, these results demonstrate the stability of our classification model and the reliability of our selected features.

After counting the number of occurrences of each voxel corresponding to the selected LASSO features in 10-fold cross-validation, 10 GM predictive regions were finally defined. **Figure 2A** and **Table S3** show the spatial distribution of these 10 GM predictive regions and the detailed regional information. Next, a Radiomics score (Rad-score) coefficient was constructed

in accordance with the weight value of each GM predictive region in the linear SVM model (**Supplementary Materials**, Results) where a Rad-score of <0 represents a responder and a Rad-score of >0 represents a non-responder.

Baseline clinical features and imaging data were also combined to perform prediction analysis. Details were provided in the **Supplementary Materials** (Results).

## Correlation Analysis and Longitudinal Changes

Among 10 predictive regions, the Δmigraine days in all patients was correlated with the baseline GM volume of four regions, including the left cuneus ($r = -0.455$, $P = 0.003$), right middle frontal/inferior frontal gyrus ($r = -0.460$, $P = 0.002$), left inferior parietal gyrus ($r = 0.433$, $P = 0.004$), and superior/inferior parietal gyrus ($r = 0.549$, $P = 0.0002$) (**Figure 3**). In addition, the baseline GM volume in all predictive regions significantly differed between responders and non-responders (**Figure 4**).

In the longitudinal analysis, the GM volume of the left cuneus showed a significant group × time interaction ($F = 9.159$, $P = 0.004$, **Figure 4**), in which the responders achieved an increase in GM volume after 4-weeks acupuncture treatment, while the non-responders did not. However, no correlation was found between the ΔGM volume of the left cuneus and the Δmigraine days in responders.

**TABLE 2 |** Clinical outcome measures.

| | Time point | Responders ($n = 19$) | Non-responders ($n = 22$) | *P* |
|---|---|---|---|---|
| Difference from baseline in days of migraine (SD) | Week 4 | 4.8 (3.7) | 0.5 (2.6) | $8.253 \times 10^{-5}$[a] |
| Visual analog scale (SD) | Baseline | 7.7 (1.6) | 7.2 (1.5) | $1.106 \times 10^{-4}$[c] |
| | Week 4 | 4.0 (2.9)*** | 6.6 (1.6)# | |
| Number of people with acute medication, *n* (%) | Baseline | 6 (31.6) | 9 (40.9) | 0.536[b] |
| | Week 4 | 6 (31.6) | 9 (40.9) | 0.536[b] |

*Data were presented as mean ± standard deviation (SD), number (percentage).*
*[a]P-values based on the independent two sample t-test.*
*[b]P-values based on the chi-squared test.*
*[c]P-values based on repeated measurement analysis of variance.*
****P < 0.001 for the post-hoc comparison of pre- vs. post-treatment values in responders.*
*#P < 0.05, for the post-hoc comparison of responders vs. non-responders in post-treatment values.*

## DISCUSSION

Treatment personalization is an important trend for the future in medicine. The use of medical imaging information to assist in disease diagnosis is being increasingly applied in the fields of cancer medicine (25) and psychology (19–21). However, few studies have used medical images to predict the efficacy of acupuncture. The present study used the machine learning classification method to establish a predictive model of acupuncture efficacy in patients with MwoA based on pre-treatment brain GM structure. The model had an 83% accuracy rate in distinguishing the acupuncture responders from the non-responders. These results provide an objective potential biomarker for the acupuncture treatment response of patients with migraine and also offer a new strategy for the development of personalized medicine for MwoA.

A common problem in traditional Chinese medicine is the individual differences in the efficacy of acupuncture. As shown in the present study, only about 50% of patients achieved substantial symptom improvement after 1 month of acupuncture treatment. Thus, the prediction of acupuncture response could reduce medical costs for patients identified as probable non-responders. Several previous studies have investigated the

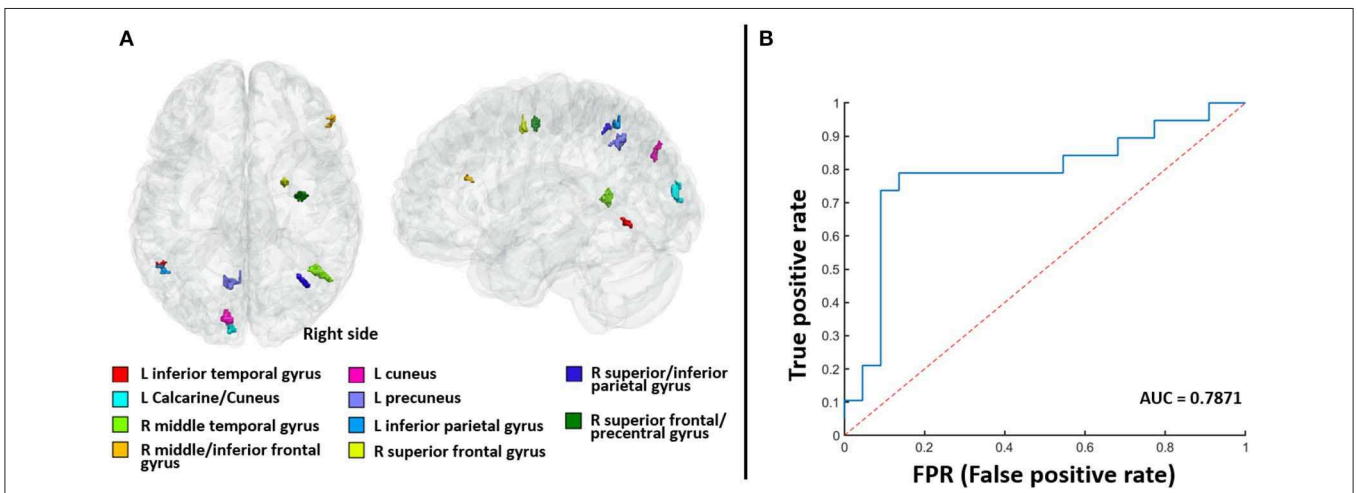


**FIGURE 2 |** The 10 identified gray matter predictive regions **(A)** and the receiver operating characteristic curve of the classification model **(B)**. The area under the curve (AUC) is 0.7871.

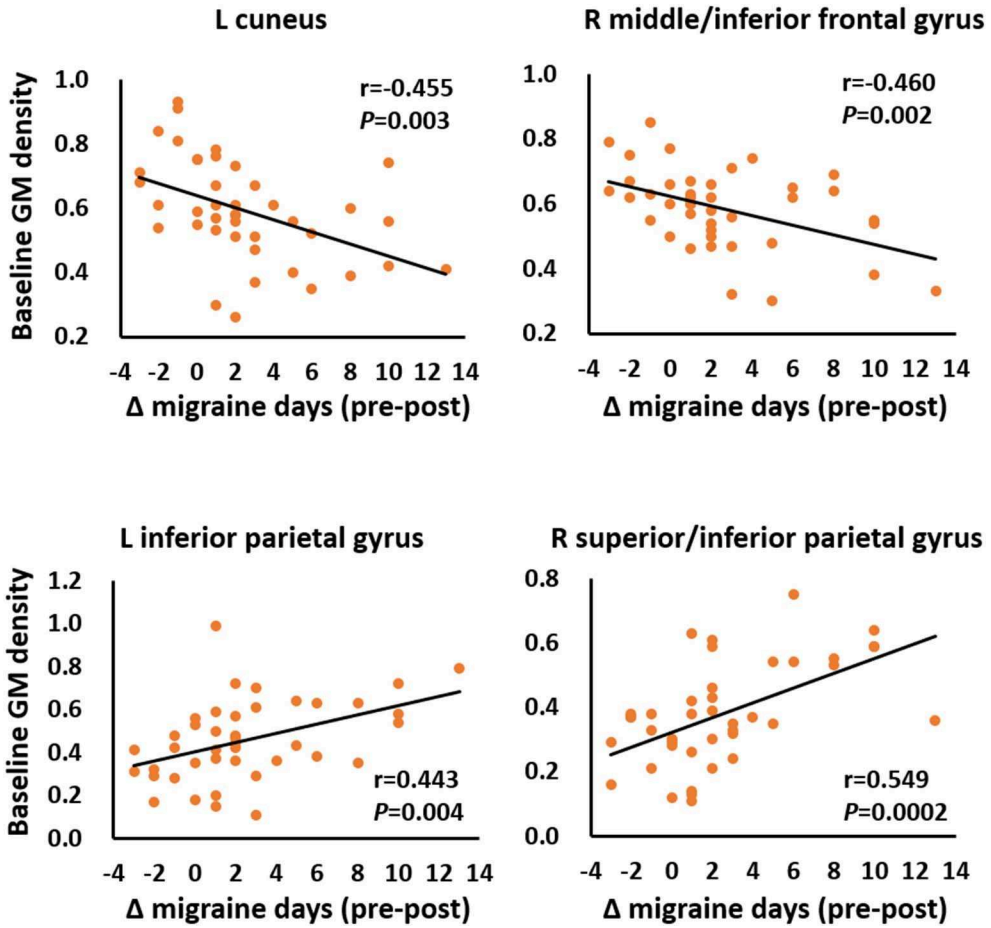


**FIGURE 3 |** Correlations between the reduction in the number of migraine days (Δ migraine days) and the baseline gray matter (GM) volume of the predictive regions.

prediction of the outcome of migraine treatment. In patients with headache, genetic factors, migraine characteristics, and autonomic symptoms have been evaluated to predict treatment response to triptan and topiramate (26–28). In addition, white matter hyperintensity was found to predict migraine prognosis (29); however, the correlation and regression analysis between predictors and patient outcomes used in this previous study were insufficient. The present study used a linear SVM-based classification to distinguish between responders and non-responders. This method can be used to identify a hyperplane to separate the two groups by minimizing the empirical classification error in training data and achieving a higher degree of accuracy for unseen data, which enables the distinction of responders from non-responders at an individual level (30, 31). A previous study achieved an accuracy of 84% using a linear SVM to predict the outcome of acupuncture placebo treatment in patients with MwoA (13). In our model (83% accuracy), the baseline GM volume in 10 regions located in the temporal, frontal, parietal, cuneus, and precuneus gyri that differs between responders and non-responders at baseline was able to predict acupuncture efficacy in patients with MwoA. Previous neuroimaging studies have found that most of these regions were correlated with the pathophysiology of migraine. There is a marked decrease in the GM volume in the frontal, temporal, occipital, and precentral gyri in patients with migraine (32–34), and acupuncture might modulate the abnormal function of the frontal gyrus, temporal gyrus, precuneus, and cuneus in patients with migraine (35–37). Our study revealed the value of these regions in migraine acupuncture therapy from the perspective of individualized prognosis.

The present results also showed that the baseline GM volume in four regions was directly correlated with the acupuncture outcome. The efficacy of acupuncture was greatest in those patients with the lowest baseline GM volume in the middle frontal/inferior gyrus and cuneus and the greatest baseline GM volume in the parietal gyrus; this was consistent with the GM features in responders. At baseline, responders had less GM volume in the middle frontal/inferior gyrus and cuneus and greater GM volume in the parietal gyrus compared with non-responders. Combined with the contribution of these regions in the predictive model, the present results suggest that the baseline GM structure in these regions may play an important role in determining the clinical outcome of acupuncture treatment.

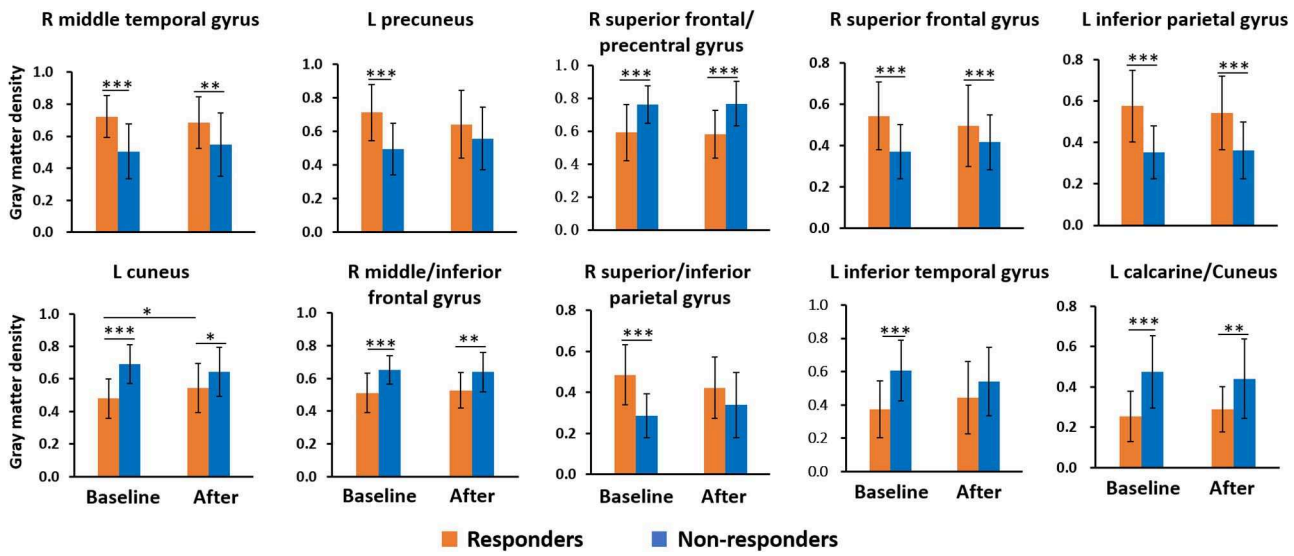


**FIGURE 4 |** Longitudinal changes in gray matter volume among responders and non-responders. All predictive regions showed a significant difference in baseline gray matter volume between responders and non-responders. The left cuneus in responders showed a longitudinal increase in gray matter volume. L, left; R, right. $^{*}P < 0.05$; $^{**}P < 0.01$; and $^{***}P < 0.001$.

The GM volume of the left cuneus in responders had significant longitudinal change after 1 month of acupuncture treatment. A previous study revealed an increase in the regional function in the cuneus after acupuncture treatment in patients with MwoA (36). Therefore, the plasticity change of the cuneus may be involved in the mechanism in acupuncture efficacy in treating migraine disease. However, the present study and the study by Zhang et al. (36) did not identify a correlation between the structural or functional changes of the cuneus and the clinical efficacy of acupuncture for MwoA. In addition, the present study lacked healthy controls, and so it was not possible to assess whether the GM volume after acupuncture in responders was turned to the GM volume in healthy people. Therefore, it is unclear whether the post-treatment change in GM volume was beneficial. More studies are needed to determine whether acupuncture exerts its effects by regulating the GM structure or the function of the cuneus in responders.

The present study had several limitations. First, there were insufficient follow-up data collected because of a relatively high dropout rate, and so it was not possible to analyze the prediction of long-term outcome. The prediction of long-term acupuncture efficacy requires further study. Second, a large sample study of multimodal imaging information (cortical thickness, white matter structure, and brain function) should be considered as the next step in developing more precise and objective predictive models related to the outcome of acupuncture treatment. Third, the present study only included one dataset, and so the repeatability of the results cannot be verified. In the future, it is necessary to test the repeatability of the predictive model in more datasets related to acupuncture treatment of migraine, in order to establish a reliable predictive model that is helpful in clinical practice.

## CONCLUSION

With the increasing use of acupuncture therapy worldwide (38), the ability to predict the acupuncture outcome would contribute to the development of individualized treatment and promote its wider application. The current study used the machine learning classification method to establish a data-driven prediction model for acupuncture efficacy, which demonstrates that pre-treatment GM volume might be a novel biomarker for acupuncture outcomes in MwoA. In the future, MRI structure could be explored in more diseases to identify neuroimaging markers that predict the treatment response to acupuncture.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine (ref: 2016BL-081-02). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

X-JY contributed to the study design, data analysis, interpretation of the data, and drafting of the manuscript. LL contributed

to the data acquisition and drafting of the manuscript. Z-LX contributed to the data analysis and drafting of the manuscript. Y-JZ contributed to the acquisition. LZ contributed to the data analysis. D-PL contributed to the data acquisition. MF critically revised the manuscript for intellectual content. J-BS, PL, and XZ contributed to the interpretation of the data. L-PW contributed to the study design and conceptualization and data interpretation. WQ contributed to the study design and conceptualization, data analysis, and interpretation.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00111/full#supplementary-material

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ORIGINAL RESEARCH
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# MR-Guided Focused Ultrasound Central Lateral Thalamotomy for Trigeminal Neuralgia. Single Center Experience

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**Background:** Trigeminal neuralgia (TN) is a recognized pain condition the treatment of which can be very challenging. Various surgical interventions can be applied in cases of therapy-resistance to drug treatments. The central lateral thalamotomy (CLT) against neurogenic (or neuropathic) pain is based on multiarchitectonic histological as well as physiopathological studies, and integrates the nucleus in a large thalamocortical (TC) and corticocortical network responsible for the sensory, cognitive and affective/emotional components of pain. The advent of the magnetic resonance imaging guided high intensity focused ultrasound (MRgFUS) brought a strong reduction in morbidity and increase in accuracy compared to penetration techniques.

**Objective:** This study was aimed at analyzing the outcome of bilateral MRgFUS CLT for chronic therapy-resistant trigeminal pain, all performed in one single center.

**Methods:** Patients were categorized in Classical, Idiopathic and Secondary TN. By definition, paroxysms lasted for seconds up to 2 min. All patients were screened for trigeminal neurovascular conflict. In case of classical TN, microvascular decompression was proposed. Therapy-resistance and thus indication for MRgFUS CLT was based on the lack of efficacy and/or side effects of antiepileptic and antidepressant drugs. Good outcome was defined by a pain relief $\geq$50%.

**Results:** Eight patients suffering from chronic therapy-resistant trigeminal neuralgia were treated. All suffered from pain with paroxysmal character. Six patients reported additionally continuous pain. Mean follow-up was 53 months (range: 12–92, median: 60 months). The mean pain relief assessed by patients was 51% (median: 58%, range: 0–90%) at 3 months, 71% (median: 65%, range: 40–100%) at 1 year and 78% (median: 75%, range: 50–100%) at their longest follow-up. This represents 63% good outcomes at 3 months, 88% at 1 year and 100% at last follow-up. Frequency of the mean pain paroxysms decreased from 84 per day preoperative to 3.9 at 1 year postoperatively. There were no serious adverse events in this series.

**Conclusion:** Our study provides preliminary support for the safety and efficacy of MRgFUS CLT, a histologically and pathophysiologically based medial thalamotomy against chronic therapy-resistant trigeminal neuralgia.

**Keywords: trigeminal neuralgia, trigeminal pain, MR-guided high intensity focused ultrasound, central lateral thalamotomy, stereotactic functional neurosurgery**

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## INTRODUCTION

At the beginning of the 20th century, Head and Holmes postulated the presence of an "essential medial thalamic center," anatomically located medially to a pain-generating lesion in the thalamic ventral posterior complex (VP) and responsible for the pathogenesis of central pain (1). Sano proposed the generation of abnormal impulses in VP and their amplification in a reverberating circuit between lateral and medial thalamic nuclei (2). Experimental and clinical data reported by Cesaro et al. (3) and Pierre et al. (4) supported an imbalanced interaction between medial and lateral thalamic areas, with a postulated disinhibition of the medial thalamus. The medial thalamotomy was one of the first stereotactic interventions performed on the human brain in the early 1950s. Unlike other lesional surgeries, medial thalamotomies against neurogenic (or neuropathic, or de-afferentation) pain have been recognized as interventions with a low complication rate and without the risk for developing iatrogenic pain manifestations or somatosensory deficits. They have been shown to provide pain relief for all body locations, and bilateral medial thalamotomies were shown to be more efficient than unilateral contralateral ones (5–7). This is in concordance with the fact that thalamic low threshold calcium spike bursts (6, 8) were found bilaterally and quantitative electroencephalographic (EEG) recordings showed evidence of bilateral physiopathology (see below). Although cases of total and stable pain relief have been published, recurrence of initial pain was frequent (2, 7, 9–16). These first reports led us from the late 1980s onward to re-investigate the medial thalamus and finally establish the posterior part of the Central Lateral nucleus (CLp) as target in chronic therapy-resistant neurogenic pain (5, 6, 8, 17–21), The central lateral thalamotomy (CLT) as a surgical intervention against neurogenic pain is based on multiarchitectonic histological studies and integrated in a large thalamocortical (TC) network responsible for the sensory, cognitive and affective/emotional components of pain. The CLp is in a position to transfer nociceptive information's conveyed through the spinothalamic and spinoreticulothalamic pathways to relatively large domains of cortex, including areas involved in nociception, mainly SII, insula and anterior cingulate cortex. In addition, single unit recordings of CLp thalamic cells (5, 6, 8, 18) and quantitative EEG and MEG analyses (22–24) have demonstrated TC overactivities located on cortical pain areas, constituting the final product of a TC process named thalamocortical dysrhythmia. This process is based on the de-afferentation of thalamic cells, which causes an increase of EEG low and high frequency activities at the source of pain perception. These microphysiological and quantitative EEG/MEG studies have shown the same pathophysiology for all neurogenic pain syndromes, whatever their location in the body, and thus including the trigeminal location. The absence of somatosensory deficits in most of the classical TN patients is likely due to the great compensatory capacities of the peripheral sensory trigeminal system and of the thalamocortical network, in addition to limitations of sensitivity of the physical examination.

The results obtained years ago in the medial thalamus by a few neurosurgical groups tend to support the primacy and possible exclusivity of CLp as a regulatory medial thalamic target: Sano (2), as an exception in his time, focused his efforts on the posterior part of the medial thalamus using a posterior approach, thus approaching more than anyone else the CLp, which was not or only partly reached by others. Hitchcock and Teixeira (7) as well as Young and col. (25) placed relatively large lesions in the posterior part of centrum medianum (CM)/Parafascicular nucleus (Pf), probably involving parts of the CLp. Urgosik and Liscak recently reported an overall pain relief success rate in 43% of their patients targeting the medial thalamus (CM/Pf complex) with the gamma knife (26). Those results were recently replicated by another group (27).

Since the first clinical experience with the MRgFUS (28) and a series with 1 year follow-ups against neurogenic pain (19), safety and accuracy data on this technique have been published several times (29–31).

This case series analyze the clinical results of consecutive MRgFUS treatments performed for chronic therapy-resistant trigeminal neuralgia with a mean follow-up of 4 years. This report reflects our current practice of treating chronic therapy-resistant neurogenic pain regardless of which body part is involved.

## METHODS

All patients treated with this protocol signed an informed consent form after having been fully informed about the treatment, its results and risks. No additional ethical approval was sought because MRgFUS CLT has been approved by the Federal Office of Public Health (FOPH) of Switzerland and is covered by swiss social insurances.

Patients were categorized according to Cruccu et al. (32) in Classical TN, Idiopathic TN and Secondary TN. Classical TN is defined as a specific category of TN in which MR demonstrates vascular compression of the trigeminal nerve root, Idiopathic TN occurs without apparent cause and secondary TN is the consequence of a major neurological disease (32). Outcome measures followed the criteria proposed by Zakrzewska and Lopez (33). By definition, paroxysms lasted from seconds up to 2 min. All patients were screened for trigeminal neurovascular conflict. In the case of such a conflict, microvascular decompression was proposed. Therapy-resistance and thus indication for MRgFUS CLT was based on the lack of efficacy and/or side effects of antiepileptic and antidepressant drugs during at least a year. Diagnosis was always ascertained by at least one neurologist. All Swiss patients operated between 2015 and 2017 were included in the Swiss registry for the incisionless MRgFUS therapy in functional neurosurgery and were seen postoperatively by an independent neurologist. Antiaggregant therapy was stopped 10 days before the intervention. Normal coagulation and blood pressure were checked for all patients prior to surgery.

## Surgical Procedure and Target Determination

The surgical procedure using the MRgFUS to perform CLT (19, 28), target reconstruction and accuracy determination (29–31) were described in prior publications. CLT was planned on maps of the Morel's Atlas of the human thalamus and Basal Ganglia (21) and modified according to individual anatomy as seen on the preoperative MR high resolution images cut in stereotactic planes. Target determination and coverage of the CLT target evolved over the years of clinical experience with at first placement where CLp output fibers converge, i.e., one sonication spot 6 mm dorsal to the intercommissural plane and 8 mm from the medial thalamic border. Our present and latest targeting strategy has as a goal to optimize CLT target coverage and consists of a set of 4 target sub-units placed at 6 mm (2 sub-units) and 8–9 mm (2 sub-units) dorsal to the intercommissural plane. The anteroposterior position of the sub-units is determined based on visualization on preoperative MR T2 axial images of the junction

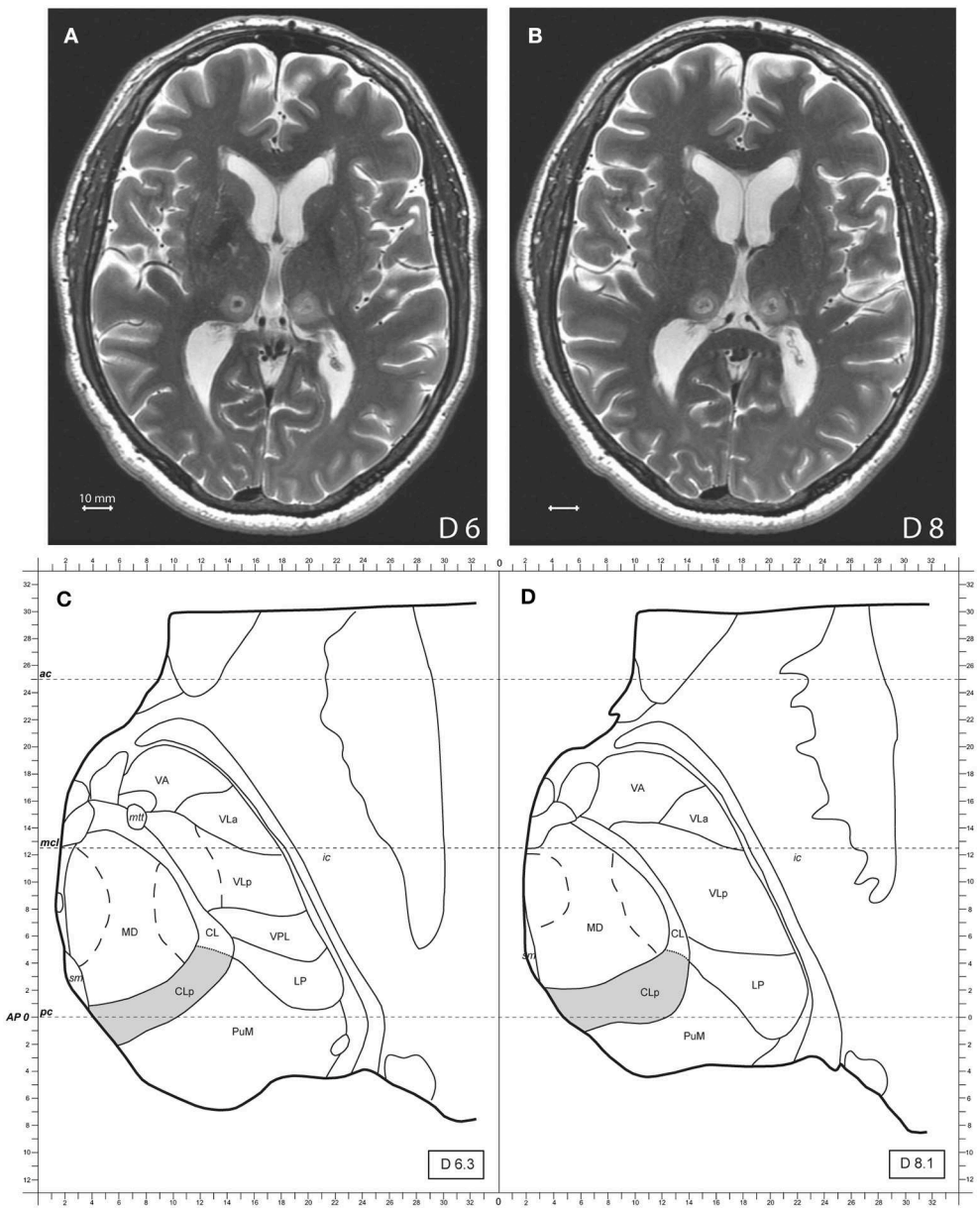


**FIGURE 1 | (A,B)** Show axial MR T2 images two days after the treatment, 6 and 8 mm dorsal to the intercommissural plane of a bilateral MRgFUS CLT. **(C,D)** Show modified atlas maps of the Morel's Atlas 6.3 and 8.1 mm dorsal to the intercommissural plane with the posterior Central Lateral nucleus (CLp) in gray. Mammillothalamic tract (mtt), ventral anterior nucleus (VA), ventral lateral anterior nucleus (VLa), ventral lateral posterior nucleus (VLp), ventral posterior lateral nucleus (VPL), lateral posterior nucleus (LP), medial pulvinar (PuM), mediodorsal nucleus (MD), internal capsule (ic), posterior commissure (pc), anterior commissure (ac).

**TABLE 1 |** Patients characteristics.

| Patient no. | Pain duration (yrs) | Side | Pain location | Etiology | Targets | Previous interventions | Primary headache history | Last follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 4 | Right | V1,V2,V3 | I | CLT bilat | – | – | 90 |
| 2 | 37 | Left | V2,V3 | I | CLT bilat | Thermocoagulation | Migraine | 92 |
| 3 | 12 | Right | V1,V2,V3 | C | CLT bilat | – | – | 84 |
| 4 | 21 | Left | V1,V2 | S (Tumor) | CLT R* + CMT R | Bilateral RF CLT | Tension-type headache | 62 |
| 5 | 30 | Right | V2,V3 | I | CLT bilat | Thermocoagulation | – | 58 |
| 6 | 6 | Left | V1,V2,V3 | S (MS) | CLT R† | Bilateral MRgFUS CLT | – | 14 |
| 7 | 20 | Right | V1,V2,V3 | C | CLT bilat | MDV, Glycerol rhizotomy, 2 Thermocoagulations, GKS | – | 15 |
| 8 | 4 | Right | V3 | C | CLT bilat | – | | 12 |
| Mean (SD) | 17 (12) | | | | | | | 53 (35) |
| Median | 16 | | | | | | | 60 |

**complement of radiofrequency ablation of the Central Lateral posterior nucleus (RF CLT), †complement of right CLT. C: classical. GKS, Gamma knife radiosurgery; I, idiopathic; MS, Multiple sclerosis; MVD, Microvascular decompression; S, secondary.*

between the medial dorsal nucleus (MD) and medial pulvinar (PuM) corresponding to the position of the CLp, centered in our experience between 3 mm anterior and 1 mm posterior to the posterior commissure. In the mediolateral (ML) dimension, 2 sub-units are placed to cover the ML extent of the CLp, i.e., from medial thalamic border to 10 mm laterally, e.g., 5 and 8 mm laterally for ML position of the sub-unit centers. **Figure 1** shows a bilateral MRgFUS CLT.

Ten mg domperidone (Motilium lingual®) were given prior starting sonications. The last patient of this series, received in accordance to our actual routine operation protocol 20 mg intravenous methylprednisolone in the hour following the end of the operation, 20 mg after 12 h and dexamethasone 2 mg three times daily for 3–4 days in order to control/limit the perifocal edema of the lesion. Control MR was performed 2 days postoperatively. Accuracy determination and target reconstruction were performed according to Moser et al. (30, 31).

## Follow-Up

Detailed pain assessments with a full neurological examination including assessment of esthesia and algesia were performed preoperatively and postoperatively after two days, 3 months and 1 year. Later follow-up assessments were mostly performed through e-mail and phone conversations. Pre- and postoperative assessments included the items of the McGill Pain Questionnaire. Pain intensity was noted on a visual analog scale (VAS) for the least, the worst and mean pain intensities on a scale between 0 and 100. Patients were asked for a percentage value of postoperative pain relief as compared with their preoperative state. Mini-mental test and later Montreal Cognitive Assessments were performed preoperatively and after 2 days and 1 year follow-up. Good outcome was defined by a pain relief $\geq$50%. A recurrence was defined as initial good outcome (pain relief $\geq$ 50%) and later decrease of pain relief $<$50% and/or recurrence of pain attacks.

## Statistics

Statistical analysis of quantitative scores compared with baseline was carried out by repeated ANOVA measures and multiple comparisons were applied using a *post hoc* analysis with Bonferroni-Holm testing (Daniel's XL toolbox; https://www.xltoolbox.net/).

# RESULTS

Patient's characteristics are summarized in **Table 1**. Mean symptoms duration was 17 $\pm$ 12 years (range 4–37). Mean age at treatment was 62 $\pm$ 12 years (46–79). Three patients were female. Mean follow-up was 53 $\pm$ 35 months (12–92). Median follow-up was 60 months. No patient was lost to follow-up.

Eight consecutive trigeminal neuralgia patients treated between 06/2011 and 11/2017 were analyzed here. All patients suffered from pain with paroxysmal character. 6 patients reported additionally continuous pain. Three patients were classified as Idiopathic TN, 3 as Classical TN and 2 as Secondary TN. Secondary causes for TN were multiple sclerosis (1) and 1 trigeminal schwannoma operated 20 years prior to MRgFUS intervention. There has been no sign of recurrence The patient with multiple sclerosis did not present MR signs of active demyelination, i.e., plaques accounting for a new potential source of pain in addition to the known causal brainstem plaque. All patients showed at least mild somatosensory deficits at detailed clinical examination. Nine surgical interventions for pain were performed in 5 patients previously (4 trigeminal thermocoagulation, 1 microvascular decompression, 1 glycerol injection, 1 gamma knife irradiation of the root of the trigeminal nerve, and 1 bilateral radiofrequency CLT and 1 bilateral CLT with MRgFUS). Two patients with classical TN refused microvascular decompression (MVD) prior to this study time.

**TABLE 2 |** Summary of pain reliefs, baseline and postoperative pain intensities.

| Patient no. | Pain relief (%) at 3 months | Pain relief (%) at 1 year | Pain relief (%) last follow-up | Somatosensory deficits preoperatively | Sensory improvements at 1 year | baseline cont. pain min-max VAS | baseline cont. pain mean VAS | baseline pain paroxysms min-max VAS | baseline pain paroxysms mean VAS | 3 months cont. pain min-max VAS | 3 months cont. pain mean VAS | 3 months pain paroxysms min-max | 3 months pain paroxysms mean VAS | 1 year cont. pain min-max VAS | 1 year cont. pain mean VAS | 1 year pain paroxysms min-max VAS | 1 year pain paroxysms mean VAS | last follow-up cont. pain min-max VAS | last follow-up cont. pain mean VAS | last follow-up pain paroxysms min-max VAS | last follow-up pain paroxysms mean VAS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 75 | 90 | 60 | + | + | 27–55 | 41 | 62–99 | 81 | 0–60 | 30 | 0 | 0 | 0–20 | 10 | 0 | 0 | 0–55 | 28 | 0 | 0 |
| 2 | 50 | 60 | 100 | + | 0 | 44–91 | 68 | 52–90 | 71 | 10–60 | 35 | 0 | 0 | 0–50 | 25 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 80 | 100 | 100 | + | + | no | no | 35–100 | 68 | – | – | 5–20 | 13 | – | – | 0 | 0 | – | – | 0 | 0 |
| 4 | 30 | 40 | 80 | + | 0 | 38–65 | 52 | 43–97 | 70 | 0 | 0 | 84 | 84 | 0 | 0 | 84–84 | 84 | 0 | 0 | 84 | 84 |
| 5 | 20 | 50 | 50 | + | + | 16–86 | 52 | 26 | 26 | 8–78 | 43 | 18 | 18 | 0–74 | 37 | 34–34 | 34 | 21–80 | 67 | 44 | 44 |
| 6 | 0 | 60 | 60 | + | 0 | 21–44 | 33 | 58–82 | 70 | 0 | 0 | 82 | 82 | 0 | 0 | 24–58 | 41 | 0 | 0 | 24–58 | 41 |
| 7 | 65 | 70 | 70 | + | + | 12–100 | 56 | 95–100 | 98 | 21–45 | 28 | 25–65 | 45 | 0 | 0 | 15–60 | 38 | 0 | 0 | 15–60 | 38 |
| 8 | 90 | 100 | 100 | + | + | no | no | 80 | 80 | – | – | 12 | 12 | – | – | 10 | 10 | – | – | 10 | 10 |
| Mean | 51 | 71 | 78 | | | | 50 | | 70 | | 23 | | 32 | | 12 | | 26 | | 16 | | 27 |
| Median | 58 | 65 | 75 | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | $p = 0.01$ | | $p = 0.02$ | | $p = 0.0008$* | | $p = 0.003$* | | $p = 0.02$ | | $p = 0.005$* |

*P-values given after Bonferroni–Holm correction for multiple testing with baseline. *values which reached statistical significance after correction.*

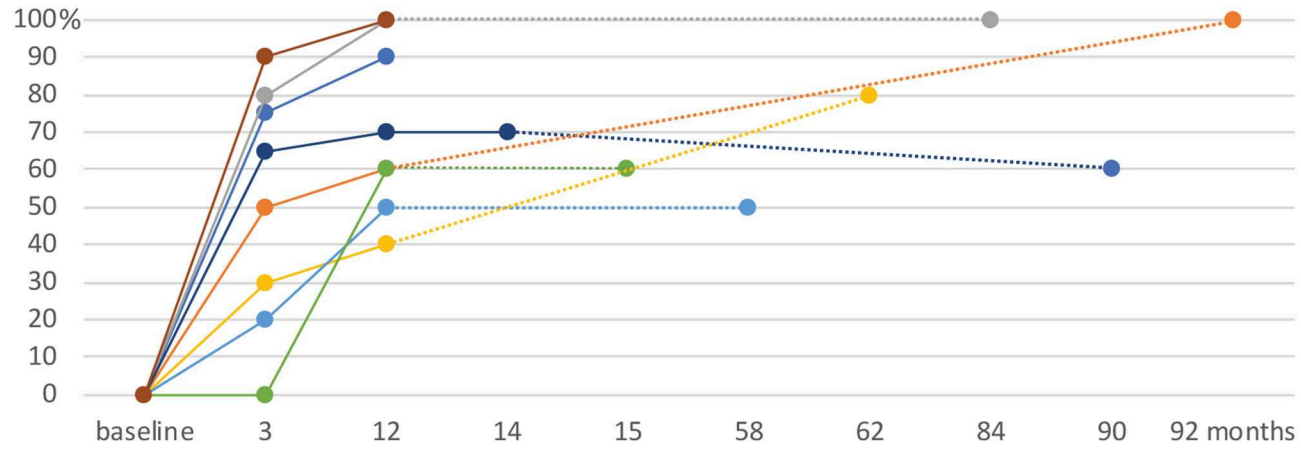


**FIGURE 2 |** Pain relief in % as rated by the patients over time (months), from baseline to the last follow-up. Intervals between consultations of more than 12 months are connected with dotted lines.

**TABLE 3 |** Pain qualities at baseline and follow-up examinations and Frequency of pain paroxysms.

| Patient no. | Pain qualities preoperative | Pain qualities at 3 months FU | Pain qualities at 1 year FU | preoperative frequency of spontaneous pain paroxysms [$d^{-1}$] | 3 months FU frequency of spontaneous pain paroxysms [$d^{-1}$] | 1 year FU frequency of spontaneous pain paroxysms [$d^{-1}$] | last control FU frequency of spontaneous pain paroxysms [$d^{-1}$] |
|---|---|---|---|---|---|---|---|
| 1 | B, P, E, L | T, B | B | 240 | 0 | 0 | 0 |
| 2 | St, P, B, E, L, C, T | P, B, C | B, S | 8 | 0 | 0 | 0 |
| 3 | E, L, C, T | 0 | 0 | * | * | 0 | 0 |
| 4 | S, St, B, C | Cut, C | T, B, S | 3.5 | 2.0 | 0.5 | 0.1 |
| 5 | P, S, B, E, T | P, B, L | P, A, L | 2 | 0.03 | 0.05 | 0.02 |
| 6 | P, E, C, T | St | E, A, T | 100 | * | * | * |
| 7 | E, B | E, P, B | B, P | 150 | – | 23 | 23 |
| 8 | P, A | P | P | * | * | * | * |
| Mean (SD) | | | | 84 (98) | | 4.0 (9.3) | 3.9 (9.4) |

*Pins and needles (P), tearing (T), stinging (S), aching (A), burning (B), stabbing (St), compression (C), electricity (E), lightning (L), cutting (Cut), *provoked attacks only. Follow-up (FU).*

All patients had unilateral pain syndromes, 5 of them on the right side. Distribution of the pain in the trigeminal territories is given in **Table 1**.

## Surgery

Bilateral CLT in one session was performed in 6 patients. In Patient 4 previously treated with bilateral CLT RF, unilateral CLT complement as well as 1 centrum medianum (CM) target were performed. Patient 6 received a complementation on the right side of his bilateral MRgFUS CLT performed 14 months previously. The complement of the CLT target was offered because of symptom recurrence due to partial target coverage.

Average number of sonications was 15 ± 8 (5–31) and their duration was between 20 and 31 s. The average power of final sonications was 1020 ± 236 [W] (650–1300). Final temperatures were between 54 and 58°C. Mean lesion volume measured on MR T2 axial and sagittal images 2 days after treatment was 153 ± 85 $mm^3$ (51–247 $mm^3$). All patients were discharged after one night hospital stay.

## Pain Relief

The mean pain relief assessed by patients was 51% (median: 58%, range: 0–90%) at 3 months, 71% (median: 65%, range: 40–100%) at 1 year and 78% (median: 75%, range: 50–100%) at their longest follow-up (see **Table 2** and **Figure 2**). This represents 63% good outcomes at 3 months, 88% at 1 year and 100% at last follow-up. As defined above, no patients had a recurrence during the study period. Patient 6, who had a recurrence after a previous bilateral MRgFUS CLT enjoyed a 60% pain relief 1 year after right-sided CLT target complementation. Between 3 months and 12 months, 2 patients went from an insufficient to a good pain outcome. One patient had insufficient pain relief (40%) at 1 year, but reached 80% at last follow-up (62 months).

At last follow-up, pain paroxysms were still present in 5 patients (63%) but their mean intensity was 27 ± 30/100 compared to 70 ± 20 preoperatively on VAS. Of the 6 patients reporting continuous pain preoperatively, 2 still reported continuous pain at last follow-up. Their mean continuous pain level was 16 ± 27/100 at last follow-up, compared with 50 ±

**TABLE 4 |** Drug intakes.

| No. | tried drugs, already stopped | preoperative drug intake | 3 months drug intake | 1 year drug intake | drug intake at last follow-up |
|---|---|---|---|---|---|
| 1 | Pregabaline<br>various opiates | Carbamazepine 1,200 mg<br>Anafranil 75 mg<br>Tramadol<br>and Buprenorphine-Patch | Carbamazepine 800 mg<br>Anafranil 75 mg | Carbamazepine 800 mg | Carbamazepine 1,200 mg |
| 2 | Carbamazepine<br>Opiates | Tramadol 200mg<br>Ibuprofen 1800mg<br>Pregabaline 100 mg<br>Rivotril 1 mg | Pregabaline 100 mg<br>Venlafaxine 150 mg<br>Rivotril 0,5 mg | Pregabaline 100 mg<br>Venlafaxine 150 mg | 0 |
| 3 | Amitriptyline | Carbamazepine 800mg<br>Gabapentine 600 mg | Carbamazepine 600 mg | Carbamazepine 200mg | 0 |
| 4 | Pregabaline | Diclofenac | 0 | 0 | 0 |
| 5 | Carbamazepine,<br>Pregabaline<br>Gabapentine, Tramal,<br>Amitriptyline, Naproxen,<br>Paracetamol, Tizanidin | Durogesic-Patch 25 und<br>12 μg<br>Targin i.R.<br>Venlaflaxine 75 mg<br>Trimipramine 25 mg | Targin 5 mg<br>Trimipramine 25 mg | Targin 5 mg<br>Trimipramine 25 mg | Oxynorm 1-0-1*<br>Trimipramine 25 mg |
| 6 | – | Carbamazepine CR<br>1000mg,<br>Pregabaline 200mg,<br>Clomipramine 50 mg<br>Modafinil 400 mg | Carbamazepine CR<br>900 mg,<br>Pregabaline 375 mg<br>Clomipramine SR 75 mg<br>Modafinil 400 mg | Clomipramine SR 75 mg<br>Oxcarbazepine 900 mg | Clomipramine SR 75 mg<br>Oxcarbazepine 900 mg |
| 7 | Pregabaline<br>Carbamazepine<br>Morphium | Oxcarbazepine 900 mg,<br>Cymbalta 60 mg 0/0/1,<br>Tapentadol 300 mg | Oxcarbazepine 450 mg | Oxcarbazepine 900mg | Oxcarbazepine 900mg |
| 8 | - | Carbamazepine 800 mg | Carbamazepine 200 mg | Carbamazepine 200 mg | Carbamazepine 200 mg |

**taken in a context of chronic lumbovertebral pain syndrome.*

12/100 preoperatively. At last follow-up, statistical significance was reached for pain paroxysms but not for continuous pain. Pain qualities of both (continuous and paroxysmal) pain components as well as frequency of spontaneous pain paroxysms are detailed in **Table 3**. Frequency of spontaneous pain paroxysms decreased from 84 (2–240) daily preoperatively, to 4.0 (0–2) at 3 months and 3.9 (0–23) 1 year postoperatively. Sensory improvements (reduction of esthesia and/or algesia deficits) were documented during postoperative clinical neurological examinations in 5 patients.

## Secondary Outcome Measures

Mean Anxiety and Depression Scale (HADS) scoring was 14.4 ± 5.8 (5–21) preoperatively, 8.5 ± 3.7 (2–14) at 3 months ($p = 0.03$) and 7.6 ± 4.1 (2–16) ($n = 8$, $p = 0.017$) at 1 year follow-up. They were no cognitive changes, as assessed with MMST ($n = 3$) or MoCA ($n = 5$). Mean MMST scores were 29.3 ± 0.6 preoperatively, 29.7 ± 0.6 at 2 days, 3 months and 1 year follow-up. Mean MoCA scores were 26.8 ± 4.1 (20–30) preoperatively, 28.0 ± 2.5 at 2 days (24–30) and 28.6 ± 2.1 (25–30) ($p = 0.28$) at 1 year follow-up.

## Morbidity

There were no serious adverse events in this series. Sonications were painful for a few seconds in 2 patients. No patients reported lasting headache >6 h after the procedure. There were 3 mild side effects, one postoperative frontal scalp swelling which resolved within a week and 2 mild cases of transient vertigo. There were no new somatosensory deficits, bleeding, infection or mortality in this series.

## Drugs

The drug intake of all patients was detailed in **Table 4**. Antiepileptic drug intake could be stopped in 2 patients and reduced in 2.

# DISCUSSION

The CLT with MRgFUS has already been demonstrated to be a safe therapeutic option in chronic neurogenic pain with over 100 targets performed (19, 28, 29). This case series on 8 bilateral MRgFUS CLT for trigeminal pain with a mean follow-up over 4 years confirmed the very low risk profile of the intervention. It provided specific pain relief values for patients suffering from chronic therapy-resistant pain of trigeminal location. Pain relief after more than 1 year of follow-up averaged 78% (median: 75%) and was sensibly better than previously published series for other neurogenic pain locations (6, 8, 17, 19). The observed progression of pain relief over time is in accordance with a progressive reduction of the TC physiopathology (19, 24). All patients in this series acknowledged a pain relief of ≥50 % and the frequency of pain paroxysms was reduced by more than 95%. A positive bias cannot be excluded in view of the small patient number.

No lesional intervention (i.e., gamma knife surgery, radiofrequency thermocoagulation, glycerol rhizotomy, balloon compression) reached more than a low level of evidence supporting primacy over the others (34). According to our data summarized in the Introduction and to Finnerup et al. (35), trigeminal neuralgia, central post-stroke pain involving the face and central neurogenic pain associated with multiple sclerosis are recognized as neurogenic pain conditions. In this context, any further de-afferentation of the trigeminal nerve, be it either by irradiation, thermocoagulation, toxic or compression lesioning brings a risk of worsening of the neurogenic pain condition. This risk is recognized in the literature as dysesthesias or anesthesia dolorosa. As expected from the role of the medial thalamus in the TC dynamics, and as recognized in the early literature, such a iatrogenic pain production does not arise after CLT. In addition, the high plasticity of the TC network (36) can be proposed to be at the source of the absence of any somatosensory, motor or cognitive deficits, even in the acute postoperative phase: the pathophysiological basis for such a sparing capacity is the suppression of receptive fields in more than 99% of recorded CLp cells (18). These cells maintain the TC overactivity, but in addition lose their normal functions in the process, which are most probably taken over by other medial TC partners.

The CLp target, which was selected on the basis of the pathophysiological presence of low threshold calcium spike bursts discharging at 4 Hz, offers advantages over other medial thalamic targets. In contrast to the CM/Pf or to PuM, all targeted in the past (2, 7, 10, 16, 37), the CLp has known afferents from the spinothalamic tract. It is distant from primary somatosensory nuclei [ventral posterior medial (VPM) and lateral (VPL) nuclei]. An encroachment of lesioning onto adjacent structures, i.e., PuM or posterior part of MD never caused unwanted neurological or cognitive effects in the past experience (6, 8, 17, 19). The PuM provided even pain relief, which was howerver not long-lasting (16). Connections of the CLp concern large cortical domains, including areas mediating discriminative (SI, SII, posterior insula), affective-motivational (anterior cingulate, anterior insula), cognitive (prefrontal and posterior parietal cortex) and premotor aspects of pain (17, 38). This is not the case for the other medial thalamic targets.

Despite our active proposition to perform a microvascular decompression, two classical TN patients chose MRgFUS CLT and showed high pain relief at follow-up. The MRgFUS CLT represents a chance for patients who have a vascular compression but cannot or do not want to undergo a MVD.

## CONCLUSION

The bilateral MRgFUS CLT offers a physiopathologically based approach combining very low morbidity, good efficacy, absence of pain worsening and long term relief from neurogenic pain. Results of this small case series on chronic therapy-resistant trigeminal neuralgia, with a mean follow-up over 4 years, provides support for these characteristics in a given specific neurogenic pain location. Only a larger experience with this approach will demonstrate if it represents a treatment of first choice for patients who are not candidates for MVD.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. All patients treated with this protocol signed an informed consent form after having been fully informed about the treatment, its results and risks.

## AUTHOR CONTRIBUTIONS

MG and DJ contributed to the conception, design of the study, acquisition, analysis, interpretation of the data and co-drafted the manuscript. DM co-drafted the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest:** MG, DM, and DJ were employed by SoniModul Ltd., Center of Ultrasound Functional Neurosurgery, Solothurn, Switzerland.

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# Erenumab in Chronic Migraine Patients Who Previously Failed Five First-Line Oral Prophylactics and OnabotulinumtoxinA: A Dual-Center Retrospective Observational Study

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Raffaelli B, Kalantzis R, Mecklenburg J, Overeem LH, Neeb L, Gendolla A and Reuter U (2020) Erenumab in Chronic Migraine Patients Who Previously Failed Five First-Line Oral Prophylactics and OnabotulinumtoxinA: A Dual-Center Retrospective Observational Study. Front. Neurol. 11:417. doi: 10.3389/fneur.2020.00417

**Background:** German authorities reimburse migraine prevention with erenumab only in patients who previously did not have therapeutic success with at least five oral prophylactics or have contraindications to such. In this real-world analysis, we assessed treatment response to erenumab in patients with chronic migraine (CM) who failed five oral prophylactics and, in addition, onabotulinumtoxinA (BoNTA).

**Methods:** We analyzed retrospective data of 139 CM patients with at least one injection of erenumab from two German headache centers. Patients previously did not respond sufficiently or had contraindications to β-blockers, flunarizine, topiramate, amitriptyline, valproate, and BoNTA. Primary endpoint of this analysis was the mean change in monthly headache days from the 4-weeks baseline period over the course of a 12-weeks erenumab therapy. Secondary endpoints were changes in monthly migraine days, days with severe headache, days with acute headache medication, and triptan intake in the treatment period.

**Results:** Erenumab (starting dose 70 mg) led to a reduction of −3.7 (95% CI 2.4–5.1) monthly headache days after the first treatment and −4.7 (95% CI 2.9–6.5) after three treatment cycles ($p < 0.001$ for both). All secondary endpoint parameters were reduced over time. Half of patients (51.11%) had a >30% reduction of monthly headache days in weeks 9–12. Only 4.3% of the patients terminated erenumab treatment due to side effects.

**Conclusion:** In this treatment-refractory CM population, erenumab showed efficacy in a real-world setting similar to data from clinical trials. Tolerability was good, and no safety issues emerged. Erenumabis is a treatment option for CM patients who failed all first-line preventives in addition to BoNTA.

**Keywords: chronic migraine, prevention, calcitonin gene-related peptide, erenumab, onabotulinumtoxinA**

## INTRODUCTION

Migraine prevention is hampered by poor tolerability of available oral drugs, low therapeutic adherence, and insufficient efficacy in a substantial percentage of patients (1, 2). Prior to the approval of the calcitonin gene-related peptide (CGRP)-(receptor) monoclonal antibodies (mAbs), topiramate, and onabotulinumtoxinA (BoNTA) had been the only approved preventative medications in the United States and Europe for the prophylaxis of chronic migraine (CM) (3). mAbs have shown in clinical trials a favorable profile in terms of safety and efficacy, along with significant improvement in daily functioning and quality of life (4, 5). They have several potential advantages compared to standard oral preventives, including a rapid onset of efficacy, ease of use, persistent therapeutic effect, and lack of pharmacological interactions with other medications (6–8).

Erenumab, which blocks the calcitonin gene-related peptide (CGRP) receptor, was launched in Germany in November 2018 and is approved by the European Medicine Agencies (EMA) for the treatment of CM (9). Approval was based on the phase II registration trial (NCT02066415) (10). In this trial, both erenumab doses (70 and 140 mg) led to a significantly greater reduction of monthly migraine days (MMD) than placebo in the last four of the 12 study weeks (−6.6 days for erenumab vs. −4.2 for placebo) (10). Over two-thirds (73.8%) of the patients in the trial had tried at least one prior preventive treatment, and 92.1% of these reported at least one treatment failure due to poor efficacy or tolerability (11). Of note, 66.5% of patients who had previously tried BoNTA therapy for CM had failed this treatment (11). Failure to respond to more than three preventives previously was an exclusion criterion in this trial (10). Erenumab and other CGRP antibodies have not been studied in a migraine population with more than four treatment failures.

Owing to the lack of evidence that erenumab or any other CGRP mAb is superior to established first-line migraine preventive drugs, the European Headache Federation (EHF) and other international guidelines as well as expert opinion suggest the use of mAbs in patients who failed at least two previous oral prophylactic therapies or BoNTA in CM (6, 12, 13). In Germany, the German Federal Joint Committee (Gemeinsamer Bundesausschuss = GBA), a board that sets medical therapy regulations for the public health insurance sector, has identified a specific group of patients for whom the treatment with a mAb will be reimbursed (14). The suitable group consists of patients who previously failed or had contraindications for at least five different anti-migraine treatment classes. According to the authorities, these include the following first-line preventives: one beta blocker (metoprolol or propranolol), flunarizine, topiramate, amitriptyline, and valproate (14). In CM patients, previous failure to BoNTA is additionally required for the reimbursement of erenumab (14). The rationale for these six recommended classes is not based on rigorous scientific data, but rather on the responsible body's (GBA) majority decision (14). This rule applies to the public health insurance sector, which covers the costs of 90% of the population in Germany. Although not favorable to the patients, the GBA's ruling allows us the real-world analysis of data from a patient population that has, at least to our knowledge, never been studied in a clinical migraine trial.

Therefore, we conducted an analysis of CM patients on erenumab therapy who had previously failed or had contraindications to all first-line oral preventives and additionally BoNTA.

## MATERIALS AND METHODS

We analyzed the pharmacy prescriptions for erenumab between November 1, 2018 and April 30, 2019 of the headache center at the Charité—Universitätsmedizin Berlin and the headache specialist's practice Praxis Gendolla in Essen, Germany, retrospectively. This was followed by the review of the electronic chart of every patient with a registered erenumab order and the diagnosis of CM. Other headache diagnoses were exclusion criteria. Only patients who received at least one erenumab s.c. injection and also had history of a non-successful BoNTA therapy following the PREEMPT protocol (15) were included in this analysis. In addition, all patients had failed five first-line migraine preventive medications (metoprolol/propranolol, flunarizine, topiramate, amitriptyline, and valproate) or were unsuitable for these therapies due to contraindications.

In line with a recent study (16), failure to previous medications including BoNTA was defined as treatment discontinuation due to lack of efficacy and/or tolerability reasons as self-reported by patient and/or according to physician decision as documented in the patients' chart.

### Headache Characteristics and Clinical Evaluation

We collected headache data for the following periods: 4 weeks before erenumab treatment (baseline), weeks 1–4 after treatment initiation, weeks 5–8 (after the second treatment cycle), and weeks 9–12 (after the third treatment cycle).

Patients recorded their headaches in headache diaries, which are routinely used and collected in our headache centers. The standard headache diary used by our patients is provided by the German Migraine and Headache Society (Deutsche Migräne- und Kopfschmerzgesellschaft, DMKG) and is available in different languages at http://www.dmkg.de/patienten/dmkg-kopfschmerzkalender.html. When headache diaries were not available, we used the electronic documentation of headache data by the treating physician. Headache data in headache diaries or per electronic documentation included the following discrete numerical variables: monthly headache days (MHD), MMD, monthly days with severe headache (MDSH), monthly days with acute medication use (AMD), and monthly days with triptan use (TriD). We collected side effects and dosing information (70 or 140 mg) as categorical variables using the electronic documentation of the treating physician. Only patients with complete information about at least MHD during baseline were included in the efficacy analysis, i.e., analysis of headache characteristics over time. Patients with missing headache data were excluded from the efficacy analysis, but still included in the analysis of side effects.

A headache day was defined as any day on which a patient recorded any type of headache. We classified a headache day as migraine day if the ICHD-3 criteria of probable migraine applied (17), or when headache was preceded by an aura, and/or improved after triptan intake. We defined headache intensity ≥7/10 on a numeric analog scale as severe. All headache data were averaged across the respective 4-weeks period (i.e., at baseline, weeks 1–4, weeks 5–8, and weeks 9–12).

We also assessed multiple demographic and anamnestic features of the study population. This included the categorical variables sex (female or male), family history for headaches (positive or negative), and history of aura (positive or negative), the continuous numeric variables age, and age at migraine onset. For all previous prophylactic medications, we collected the numeric variable treatment duration, and time interval prior to erenumab treatment, and the categorical variable reasons for treatment failure (side effects or lack of efficacy). For BoNTA, we also recorded the number of treatment cycles and documented the side effects in detail.

## Statistical Analysis

Demographic and anamnestic variables were examined using descriptive statistics. The primary endpoint of our analysis was the change in MHD from baseline over the course of a 12-weeks treatment. The secondary endpoints were changes in MMD, MDSH, AMD, and TriD in the same time period. Normal distribution of data was assessed with the Kolmogorov–Smirnov test. Since all variables were normally distributed, we compared the 4-weeks baseline phase with the 4-weeks period following each treatment cycle using paired-samples *t*-tests (i.e., baseline vs. weeks 1–4, baseline vs. weeks 5–8, and baseline vs. weeks 9–12). Patients included in each pairwise comparison varied depending on available headache information. We reported the number of included patients for each analysis. Statistical

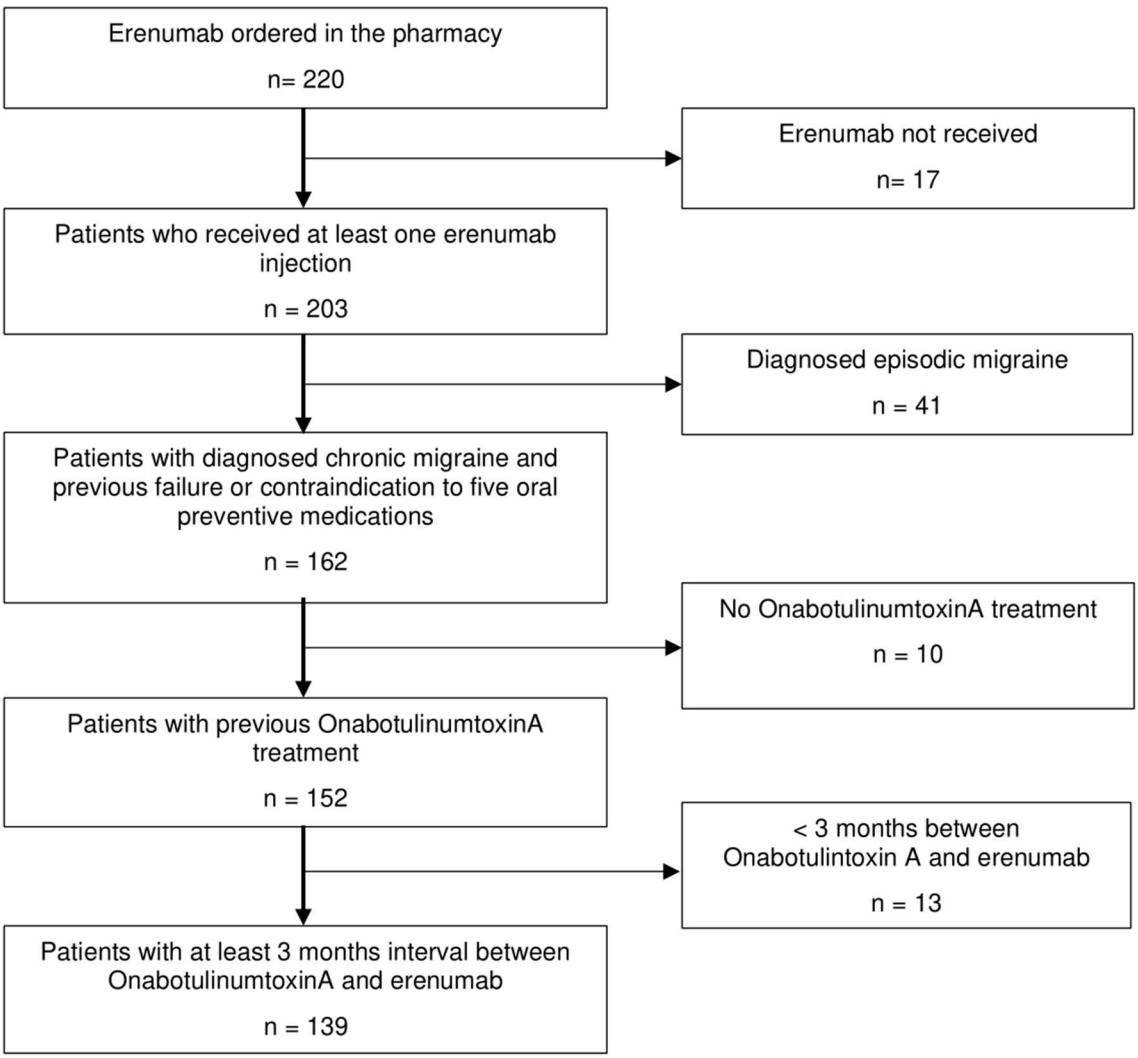


**FIGURE 1 |** Flowchart of patient selection.

analysis was performed with IBM SPSS Statistics, version 25. A value of $p \leq 0.05$ was considered statistically significant. Test for significance was corrected for multiple comparisons using Bonferroni correction. Categorical data were reported as percentage, numerical data as mean (±standard deviation or 95% confidence interval). Owing to the retrospective design of the study, we did not perform a sample size calculation but included all patients fulfilling the inclusion criteria treated at our headache centers between November 1, 2018 and April 30, 2019.

# RESULTS

## Demography

We included 139 CM patients in the analysis (**Figure 1**). All patients were eligible for erenumab therapy according to the authorities' regulations. Both headache centers contributed patient data in equal numbers [$n = 71$ in Essen (51.1%) vs. $n = 68$ in Berlin (48.9%)].

Patients were mostly female ($n = 116$, 83.5%) with an average age of 53.4 ± 10.2 years; age at migraine onset was 20.0 ± 13.6 years. A history of aura was reported in 31 patients (22.3%), and a large majority ($n = 115$, 82.7%) had a positive family history for migraine. Demographic variables were not different for patients in Berlin and in Essen (**Table 1**).

**TABLE 1 |** Selected demographic and anamnestic characteristics of patients in our two headache centers.

| | Berlin | Essen | *p* |
|---|---|---|---|
| *N* | 71 | 68 | |
| Female (%) | 78.9 | 88.2 | >0.999 |
| Age | 52.5 ± 9.7 | 54.3 ± 10.6 | >0.999 |
| Age at migraine onset | 19.5 ± 17.0 | 20.7 ± 9.0 | >0.999 |
| History of aura | 23.4% | 23.9% | >0.999 |
| Family history for headaches | 96.2% | 76.4% | 0.140 |

*n, number of patients; p, Bonferroni adjusted p-value for multiple (= 5) comparisons.*

## Migraine Prophylactic Treatments

In addition to BoNTA, patients had on average 3.6 ± 1.2 non-successful prior treatment attempts due to lack of either efficacy or tolerability issues. This number does not include medications for which contraindications exist. This was in the majority of cases valproate in women with childbearing potential. The reasons for treatment termination are shown in **Table 2**.

A large majority of patients ($n = 111$, 79.9%) also failed further prophylactic medications of second or third choice (18), most commonly venlafaxine ($n = 48$), candesartan ($n = 31$), or opipramol ($n = 28$).

Twenty patients (14.4%) continued one other concomitant migraine prophylactic treatment ($n = 7$ metoprolol, $n = 10$ topiramate, and $n = 2$ amitriptyline) during erenumab therapy. Three more patients stayed on metoprolol due to arterial hypertension, and seven on amitriptyline because of concomitant depression.

## Historic OnabotulinumtoxinA Treatment

Patients in this analysis had received 4.1 ± 3.8 BoNTA treatment cycles following the PREEMPT protocol (15). Side effects of BoNTA were reported by 17.3% of patients, among which neck pain was the most frequent (37.5%), followed by facial paralysis or ptosis (25.0%), and injection site pain (16.7%). The discontinuation rate due to side effects was 11.5%; all other patients terminated BoNTA due to insufficient headache response. All patients who discontinued BoNTA primarily due to side effects had received either one or two treatment cycles and had not reported a relevant migraine improvement until treatment discontinuation.

## Erenumab Treatment

Between November 2018 and April 2019, $n = 14$ patients had received at least one erenumab treatment cycle: $n = 26$ two, $n = 32$ three, and $n = 67$ more than three treatment cycles in a monthly subcutaneous regimen. Average time interval between the last BoNTA treatment cycle and the first erenumab treatment was 34.8 ± 37.1 months. Patients started erenumab therapy with a dose of 70 mg s.c. without any exception. Dosage escalation to 140 mg was done in 7.3% of patients after 4 weeks (second treatment) and in 29.5% after 8 weeks (third erenumab cycle). A small majority of patients (52.8%) who continued erenumab after the third cycle received thereafter a dose of 140 mg.

## Headache Characteristics During Erenumab Treatment

Eighty-four patients completed headache diaries during the four baseline weeks and reported 18.2 MHD (95% CI 16.8–19.65). MHD at baseline were similar in patients in Berlin (17.7, 95% CI 15.8–19.6) and in Essen (18.9, 95% CI 16.55–21.33, $p = 0.405$). Erenumab led on average to a reduction of MHD by 21.5% (95% CI −30.8−12.1) in weeks 1–4 ($n = 68$), by 31.1% (95% CI −40.1−22.2) in weeks 5–8 ($n = 60$), and by 27.2% (95% CI −37.9−16.4) in weeks 9–12 ($n = 45$, $n = 25$ with 70 mg and $n = 20$ with 140 mg).

Almost 40% of patients ($n = 27/68$) reported a reduction of >30% in weeks 1–4, 53.3% ($n = 32/60$) in weeks 5–8, and 51.1% ($n = 23/45$) in weeks 9–12. A 50% response to erenumab was achieved by one in three patients (31.1%) in weeks 9–12.

We also had patients without any response to erenumab treatment. Eleven patients (24.4%) showed no change or worsening of MHD in weeks 9–12, in addition to the previous failure to BoNTA and all first-line treatment classes. **Figure 2** shows response rates in weeks 9–12.

In a descriptive analysis, patients who continued on erenumab 70 mg seemed to have higher response rates than patients who switched from 70 to 140 mg: −36.6% (95% CI −49.2−24.0) for the 70-mg group and −15.3% (CI −33.8–3.1) for the 140-mg group in weeks 9–12.

Other parameters such as MMD, MDSH, and AMD showed significant improvement (**Table 3**). In particular, erenumab reduced days with the intake of a triptan by more than 50%

**TABLE 2 |** Characteristics of previous prophylactic treatment.

| Medication | *n* (%) | Treatment duration (months) | End of onabotulinumtoxinA (BoNTA) therapy to erenumab initiation in years | Reason for treatment discontinuation | |
|---|---|---|---|---|---|
| | | | | Side effects | Lack of efficacy |
| β-Blocker | 90.6 | 29.9 ± 47.9 | 6.6 ± 5.9 | 40.3% | 95.1% |
| Topiramate | 87.1 | 20.2 ± 31.1 | 5.9 ± 4.9 | 72.4% | 81.4% |
| Flunarizine | 65.5 | 5.2 ± 7.6 | 6.0 ± 6.3 | 52.0% | 89.8% |
| Valproate | 36.0 | 3.2 ± 2.9 | 6.1 ± 6.2 | 82.6% | 91.3% |
| Amitriptyline | 77.4 | 17.1 ± 26.6 | 5.2 ± 5.1 | 61.7% | 92.2% |

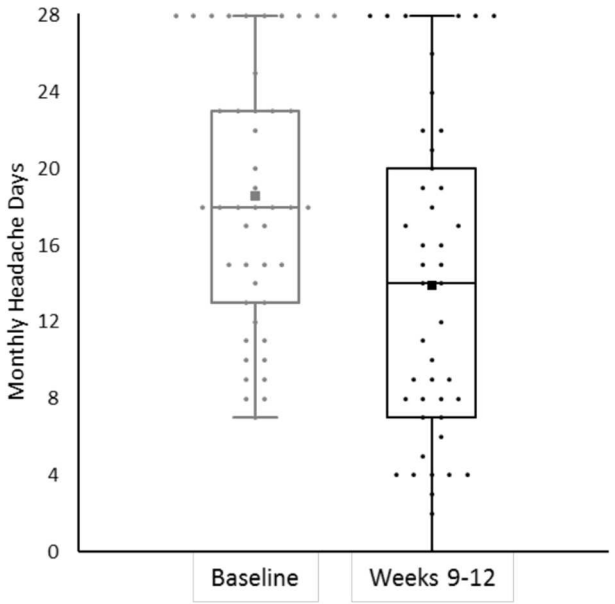


**FIGURE 2 |** The bee swarm plot shows mean monthly headache days during the 4-week baseline and in erenumab treatment at weeks 9–12 ($n = 45$).

during the observation period (baseline 10.7 TriD, 95% CI 9.1–12.3, −4.7 in weeks 9–12, 95% CI 4.6–7.7, $p < 0.001$). Patients with and without another concomitant prophylactic treatment (CCPT) did not differ in the reduction of MHD [−5.4, 95% CI −0.4–11.32 (weeks 9–12) for seven patients with CCPT, −4.5, 95% CI 2.6–6.5 for 38 patients without].

## Tolerability

In total, $n = 52$ (37.4%) patients reported side effects. The most common side effect was constipation ($n = 26$, 18.7%), followed by respiratory tract infections ($n = 6$, 4.3%), and itching at injection site ($n = 5$, 3.6%). Constipation was particularly common in patients with the parallel intake of tricyclic antidepressants: five out of 11 patients (45.1%) in this group reported constipation as a side effect.

The discontinuation rate due to side effects was 4.3% ($n = 6$) during the entire observation period. Patients recorded the following reasons for discontinuation: $n = 3$ worsening of migraine, $n = 1$ skin rash, $n = 1$ new asymptomatic ST depression in ECG, and $n = 1$ constipation.

More than 70% of patients (71.2%, $n = 99$) continued erenumab treatment after April 2019, 21.6% ($n = 30$) discontinued treatment due to insufficient response, and in further 2.9% ($n = 4$) information was missing.

# DISCUSSION

In this retrospective analysis, erenumab showed efficacy in CM patients who failed or had contraindications to five first-line migraine preventives and, in addition, BoNTA. Beginning with the first treatment cycle, erenumab led to a significant reduction in MHD in this difficult-to-treat cohort. Fifty percent of the patients reported a reduction in MHD of at least 30%, which is considered clinically meaningful (19). Migraine frequency reduction led to a reduced number of days with acute medication, in particular triptan, intake. The low discontinuation rate in this analysis indicates good tolerability of erenumab in this population.

This is the first real-world analysis, which assesses erenumab efficacy in CM patients with six prior frustrating treatment attempts (first-line oral medications plus BoNTA). Such patients have not been studied in any phase of the mAb developmental program, but reflect a substantial number of patients in headache centers. Therefore, analyses like ours help to understand the potential of this new medication class in the clinical context of the most refractory patients.

Phases II and III studies for the CGRP and CGRP-receptor mAbs demonstrated efficacy of mAbs in patients who previously did not respond to other preventives. The number of treatment failures was limited to a maximum of two to four in CM trials, with some small differences between trials (11, 16, 20, 21). Findings from our real-world study also show positive results for erenumab in a more refractory patient population.

In the phase II study of erenumab in CM, 34.8% of patients had previously failed three preventive treatments (11). A *post-hoc* analysis in this particular subgroup revealed that 34.8% of the patients with erenumab 70 mg and 38.5% with erenumab 140 mg reached an at least 50% response in MMD vs. 15.3% in the placebo group (11). This is highly consistent with our findings, with over 30% of the patients achieving at least 50% response after 3 months of treatment. The LIBERTY trial focused specifically on patients who had failed two to four preventive

**TABLE 3 |** Headache characteristics during erenumab treatment vs. baseline (4 weeks before erenumab treatment).

| | Weeks 1–4 | Weeks 5–8 | Weeks 9–12 |
|---|---|---|---|
| MHD (baseline) | 14.0 ± 8.3 (17.7 ± 6.8) | 13.4 ± 8.6 (18.7 ± 6.9) | 13.9 ± 8.5 (18.6 ± 6.8) |
| Reduction from baseline | −3.7 ± 5.5 | −5.3 ± 5.4 | −4.7 ± 5.9 |
| *N* | 68 | 60 | 45 |
| *P* | <0.001 | <0.001 | <0.001 |
| MMD (baseline) | 10.5 ± 6.4 (14.6 ± 5.3) | 10.4 ± 6.7 (15.3 ± 6.0) | 10.9 ± 6.4 (15.4 ± 5.0) |
| Reduction from baseline | −4.0 ± 5.5 | −4.9 ± 4.4 | −4.5 ± 4.6 |
| *N* | 43 | 38 | 23 |
| *P* | <0.001 | <0.001 | <0.001 |
| MDSH (baseline) | 3.4 ± 4.3 (6.7 ± 5.8) | 3.7 ± 4.7 (7.0 ± 6.3) | 3.3 ± 4.3 (7.6 ± 5.4) |
| Reduction from baseline | −3.3 ± 4.4 | −3.3 ± 4.1 | −4.3 ± 4.7 |
| *N* | 29 | 23 | 13 |
| *P* | 0.004 | 0.015 | 0.09 |
| AMD (Baseline) | 7.0 ± 4.4 (11.9 ± 4.6) | 7.0 ± 4.3 (12.3 ± 5.7) | 6.5 ± 2.9 (12.8 ± 5.0) |
| Reduction from baseline | −4.9 ± 4.0 | −5.3 ± 5.2 | −6.3 ± 4.8 |
| *N* | 43 | 35 | 22 |
| *P* | <0.001 | <0.001 | <0.001 |
| TriD (Baseline) | 6.6 ± 5.7 (10.7 ± 5.9) | 5.1 ± 4.0 (10.3 ± 6.9) | 5.6 ± 2.8 (10.3 ± 6.2) |
| Reduction from baseline | −4.1 ± 4.1 | −5.2 ± 6.1 | −4.7 ± 4.6 |
| *N* | 45 | 39 | 27 |
| *P* | <0.001 | <0.001 | <0.001 |

*MHD, monthly headache days; MMD, monthly migraine days; MDSH. monthly days with severe headache; AMD, monthly days with acute medication use; TriD, monthly days with triptan use; n, patients in the respective category with available data for analysis; p, Bonferroni adjusted p-value for multiple (=15) comparisons. Data are reported as mean ± standard deviation.*

treatments (20). Although this trial enrolled only patients with episodic migraine and a direct comparison with our analysis is not possible, responder rates were remarkably similar to our study population: in fact, three out of 10 patients on erenumab treatment reached at least 50% response (20).

The dosing of erenumab is still a matter of discussion (22). In the EM STRIVE trial, but not the CM trial, erenumab patients achieved a larger reduction of MMD with a dose of 140 mg rather than 70 mg at the time of the primary endpoint (10, 23). At the end of the open-label extension in both EM and CM, the 140-mg dose showed a numerically higher reduction of MMD than the 70-mg dose (24). In our headache centers, treatment initiation at the time of the analysis was done in line with the EMA approval of erenumab with 70 mg followed by an increase to 140 mg if the patient did not respond sufficiently. Therefore, it is not surprising that patients who were stable on 70 mg achieved higher response rates than those who switched to 140 mg as this population is more likely to be overall less responsive to erenumab. However, this analysis was purely descriptive. A dedicated outcome study is necessary to confirm this finding.

In randomized double-blind and open-label trials, erenumab demonstrates a good tolerability profile, and also, in our real-world study, only a few patients discontinued treatment due to adverse events. The most common side effect in our cohort was constipation (18.7%), which is considerably higher than in the STRIVE trial, in which about 3.5% of the patients reported constipation (23). Several factors may contribute to higher constipation rates in a real-world setting such as predisposition, co-medication with drugs that have an influence of gut mobility (e.g., antidepressants) or specific patient information before the initiation of erenumab therapy. In line, constipation rates were particularly high in patients with concomitant tricyclic antidepressant therapy, and treatment with erenumab in this patient population should be carefully evaluated.

Real-world experience with erenumab is still limited. Initial reports in an Italian headache center included 65 patients with CM who had received at least one injection of erenumab (25). These patients had 5.4 ± 2.6 prior treatment failures; data on prior medication classes including BoNTA was not reported (25). In this study, eight patients had received at least two treatment cycles of erenumab by the time of publication. MMD decreased by 6.6 ± 4 at week 8 in this population, which corresponded to an outstanding 50% responder rate of 87.5% (25). We did not reproduce these findings in our sample, possibly due to population differences and a longer observation period. A placebo response is typically reduced with a longer treatment duration.

The first data from two Australian headache centers with 64 patients who had failed at least three previous preventive medications showed a >50% reduction in MHD in 30% of cases after 3 months of treatment (26). This is in line with our findings.

In a recently published observational trial of 89 Italian patients with episodic or chronic migraine, 61.8% of the patients reached a 30% response rate after the third treatment cycle with erenumab. In this cohort, only 11 patients (12.4%) had more than four previous treatment failures, which may lead to better response rates to erenumab than in our patient group. However, in a subgroup analysis of CM patients who previously failed BoNTA

treatment, 56.8% achieved a 30% response, which is comparable to our results (27). The identification of clinical or laboratory parameters associated with a good treatment response could help us in the selection of patients for successful CGRP mAb therapy in the future (28).

The antinociceptive action of BoNTA is partially mediated by the inhibition of CGRP release from trigeminal nerve fibers (29, 30). Efficacy of erenumab in BoNTA non-responders indicates that the mechanisms of action do not fully overlap. One possible explanation is the abundance of erenumab in the entire circulation, while BoNTA has rather a local effect on CGRP release at the injection site (31).

German treatment guidelines recommend efficacy evaluation of BoNTA after three treatment cycles (32). In our analysis, BoNTA non-responders had received more than four BoNTA treatments on average, which seems in contrast to the guideline recommendations. The following explanations may apply: patients had negative experience with oral preventatives and experienced some improvement related to pain intensity under BoNTA treatment with no or very few side effects. These patients usually stayed on BoNTA treatment until a switch to mAb treatment was possible. In some patients, the placebo response associated with BoNTA injections may have contributed to an initial treatment success. Placebo effects get lower over time. We know from previous literature that a diminished benefit after long-term treatment is possible, even if rare (33). Because the BoNTA treatment period was not the scope of this analysis, we did not collect headache days during this epoch. In the chart review, we detected higher discontinuation rates from BoNTA treatment due to side effects (11.5%) than in the PREEMPT trials (3.8%) or in real-world analyses (15, 33). Because this analysis focused on patients who failed BoNTA treatment due to safety or tolerability issues, we may have a bias toward patients with poor tolerability.

The main limitations of our study are the retrospective character and missing data points. Patients are requested to complete headache diaries before treatment initiation and during treatment with mAbs as part of our clinical routine. However, a number of patients fail to provide their calendars regularly, and therefore, data is lacking. As a consequence, analyses were limited to a comparison of individual time point vs. baseline using *t*-tests rather than analysis of variance over all timepoints. Owing to better data quality for headache days rather than migraine days only, we considered MHD as a primary endpoint and calculated response rates on the basis of MHD. Based on our clinical experience, in this cohort of patients with CM and without any other headache disorder, headache days mostly correspond to migraine days, and the decrease in MHD closely resembles the decrease in MMD. Analysis of response included only patients with complete data for MHD. Patients with missing data for any reasons, including previous treatment discontinuation, were excluded. Moreover, patients with a good treatment response may be inclined to fill their headache diary in a more accurate way. This might have caused a selection bias toward overrepresentation of patients with higher response rates.

In conclusion, this real-world analysis of erenumab complements clinical trial results and suggests that erenumab shows good efficacy and tolerability even in patients who failed all first-line prophylactic treatments plus BoNTA. Our analysis indicates efficacy of erenumab in a patient population for which no data from randomized placebo controlled trials exist.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

BR and UR: study concept and design, drafting of the manuscript. BR, RK, AG, and UR: acquisition and collection of data, data analysis, and interpretation. JM, LO, LN, and AG: critical revision of the manuscript for important intellectual content. All authors: approval of the final version of the manuscript.

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SYSTEMATIC REVIEW
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# Recent Evidence Regarding the Association Between Migraine and Suicidal Behaviors: A Systematic Review

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**Objective:** The review presents a systematic analysis of literature investigating the association between migraine and suicidal behaviors.

**Introduction:** Migraine is a common neurological disorder. The prevalence of migraines increases with age from adolescence to adulthood in both sexes, and results in a substantial loss of productivity due to missing days of school or work and need for bed rest. Literature prior to 2015 suggests that migraine is a predictor of suicide. Given the worldwide public health interest in suicide prevention, we examined the literature collected from diverse, predominantly non-European, populations post-2015.

**Methods:** The databases used in this systematic review included: Medline, PsycINFO, EMBASE (Ovid), Science Direct (Elsevier), Cochrane, and PubMed for all available years of publication from January 2015 onwards. The review included participants aged 16 and over who had been diagnosed with migraines with the following outcome variables: any suicidality, both fatal and non-fatal; suicidal ideation; and suicidal behavior.

**Results:** The database searches yielded a total of 542 citations. Following title and abstract screening, 460 articles were excluded and a total of 21 citations were evaluated. After full-text review and excluding a further 11 non-eligible studies, a total of 10 studies were eligible for inclusion in the systematic review.

**Conclusions:** Current existing research highlights the important association between the increased risk of suicidal behaviors in the clinical and general population among chronic migraineurs with/without aura worldwide. Future studies are needed to facilitate the development of clinical guidelines for risk assessment, targeted interventions, and evidence-based treatment of migraine to reduce the risk of suicide among this vulnerable population.

**Keywords: migraine, migraineurs, suicidality, suicidal behaviors, suicide, suicide attempt, suicide ideation, systematic review**

## INTRODUCTION

Migraine is a neurological disorder with a prevalence rate of between 11 and 23% (1–5). Figures from the Global Burden of Disease Study (GBD) 2016 (3) highlight the detrimental effect of headache disorders, indicating migraine as a cause for 5.6% of disabilities worldwide (3, 4). According to the World Health Organization(WHO) (6), headache disorders are a worldwide public health problem that impose a major burden that negatively impact on family, social life, and employment. From a medical perspective migraine is the most prevalent, most disabling headache disorder, with frequent visits to the ER and doctors. Tension Type Headaches (TTH), meanwhile, are as common in the community but are less likely to result in visits to doctors as the headache disorder responds well to simple analgesics (7). According to WHO, about one third of people with headaches are also diagnosed with migraine (6).

Migraine is a recurrent headache disorder of 4–72 h duration and is predominantly associated with autonomic nervous system symptoms. Frequent migraine episodes are classified as chronic when they occur: (a) for a period of at least 3 months, (b) on more than 15 days per month, and (c) the headaches have migraine characteristics on more than half of the episodes (2). The prevalence of migraine increases with age from adolescence to adulthood, resulting in a substantial loss of productivity due to sick days, and is one of the main causes of disability globally. Indeed, 86% of migraine sufferers are of working age (5, 7).

The World Health Organization reports clinical anxiety and depression to be significantly more common in people with migraine vs. non-migraineurs (6, 8). Nović et al. (8) led a systematic review of the literature appearing between 1966 and 2014 and synthesized the evidence of suicidality including suicidal ideation (thoughts about suicide) and suicide behaviors (the suicide attempt itself), both fatal and non-fatal, and revealed a risk of suicidal behaviors in both clinical and non-clinical migraine populations. Some of the studies reviewed demonstrated that migraine was a predictor of suicidal behaviors even after controlling for psychiatric conditions (8). Similarly, a recent systematic review and meta-analysis (9) that investigated the relationship of migraine and suicidal ideation observed that migraine was a significant risk factor. The authors reported similar results even after some psychiatric comorbidities were considered (9). Statistics also demonstrated that suicide among children is rare while the highest rates were observed in mid-age adults (10).

Thus, in the present study we conducted a systematic analysis of the literature from 2015 to November 2019, investigating migraine specifically, as the most prevalent and debilitating headache type, and exploring its link with suicidal behaviors among adult participants of 16 years and older. This includes an analysis of previously unstudied populations in Asia, South America, and Ethiopia.

## METHODS

The Joanna Briggs Institute guidelines on etiology and risk (11, 12) and the Preferred Reporting Items for PRISMA (13) were used in this systematic review. It was registered with Prospero (registration number CRD42020158903).

### Search Strategy

A three-step search procedure was undertaken (11, 12). A preliminary search of the databases of Medline, PsycINFO, EMBASE (Ovid), Science Direct (Elsevier), Cochrane, and PubMed were taken as a first step. The second step included a more comprehensive and focused search of all the keywords. Finally, a manual search of the main web browsers was undertaken as reported by Moola et al. (11).

### Types of Studies Included

The systematic review considered all quantitative study designs including observational/cohort studies and randomized controlled trials of persons with medically diagnosed migraine aged 16 and over. Only English language papers were considered in the review due to time constraints and limited resources to interpret other languages. Studies published from January 2015 to November 2019 were included. This date range was selected in order to retrieve and investigate all studies that had not been considered in previously conducted systematic reviews, including Nović et al. (8).

### Information Sources

A systematic search was conducted on 30 November 2019 using Medline, PsycINFO, EMBASE (Ovid), Science Direct (Elsevier), Cochrane, and PubMed for all available years of publication from 2015 onwards. The following key terms were used: (a) Migraine/or chronic or tension or intractable/or headache, Migraine disorders/or Tension type, headache/or Headache disorders; or (b) Photophobia/Aphasia/facial nerve/or oculomotor nerve/or exp vasomotor system/sensory adj2 (sensitivit* or overload or anomal/Autonomic nervous system or ANS/Transient or temporary) adj2 (Hemiparesis or Speech difficult Facial or oculomotor Vasomotor system/Light sensitivit* or photophobi Light sensitivit* or photophobia; or a or b; and (c) suicide/or suicidal ideation/or suicide, attempted/ (d) Self-Mutilation/ (e) self-harm or injurious behavior mutilation or injury or destruction or killing; or c/d/e. In order to center the review on peer reviewed articles gray literature was excluded.

## INCLUSION/EXCLUSION CRITERIA

### Participants

The review included studies whose participants were older than 16 years who were diagnosed with migraine. Studies were excluded if they included participants younger than 16 years old. Patients were required to experience at least one severe migraine episode per month or more (14).

### Study Selection

All the identified articles were imported to EndNote 9 and duplicate citations were removed then imported to Covidence System (Covidence.org) for further screening. The abstracts were screened by two reviewers independently (MB, CB) followed by the full text of the included citations. Conflict opinions were resolved by a third reviewer (LK). The search results for article selection are presented in **Figure 1**.

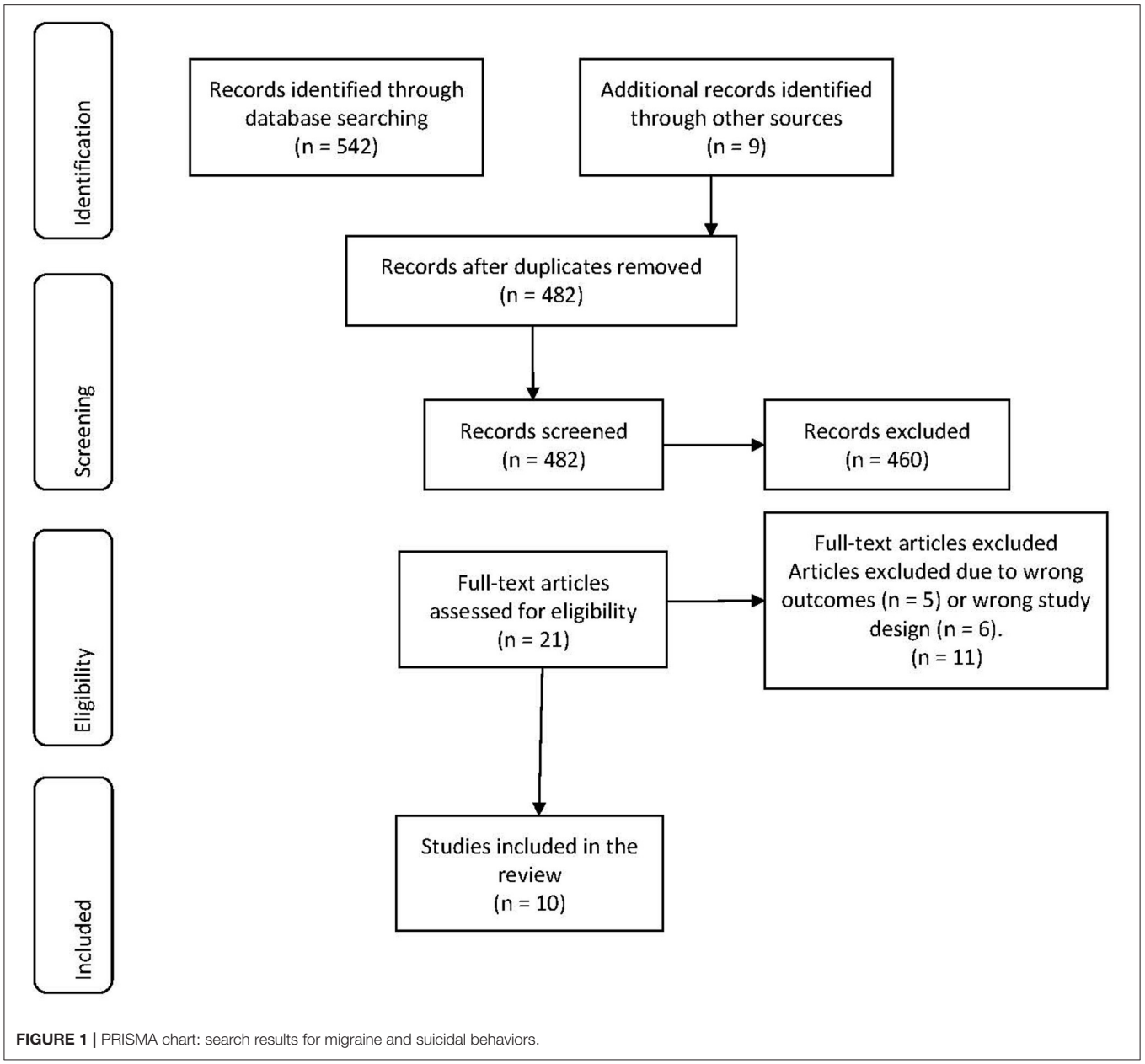


**FIGURE 1 |** PRISMA chart: search results for migraine and suicidal behaviors.

## Data Extraction

Two reviewers (MB, CB) extracted the data based on the standardized data extraction tools in Covidence. A summary of the included articles is detailed in **Table 1**.

## Assessment of Methodological Quality

Two reviewers appraised the quality of citations (MB, CB). Any disagreement that arose over a specific citation were resolved by a third reviewer (LK).

## Critical Appraisal of the Individual Studies

The reviewers critically appraised the eligible articles using the JBI Critical Appraisal checklist (16) and assigned a quality of the evidence ranking (GRADE) (17). A judgment of yes, no, unclear, or not applicable was assigned to individual study elements (16). Article quality was ranked based on the GRADE assessment principles (17). **Tables 2**, **3** outlines the critical appraisal assessment (16) and quality of evidence (GRADE) (17) ranking of the included studies.

## Quality Scores

The studies were assessed and assigned a quality score adapted from Pompili et al. (15) and Nović et al. (8). Allocated quality scores considered five study features such as the sample representativeness, which included a comparison group, the number of participants with migraine, whether follow-up was performed, the presence of a longitudinal study, and the clarity

**TABLE 1 |** Summary of characteristics of included studies.

| Reference title First Author/Country of origin | Year of publication | Sample/ Participant age | Study design/ Study duration | Clinical diagnosis of migraine | Main findings | Quality score* |
|---|---|---|---|---|---|---|
| Suicidal ideation in persons with neurological conditions: prevalence, associations, and validation of the PHQ-9 for suicidal ideation<br>Altura KC<br>Canada | 2016 | *n* = 208<br>Mean age of participants: 43.4 (range 18.1–75.1) | Prospective cohort study<br>Participants were recruited from four outpatient clinics (Epilepsy Clinic, MS Clinic, Headache Clinic, and Stroke Clinic)—Patients had to be: 18 years of age or older; (b) fluent in English; (c) free of hearing impairment because they had to complete a telephone interview; and (d) free of physician-diagnosed moderate or severe dementia, moderate or severe developmental delay, or aphasia<br>August 2012 to September 2013 | Determination of migraine diagnosis was not stated in the study design. It was assumed patients had a pre-existing diagnosis of migraine as they were recruited from various neurological outpatient clinics | Overall, factors most strongly associated with suicidal ideation were depression, migraine, and anxiety<br>The primary aim of the study was to validate the Patient Health Questionnaire (PHQ)-9 as a screening tool for suicidal ideation<br>According to the PHQ-9, the 2-week point prevalence of suicidal ideation for migraine was 15.9% and on the structured clinical interview for DSM-IV was 12%. The PHQ-9 had good sensitivity for migraine (75%) | I = 0<br>II = 1<br>III = 1<br>IV = 0<br>V = 1<br>Total score = 3 |
| B. Association between migraine and suicidal behavior among Ethiopian adults<br>Berhane HY<br>Ethiopia | 2018 | *n* = 1,060<br>Age<br>35.28 (*SD* 12.05) | Cross-sectional study<br>Eligible participants included all adults attending the outpatient facility at the Saint Paul Hospital in Addis Ababa, Ethiopia and were patients evaluated in the internal medicine, general surgery, and gynecological outpatient departments<br>December to July 2011 | Trained nurses used an interview format to administer structured questionnaires<br>A structured migraine assessment questionnaire adapted from a previously validated tool was used to classify migraine according to the ICHD-II criteria<br>The Composite International Diagnostic interview (CIDI) was employed to assess depression and suicidal behaviors that were classified as ideation, plans, and attempts based on self-report | Migraine is associated with increased odds of suicidal behavior in the population of urban-dwelling Ethiopian adults<br>The presence of migraine was associated with a 2.91-fold increased risk of suicidal behavior (OR: 2.91, 95% CI: 2.06–4.12) compared with participants without migraine (2.71-times after adjusting for confounders) | I = 0<br>II = 1<br>III = 2<br>IV = 0<br>V =1<br>Total score = 4 |
| C. Association between lifetime headache and history of suicide attempts in the elderly<br>Calati R<br>France | 2017 | *n* = 1,965<br>Age<br>72.27 (*SD* 4.76) | Prospective cohort study<br>Eligible participants were community-dwelling individuals randomly selected from the 15 electoral rolls of the Montpellier district who were aged 65 years and above<br>March 1999 to February 2001 | A neurologist assessed headache cases based on the International Headache Society guidelines | Lifetime headache was associated with lifetime suicide attempts (OR: 1.92, 95% CI: 1.17–3.15) | I = 0<br>II = 1<br>III = 0<br>IV = 0<br>V = 1<br>Total score = 2 |
| D. Association of migraine headaches with suicidal ideation among pregnant women in Lima, Peru<br>Friedman LE<br>Peru | 2016 | *n* = 3,323<br>Age 28.2 (*SD* 6.3) | Cross-sectional study<br>A cross-sectional study was conducted among pregnant women attending prenatal care clinics in Lima, Peru<br>February 2012 to March 2014 | Trained interviewers classified migraine using a questionnaire administered during early pregnancy<br>Migraine classification (including migraine and probable migraine) was based on the International Classification of Headache Disorders (ICHD)-III beta criteria<br>Suicidal ideation and depression were assessed using the Patient Health Questionnaire-9 (PHQ-9) scale during early pregnancy | Participants with migraine or probable migraine had more than a 2-fold increased risk of suicidal ideation (OR = 2.17; 95% CI: 1.80–2.61) compared with non-migraineurs. After adjusting for confounders, there was still an almost 2-fold increase in suicidal ideation (OR = 1.99; 95% CI: 1.64–2.41) | I = 0<br>II = 1<br>III = 1<br>IV = 0<br>V = 1<br>Total score = 3 |

*(Continued)*

**TABLE 1** | Continued

| Reference title First Author/Country of origin | Year of publication | Sample/ Participant age | Study design/ Study duration | Clinical diagnosis of migraine | Main findings | Quality score* |
|---|---|---|---|---|---|---|
| E. Association between migraine and suicidal behaviors: a nationwide study in the USA<br>Friedman, LE<br>United States of America | 2018 | *n* = 156,172,826<br>Mean age 47 | Cross-sectional study<br>The Nationwide Inpatient Sample of hospitalisations compiled from USA billing data was analyzed Migraine, suicidal behaviors, and psychiatric disorders were identified based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-M) diagnosis codes from hospitalization discharges (2007–2012)<br>Discharge data from 2007 to 2012 | Adult onset migraine diagnosis was based on the ICD-9-CM diagnosis codes | Individuals with migraine had a 2.07-fold increased risk of suicidal behaviors (OR = 2.07; 95% CI: 1.96–2.19) compared with non-migraineurs | I = 1<br>II = 1<br>III = 2<br>IV = 0<br>V = 1<br>Total score = 5 |
| F. Suicide attempts among those with migraine: findings from a nationally representative Canadian study<br>Fuller-Thomson E<br>Canada | 2019 | *n* = 21,744<br>(with migraine *n* = 2,223)<br>Mean age 85 | Cross-sectional study<br>This study was a nationally representative analysis of the 2012 Canadian Community Health Survey—Mental Health (CCHS-MH) | Participants were asked if they had been diagnosed with migraine headaches by a health professional (expected to last or have already lasted 6 months or more) | Individuals with migraine had an almost 3-fold higher prevalence of attempting suicide than those without migraine (males 7.5% vs. 1.9% and females 9.3% vs. 2.7%)<br>OR = 3.40; 95% CI: 2.84–4.07 | I = 1<br>II = 1<br>III = 2<br>IV = 0<br>V = 1<br>Total score = 5 |
| G. Risk and predisposing factors for suicide attempts in patients with migraine and status migrainosus: a nationwide population-based study<br>Harnod T<br>Taiwan | 2018 | *n* = 13,605 (status migrainosus cohort)<br>*n* = 21,485 (regular migraine cohort)<br>*n* = 54,379 (comparison cohort)<br>Age<br>45.7 (*SD* 14.8) (status migrainosus cohort)<br>45.6 (*SD* 15.1) (comparison cohort) | Cross-sectional study<br>An analysis was conducted of a subset of the National Health Insurance Research Database of Taiwan and enrolled patients (20 years of age and older) who had ever received a diagnosis of regular migraines (RM) or status migrainosus (SM) between 2000 and 2012 in the RM and SM cohort<br>January 2000 to December 2012 | Migraine diagnosis was based on the ICD-9-CM diagnosis codes for RM 346 excluding 346.9 and SM 346.9 excluding 346.90 and 346.91 | The status migrainosus cohort had a 1.81-fold risk of attempting suicide (OR = 1.81; 95% CI: 1.14–2.89) compared with the comparison cohort | I = 1<br>II = 1<br>III = 2<br>IV = 0<br>V = 1<br>Total score = 5 |
| H. Association of suicide risk with headache frequency among migraine patients with and without aura<br>Lin YK<br>Taiwan | 2019 | *n* = 528<br>Age<br>33.7 (*SD* 10.3) | Cross-sectional study<br>This cross-sectional study included 528 consecutive patients aged between 20 and 60 years attending a headache clinic at the Department of Neurology of the Tri-Service General Hospital (TSGH) in Taipei, Taiwan<br>Patients with migraine, both with and without aura, were analyzed<br>June 2015 to May 2017 | Patients completed a screening questionnaire and were subsequently interviewed by a board-certified neurologist and headache specialist to make a diagnosis according to the International Classification of Headache Disorders, 3rd edition (ICHD-3 beta) Patients with migraine were determined to be with or without aura, based on the criteria of the International Headache Society | The rates of suicide attempts were highest for chronic migraine with aura (ideation 47.2%; attempts 13.9%) and lowest for migraine-free controls (2.8%)<br>Migraine aura and depression were associated with higher risks of suicidal ideation and suicide attempts in patients with migraine. Suicide attempts with aura (OR = 5.8; 95% CI: 1.57–21.47) | I = 0<br>II = 1<br>III = 2<br>IV = 0<br>V = 1<br>Total score = 4 |

*(Continued)*

**TABLE 1 |** Continued

| Reference title First Author/Country of origin | Year of publication | Sample/ Participant age | Study design/ Study duration | Clinical diagnosis of migraine | Main findings | Quality score* |
|---|---|---|---|---|---|---|
| Osmophobia and allodynia are critical factors for suicidality in patients with migraine<br>Park SP<br>Republic of Korea | 2015 | *n* = 220<br>Age<br>40.3 (*SD* 13.2)<br>(range 16–73) | Cross-sectional study<br>Patients with migraine (with or without aura) were consecutively recruited from the headache clinic at the Department of Neurology at Kyungpook National University Hospital Patients were asked if they experienced photophobia, phonophobia, osmophobia, and allodynia during migraine attack<br>The Mini International Neuropsychiatric Interview was used to diagnose current major depressive disorder, current generalized anxiety disorder, and suicidality<br>The study duration was not specified | A trained neurologist diagnosed migraine based on the International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3 beta) | Patients with suicidality were more likely to have chronic migraines than those without suicidality<br>Osmophobia (Beta 0.314, adjusted OR [AOR] 3.12; 95% CI: 1.57–6.21) and allodynia (Beta 0.211, adjusted OR [AOR] 2.72; 95% CI: 1.19–6.21) were found to be critical risk factors for suicidality in patients with migraine, after controlling for depression, anxiety, and chronic migraine | I = 0<br>II = 1<br>III = 1<br>IV = 0<br>V = 1<br>Total score = 3 |
| J. Aggression and its association with suicidality in migraine patients: a case-control study<br>Park SP<br>Republic of Korea | 2018 | *n* = 144<br>Age<br>37.5 (*SD* 13.2)<br>(range 20–64) | Prospective cohort study<br>The study enrolled 144 migraine patients who were attending the headache clinic for their first visit The patients completed various questionnaires including an Aggression Questionnaire (AQ)<br>A trained neuropsychologist employed The Mini International Neuropsychiatric Interview Plus Version 5.0.0 (MINI) to identify suicidality<br>The degree of aggression in migraine patients was compared to the degree of aggression in healthy controls<br>January 2017 to September 2017 | Self-reported questionnaires that were used in this study included:<br>Aggression Questionnaire (AQ)<br>Migraine Disability Assessment Scale (MIDAS)<br>Patient Health Questionnaire-9 (PHQ-9)<br>Generalized Anxiety Disorder-7 (GAD-7)<br>Epworth Sleepiness Scale (ESS)<br>Insomnia Severity Index (ISI) | The overall AQ score and anger and hostility subscale scores were higher in migraine patients than control patients<br>Migraine patient's overall AQ score = 48.9 ± 12.6 (vs. healthy controls 45.8 ± 8.5)<br>Migraine patient's anger score = 11.6 ± 4.0 (vs. healthy controls 10.2 ± 2.6)<br>Migraine patient's hostility score = 13.7 ± 5.2 (vs. healthy controls 12.2 ± 2.7) | I = 0<br>II = 1<br>III = 1<br>IV = 0<br>V = 1<br>Total score = 3 |

**Quality ratings reported have a maximum score of 6. The criteria used to assess quality are:*
*(I) Representativeness of the sample to the general population: 0 points = not representative; 1 point = representative.*
*(II) Presence of a control/comparison group: 0 points = no control group; 1 point = control group.*
*(III) Number of participants with the condition (migraine): 0 points = <100; 1 point = between 101 and 500; 2 points = >501.*
*(IV) Longitudinal (follow-up): 0 points = no follow up; 1 point = with a follow-up.*
*(V) Data presentation: 0 points = unclear data presentation; 1 point = clear data presentation.*
*Reproduced with permission from the work of Pompili et al. (15) and Nović et al. (8).*

**TABLE 2 |** JBI Critical appraisal of included cohort studies (16) and quality of the evidence (GRADE) (17).

| Study | Similar groups recruited from same population | Exposures measured similarly for both exposed and unexposed groups | Valid and reliable measurement of exposure | Confounding factors identified | Strategies to address confounding factors are stated | Participants were free of the outcome at the start of the study |
|---|---|---|---|---|---|---|
| A. Suicidal ideation in persons with neurological conditions: prevalence, associations and validation of the PHQ-9 for suicidal ideation<br>Altura et al. (18)<br>Prospective cohort study | ☐ | ☐ | ☐ | ☐ | ☐ | Not applicable |
| B. Association between lifetime headache and history of suicide attempts in the elderly<br>Calati et al. (19)<br>Prospective cohort study | ☐ | ☐ | ☐ | ☐ | ☐ | Not applicable |
| C. Aggression and its association with suicidality in migraine patients: a case-control study<br>Park et al. (20)<br>Prospective cohort study | ☐ | ☐ | ☐ | ☐ | ☐ | Not applicable |
| A. Suicidal ideation in persons with neurological conditions: prevalence, associations and validation of the PHQ-9 for suicidal ideation<br>Altura et al. (18)<br>Prospective cohort study | ☐ | Not applicable | Not applicable | Not applicable | ☐ | ⊕⊕⊕○ Moderate[a] |
| B. Association between lifetime headache and history of suicide attempts in the elderly<br>Calati et al. (19)<br>Prospective cohort study | ☐ | Not applicable | Not applicable | Not applicable | ☐ | ⊕⊕⊕⊕ High |
| C. Aggression and its association with suicidality in migraine patients: a case-control study<br>Park et al. (20)<br>Prospective cohort study | ☐ | Not applicable | Not applicable | Not applicable | ☐ | ⊕⊕⊕⊕ High |

[a] *Risk of bias sufficient to downgrade one level.*

of presented data. The quality scores of the articles included in this review are outlined in **Tables 2**, **3**.

## Data Analysis

Extracted data was combined to determine the overall effect for each study design where possible. Information related to risk factors from the included studies such as participant age, study design, and characteristics are described in **Table 1**.

# RESULTS

## Study Selection

The database search yielded a total of 542 citations. An additional nine references were identified through other sources. After the removal of 69 duplicates, 482 articles were included for eligibility assessment. After title and abstract screening 461 articles were excluded. The remaining 21 articles (listed below) were independently assessed for eligibility based on the full text review inclusion and exclusion principles. Eleven studies were excluded due to their interest in alternative outcomes ($n = 5$) and study design ($n = 6$). Ten articles were included in this systematic review. The results for article selection are presented in the PRISMA chart in **Figure 1**.

## Study Characteristics

The articles included were published between January 2015 and November 2019. Two of the studies were conducted in Canada

**TABLE 3 |** JBI Critical appraisal of included cross-sectional studies (16) and quality of the evidence (GRADE) (17).

| Study | Clearly defined sample inclusion criteria | Detailed description of study participants and setting | Valid and reliable measurement of exposure | Objective and standard criteria used for condition measurement | Confounding factors identified | Strategies to address confounding factors are stated | Appropriate statistical analysis performed | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|---|---|---|
| D. Association between migraine and suicidal behavior among Ethiopian adults<br>Berhane et al. (25)<br>Cross-sectional study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ⊕⊕⊕◯<br>Moderate[b] |
| E. Association of migraine headaches with suicidal ideation among pregnant women in Lima, Peru<br>Friedman, et al. (26)<br>Cross-sectional study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ⊕⊕⊕⊕<br>High |
| F. Association between migraine and suicidal behaviors: a nationwide study in the USA<br>Friedman et al. (27)<br>Cross-sectional study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ⊕⊕<br>⊕<br>High |
| G. Suicide attempts among those with migraine: findings from a nationally representative Canadian study<br>Fuller-Thomson et al. (21)<br>Cross-sectional study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ⊕<br>⊕⊕⊕<br>High |
| H. Risk and predisposing factors for suicide attempts in patients with migraine and status migrainosus: A nationwide population-based study<br>Harnod et al. (22)<br>Cross-sectional study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ⊕⊕<br>⊕<br>High |

*(Continued)*

**TABLE 3** | Continued

| Study | Clearly defined sample inclusion criteria | Detailed description of study participants and setting | Valid and reliable measurement of exposure | Objective and standard criteria used for condition measurement | Confounding factors identified | Strategies to address confounding factors are stated | Appropriate statistical analysis performed | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|---|---|---|
| I. Association of suicide risk with headache frequency among migraine patients with and without aura<br>Lin et al. (23)<br>Cross-sectional study | ⊟ | ⊟ | ⊟ | ⊟ | ⊟ | ⊟ | ⊟ | ⊕⊕⊕◯ Moderate[c] |
| J. Osmophobia and allodynia are critical factors for suicidality in patients with migraine<br>Park et al. (24)<br>Cross-sectional study | ⊟ | ⊟ | ⊟ | ⊟ | ⊟ | ⊟ | ⊟ | ⊕⊕⊕⊕ High |

[b] *Risk of bias sufficient to downgrade one level.*

[c] *Risk of bias and inconsistencies sufficient to downgrade one level.*

(18, 21), two studies in Taiwan (22, 23), two in the Republic of Korea (20, 24), and one study each in Ethiopia (25), France (19), Peru (26), and the USA (27). Seven of the studies used a cross-sectional study design (21–27) and three were prospective cohort studies (18–20).

Participants were recruited from outpatient clinics in six of the studies (18, 20, 23–26) and from nationwide samples in three studies (21, 22, 27). Clinic populations were recruited from the following outpatient clinics:

- Epilepsy (18)
- Multiple Sclerosis (18)
- Stroke (18)
- Internal medicine (25)
- General surgery (25)
- Gynaecology (25)
- Prenatal care (26)
- Headache (18, 20, 23, 24).

The nationwide samples were selected from hospital billing data (27), community-based mental health survey data (21), and a national health database (22). A single study used population-based samples of participants from the electoral role of the Montpellier district (19).

The number of participants diagnosed with migraine was <100 in one study (19) and between 100 and 500 in four studies (18, 20, 24, 26). Whilst the sample population was over 500 in five of the studies (21–23, 25, 27), two of those reported limitations regarding generalizability (23, 25). Berhane et al. (25) and Lin et al. (23) focused on a hospital-based population. The remaining three studies used a large sample size that was nationally representative of the population (21, 22, 27). Longitudinal follow up was not conducted in any of the studies. All of the studies included a control or comparison group and presented their data clearly.

## Risk of Bias Within Studies

The Cochrane Risk of Bias comparison tool (28) was used to assess internal validity based on key criteria with each rated as high, low, or unclear. Two independent reviewers evaluated the quality of the identified citations. The majority of the studies were appraised as having a low risk of detection bias with the exception of two studies that were assessed as high risk (21, 26). The risk of performance bias was assessed as low for three of the studies (22, 24, 27). Other sources of bias were appraised as high risk for eight of the studies (18–21, 23, 25–27). These included:

- Social desirability bias and underreporting (18, 20, 21, 23, 25, 27)
- Recall bias (18–20, 23, 25, 26)
- Bias introduced by sample pooling for multivariate analysis (19, 23)
- Bias introduced by focusing on specific age groups, for example, the elderly (19)
- Coding and data errors (27).

A low risk rating was allocated for reporting bias and attrition bias in all studies. Overall, 20% of the included studies (22, 24) were assessed as high quality associated with less risk of bias, 60%

were of moderate quality (18–20, 25–27), and 20% were between moderate and low quality (21, 23). The ratings of all included studies are shown in **Table 1**.

## Diagnosis and Assessment of Migraine

Diagnosis and assessment of migraine varied between the studies. Altura et al. (18) did not discuss diagnosis and assessment of migraine. The primary aim of this study was to validate the Patient Health Questionnaire (PHQ)-9 (18, 29). It was assumed that patients had a pre-existing diagnosis of migraine as they were recruited from an outpatient headache clinic.

Four studies of migraine applied the International Classification of Headache Disorders-2 or 3 diagnostic criteria (ICHD-II or III criteria) (2, 23–26). Berhane et al. (25) employed a trained nurse to administer a structured migraine questionnaire to classify migraine disorder based on the ICHD-II criteria (25). Similarly, Friedman et al. (26) used trained interviewers to classify migraine by administering a questionnaire during early pregnancy, including migraine and probable migraine, based on the ICHD-III beta criteria. Lin et al. (23) participants were identified as with aura or without aura based on the ICHD principles (2). Park et al. (24) reported migraine diagnosed by a trained neurologist based on the ICHC-III beta criteria (2). Two studies used the International Classification of Diseases, 9th Revision, Classification Modification (ICD-9-M) (22, 27, 30) diagnosis codes to diagnose migraine.

In addition, Harnod et al. (22) analyzed the data according to diagnosis codes for different cohorts including regular migraine and status migrainosus (31). In one study, a neurologist assessed headache cases based on the International Headache Society guidelines (2, 19) and Park et al. (20) enrolled patients who were attending a headache clinic for their first visit and used the self-report Migraine Disability Assessment Scale (MIDAS) (32) to determine a diagnosis of migraine.

Three of the studies did not specify migraine types and reported on the presence of migraine only (18, 21, 22). Altura et al. (18) recruited patients from a headache clinic whilst Fuller-Thomson et al. (21) included patients with migraine that had being occurring for 6 months or more. Harnod et al. (22) differentiated regular migraine from status migrainosus. The remaining seven studies categorized migraine types and symptoms to varying degrees. Migraine types were specified in three studies (19, 26, 27). Calati et al. (19) included both migrainosus and non-migrainous lifetime headache types whilst Friedman et al. (26) classified migraine and probable migraine in pregnant women. In addition to migraine, Friedman et al. (27) included other headache types according to the ICD-9-CM diagnosis codes (30) for tension headaches and headache. Four studies analyzed subtypes of migraine and associated migraine symptoms (20, 23–25). Berhane et al. (25) defined frequency and pain characteristics and common symptoms. Lin et al. (23) investigated migraine with or without aura, categorized migraine frequency as chronic, high, medium, and low, and also included a control group with no history of migraine in their family. Park et al. (24) considered episodic and chronic migraine with or without aura and associated symptoms whilst also reporting on medication overuse headaches and high headache intensity. Park et al. (20) also investigated these subtypes with the exception of the presence of migraine with or without aura.

## Diagnosis and Assessment of Suicidal Behaviors

Diagnosis and assessment of suicidal behaviors also varied between the studies. Three studies used the Mini-International Neuropsychiatry Interview (MINI) (33), a Diagnostic and Statistical Manual of Mental Disorders (DSMV-IV) (34) criteria to identify suicidal behaviors (19, 20, 24). In all three studies, a trained interviewer (either a nurse, psychologist, or neuropsychologist) administered the MINI to identify suicidality (19, 20, 24). In addition, Calati et al. (19) referred positive cases to a panel of three psychologists for review. Whilst Calati et al. (19) employed the MINI to identify suicide attempts only, Park et al. (20, 24) examined suicide attempts, suicidal ideation, and suicide plans.

Two studies (22, 27) identified suicidal behaviors based on the ICD-9-M (30) diagnosis. Harnod et al. (22) examined suicide attempts only whilst Friedman et al. (27) identified suicidal ideation, suicide attempts, and was the only study in this review to include self-inflicted injury. In two studies, trained health professionals used the Semi Structured Composite International Diagnostic (SCID) and interviewed participants to identify suicidal ideation, suicide plans, and suicide attempts (18, 25, 34). Berhane et al. (25) used the Composite International Diagnostic interview (CIDI) (35) to evaluate depression as well as self-reported suicidal behaviors that were identified as ideation, plans, and attempts. Friedman et al. (26) used the Patient Health Questionnaire-9 (PHQ-9) (29) and assessed suicidal ideation. Two studies examined responses to survey questions to identify suicide attempts (21, 23) and suicidal ideation (23).

## Comorbidities and Other Associated Conditions

All of the studies included other comorbidities and conditions that were mainly associated with mental health. Nine studies included anxiety (18–25, 27) and depression or major depressive disorder (18, 19, 21–27). Four studies in total investigated substance abuse and dependence related to either alcohol (19, 21, 22, 27) or drugs and other substances (21). Three studies investigated participant responses to questions about sleep quality and insomnia (19, 22, 23). Three studies also examined other psychiatric conditions including psychosis, manic and hypomanic episodes, schizophrenia, post-traumatic stress disorder, and childhood and adolescent trauma (19, 22, 27). In addition, Calati et al. (19) collated data on risk factors associated with hypertension, hypercholesterolemia, and diabetes. Friedman et al. (26) included pregnant participants in their study, whilst Park et al. (20) examined the degree of aggression (physical and verbal aggression, anger, and hostility) among migraineurs compared to healthy participants (20). Finally, only one study assessed chronic pain and suicide attempts (21).

## Migraine and Suicidal Ideation

Two studies analyzed the migraine and suicidal ideation link only (18, 26) whilst a third study also included suicide attempts

(23). Altura et al. (18) indicated that the prevalence of suicidal ideation in migraineurs was higher than that reported in general populations. The factors related with suicidal ideation included depression, migraine, and anxiety. Similarly, Friedman et al. (26) reported that, after adjusting for some confounders, pregnant women with migraine showed almost a two times higher incidence of suicidal ideation. Similarly, women who were experiencing both migraine and depression showed an almost four times higher rate of suicidal ideation compared to those who didn't have any of those disorders. (26) Lin et al. (23) observed that migraine aura and depression were correlated with suicidal ideation and suicide attempts (23). Migraine aura and depression severity projected suicidal ideation of migraineurs, especially with chronic migraine with aura (23).

## Migraine and Suicide Attempt

Three studies assessed the link between migraine and suicide attempt (19, 21, 22). Interestingly, all three studies recruited participants from the general population. Whilst Fuller-Thomson et al. (21) and Harnod et al. (22) examined nationwide population data of Canada and Taiwan, Calati et al. (19) study participants were community-dwelling individuals recruited out of the 15 electoral rolls of the Montpellier district in France and were aged 65 years and above (19). Calati et al. (19) reported that lifetime headache (both migraine and non-migraine) was associated with lifetime suicide attempts. Fuller-Thomson et al. (21) revealed that individuals with migraine had an almost 3-fold higher risk of attempting suicide compared with non-migraineurs. Harnod et al. (22) reported that patients who experienced status migrainosus had around a twice higher likelihood of suicidal attempts in comparison to the control group (22). Suicide attempts were higher in participants with depression, anxiety, insomnia, and alcohol-related illnesses (22).

## Migraine and Suicidal Behaviors

Three studies analyzed the relationship of migraine with a range of suicidal behaviors (20, 24, 25). A single study (27) also included self-inflicted injury in their analysis. Friedman et al. (27) analyzed a national cohort of hospitalizations in the USA (27) and reported on migraineurs with depression, anxiety, or post-traumatic stress disorder (PTSD) (27). They reported that individuals with migraine had around twice the likelihood of suicidal behaviors (including self-inflicted injury) compared with non-migraineurs (OR = 2.17; 95% CI: 1.80–2.61) (27). Friedman et al. (27) performed separate analyses and found that migraine was linked with some psychiatric disorders, such as anxiety, depression, and PTSD, and could lead to higher chances of suicidal behaviors (27). Park et al. (24) recruited patients from a headache clinic in a hospital (24) and found that patients with suicidality were about three times more likely to have chronic migraines than those without suicidality.

Berhane et al. (25) noted that migraine and suicidal behaviors are highly correlated even after adjusting for some confounders (such as substance use and socio-demographic factors) (25). The reported rates of suicidal ideation, suicide plans, and suicide attempts were consistently higher in the migraine cohort compared with non-migraineurs (25). Berhane et al. (25) reported that after stratifying by history of depression, the odds of suicidal behavior was twice as high amongst migraineurs than non-migraineurs (25).

Park et al. (24) also reported that osmophobia (or olfactophobia that refers to a fear, aversion, or psychological hypersensitivity to odors) and allodynia ("refers to central pain sensitization increased response of neurons following normally non-painful, often repetitive, stimulation") (24) were found to be critical predictors of suicide after adjusting for depression, anxiety, and chronic migraine (OR = 3.12; 95% CI: 1.57–6.21 and OR = 2.72; 95% CI: 1.19–6.21, in order) (24). In a second study, Park et al. (20) enrolled 144 migraine patients to the study. The suicide rate was higher among chronic migraine patients (42.9%) compared with episodic migraine patients (12.5%) (20). The patients completed various questionnaires, including an Aggression Questionnaire (AQ) (36). Those suffering from migraine compared with the control group (20) showed higher anger, hostility, and overall scores.

# DISCUSSION

The aim of this review was to systematically examine the likelihood of suicidal behaviors such as suicidal ideation, suicide attempts, suicide plans, and self-harm or self-inflicted injury among populations of migraine patients older than age 16 years. Adolescent and adult migraineurs were chosen for this systematic review, given that migraine is recognized as the most prevalent and debilitating headache types (in terms of hospital and clinic visits) and the increase in prevalence among young adults makes it one of the major causes of disability among working age adults (7). Similarly, suicide among children is rare while the highest rates are observed in middle age. The studies that achieved a low bias rating overwhelmingly support a strong relationship between migraine and suicidal behaviors, as have earlier publications.

The observed trend of a strong correlation between migraine and suicidal ideation observed after adjusting for confounders by Friedmann et al. (9) was reflected in five of the articles reviewed in this study (19, 21–23, 26). Calati et al. (19) reported a strong link between lifetime suicide attempts and lifetime headache in an elderly sample population after adjusting for confounding variables such as depression. Friedman et al. (26) also noted that pregnant women with migraines in Peru had a higher rate of suicidal ideation after adjusting for depression and other confounders. Harnod et al. (22) controlled for most psychiatric comorbidities in their analysis and found that suicide attempts among patients with status migrainosus (22) and specific psychiatric comorbidities was high (22). Lin et al. (23) also reported that migraine aura and depression severity were predictors of suicidal ideation among migraineurs (23) after adjusting for possible confounding factors.

Aly et al. in their study of migraine and the risk of suicide highlighted the fact that migraine and depression are common comorbid conditions and that both episodic and chronic migraine have been associated with comorbid psychiatric conditions such as depression. Previous systematic reviews have

explored this relationship, as did all of the articles reported in this review (8, 9). Friedman et al. (26) also discussed the association between environmental risk factors, migraine, depression, and suicidal behaviors. Fuller-Thomson et al. (21) provided an additional dimension to their research and highlighted a number of possible risk factors, such as adverse childhood events that might predispose migraineurs to suicidal attempts (21). Fuller-Thomson et al. (21) also found that patients who had witnessed or experienced domestic violence demonstrated higher rates of suicidal attempts compared with those who had not experienced any adverse childhood events, whether or not they were migraineurs. In addition, they suggested that the bi-directional relationship between migraine and depression might also be extended to include other variables such as drug and alcohol abuse (21).

Lin et al. (23) examined the relationship of migraine with depression and other comorbidities such as anxiety and sleep quality (23). Park et al. (24) focused on the association of sensory hypersensitivities and suicidality in migraineurs and did not examine the effects of comorbid diseases. They excluded patients with serious medical, neurological, and psychiatric disorders from their study (24). They reported that osmophobia and allodynia are as significant as psychiatric disorders (24) in the determination of suicidality in patients with migraine (24). In a different study, Park et al. (20) focused on an area of minimal research to date and studied aggression and suicidality in migraine patients. They found higher rates of aggressive behaviors among chronic migraine patients (20) Friedman et al. (9) reported on the association of anxiety, depression, and anger with headache triggers, intensity of headache pain, and response to treatment.

Studies previously reviewed by Nović et al. (8) have already suggested that the severity, frequency, and intensity of migraine pain influences the risk of suicidal behavior in migraineurs, with some authors suggesting that pain might be an independent risk factor. Four studies in this review have also discussed this association (19, 22, 23, 25). Calati et al. (19) recommended further investigation of suicidality and the role of pain chronicity and severity. The comorbidity of suicidal tendencies and migraineur pain severity was also highlighted by Berhane et al. (25) and Harnod et al. (22) who revealed that suicide attempts increased after 5 years following status migrainosus diagnosis (22) and considered that the severity and duration of pain might play a critical role.

Nović et al. (8) commented on the limitation among retrieved studies related to the variability in the classification of migraine and its subtypes within the studies. Some studies looked at migraine as a whole while others specified subtypes. They noted that some studies did not differentiate among migraine types, such as with aura or without aura (8). The systematic review revealed that migraine with aura shows a stronger relationship with suicidal behavior than migraine without aura, and this remains evident even after controlling for other factors such as age, gender, and psychiatric conditions, suggesting an independent association between migraine with aura and suicidal behaviors (8). This finding was supported by Friedman et al. (9) who stated that migraine with aura is consistently more strongly associated with suicide ideation compared with migraine without aura. Similarly, this review revealed that studies varied in their investigation and analysis of headache subtypes. Calati et al. (19) were unable to investigate migraine and non-migraine headache subtypes as the lifetime suicide attempt sample was too small for analysis. In addition, they focused on lifetime suicide attempts only and recommended that further studies should investigate different suicidal phenotypes including suicide, suicidal ideation, and self-harm (19).

Friedman et al. (26) recommended that further studies investigate the relationship between migraine phenotypes with suicidal ideation. Similarly, Friedman et al. (27) could not distinguish between migraine subtypes with or without aura as they analyzed hospital diagnosis codes and found that there was a coding error for migraine subtypes (27). Fuller-Thomson et al. (21) investigated data from a population-based sample that did not allow for differentiation between migraine subtypes such as chronic and episodic (21), with aura or without aura, and degree of severity (21). In addition, age of onset and timing of suicide attempts was unreported in the data set and self-reported migraine could not be validated (21). Harnod et al. (22) differentiated between migraine and status migrainosus only whilst Lin et al. (23) examined migraine with aura and without aura and found that migraine with aura was a strong risk factor of suicidal ideation/attempt in the clinic-based population (23). Park et al. (24) did not find such results and noted that this finding might have been because the hospital-based population had a low number of migraine patients with aura ($n = 17$) and the cohort age range was wide compared with other studies that identified the association with aura.

Nović et al. (8) noted that there were limitations in the variations of the way suicidality was measured. This review also revealed variations in data collection and measurement. Altura et al. (18) conducted telephone interviews and acknowledged that PHQ-9 questionnaires were not always completed on the same day as the SCID interview. Friedman et al. (27) based their findings on ICD-9 hospital diagnosis codes that did not differentiate between suicidal ideation, suicide attempt, and non-suicidal self-inflicted harm (27). The authors reported that this might introduce the potential error of misclassifications of suicidal behaviors (27). Fuller-Thomson et al. (21) acknowledged that their study used a crude measure to assess pain that minimized the ability to identify those with the most severe pain. In addition, only one self-report question assessed suicide attempt (21). Harnod et al. (22) cited the possible miscoding and under-diagnosis of suicide events in the database as a potential study limitation in addition to restrictions around obtaining further information, as patients were anonymized and therefore not contactable.

Nović et al. (8) discussed the shared biological mechanisms for migraine, suicidal behavior, and major affective disorders. Similarly, Friedman et al. (9) reported that migraine, major depressive disorder, and suicidal ideation may be influenced by both genetic and environmental factors including stressful life events that affect the neurobiological systems. Furthermore, serotonin transported polymorphisms have been associated with the frequency of migraine attacks, depressive symptoms, and

suicidal behaviors (9). Aly et al. (1) provided the opinion that genetics are partially responsible for the risk of suicide and reduced serotonergic activity is linked with suicidal behavior. Whilst the evidence is limited, six of the studies in this review discussed the connection between biological mechanisms and migraine, psychiatric disorders, and suicidal behaviors (19, 21–23, 25, 26). Two studies discussed psychosocial and environmental influences (19, 26) and five studies explored the role of genetic variability (19, 21–23, 25, 26). Two of the studies discussed the cultural and ethnic differences between Asian and Western populations (22, 24). Harnod et al. (22) reported that these distinctions be for the difference between their Taiwanese study and other studies carried on in Western societies (24).

Given that the results of this study support the fact that people with migraine are at an increased risk of suicide, they are also more likely to experience anxiety which is considered as a strong risk factor for suicide (Sareen, 2011). Therapeutic strategies should consider screening for anxiety, suicidal behavior or ideation, and other psychiatric disorders. The treatment strategies targeting both migraine and comorbid disorders will have a better outcome for the migraine sufferers and could prevent more serious actions such as suicide.

Based on a rigorous recent metanalysis, the communication of suicidal intentions occurs in almost half of people who decide to end their life by suicide (37). Thus, promoting better care for migraine is the first step in preventing suicidal behaviors among patients with migraine. Despite being a common neurological disorder in the world, affecting one in seven people worldwide, migraine continues to be underrecognized, underdiagnosed, and undertreated (7, 38).

Despite this sad truth, migraine continues to be worst managed medical disorder worldwide, resulting in the first ever global campaign on migraine, the "painful truth" during World Brain Day 2019 (7).

It is critical to recognize and promote the global, regional, and local interest of people with migraine. All patients with migraine should have access to appropriate medical care. All health care professionals including physicians, nurses, and psychologists should have access to adequate and up to date training in migraine, associated comorbidities, and management as a matter of priority (38).

Nović et al. (8) found that the international representativeness of the studies retrieved for the systematic review was limited. Thus, this review retrieved more recent studies from Peru, Ethiopia, Canada, and Taiwan, as well as the US, though five of these studies used clinic-based patients and therefore the results may only be generalizable to worldwide hospitalized populations (18, 20, 23–25). The two studies conducted by Friedman et al. (26, 27) both assessed large samples, though one study focused on pregnant women only (26) and the other was a nationally representative sample of American adult hospital inpatients and again warrants caution when generalizing to community-based patients (27). The large representative data sets of Fuller-Thompson et al. (21) and Harnod et al. (22) must also be seen as study strengths (21, 22).

Underreporting in the form of recall bias was reported in three studies (19, 25, 26) and social desirability bias was reported in two others (25, 27), while Harnod et al. (22) acknowledged underestimation bias in their report due to the exclusion of a number of factors.

This review is also limited in consideration of only late adolescents and adult cohorts and the design methodology used in the retrieved English language studies. Seven of the studies used a cross-sectional study design (21–27), thereby limiting conclusions based on causality, and not surprisingly leading to a recommendation of future longitudinal studies and population-based research. Nović et al. (8) also highlighted these limitations several years ago. Further studies should broaden the populations to be examined to include younger adolescents and people from other cultural cohorts. Consideration of other prevalent headaches types such as tension headaches and their relationship to suicidal behaviors or other psychiatric disorders also remains necessary.

In all studies, the clinical implications of migraine as such a common underrecognized, underdiagnosed, undertreated (7, 38), and poorly managed neurological disorder affecting one in seven people worldwide, have been highlighted. Whether previous systematic reviews (8, 9) or the expert opinion of Aly et al. (1), all recommend screening and early identification of suicidal behaviors and psychiatric comorbidities in at-risk migraineurs (1, 9, 18–27). Collectively, all the studies in this review recognize and promote the need for enhanced medical care of people with migraine and on-going training for health care professionals in migraine, associated comorbidities, and management (8) as a matter of priority (38).

## CONCLUSION

Migraine is often associated with lifetime disability and negative quality of life. This review has investigated the association between migraine and suicidal behaviors as reported in ten recent international studies. Collectively, all the studies suggest an association between migraine, suicidal behaviors, and comorbidities, including psychiatric disorders, and demonstrate an increased risk of suicidal behaviors in both clinical and general population migraineurs.

Future studies are needed to facilitate the development of clinical guidelines for risk assessment, targeted interventions, and evidence-based treatment of migraine to minimize the risk of suicide among this vulnerable population.

## AUTHOR CONTRIBUTIONS

LK, CB, and MB carried out the database search, screening, quality assessment, data extraction, and analysis. LK and DH wrote the first draft of the manuscript. TW and SC revised the initial drafts and gave scientific contribution. All authors provided critical feedback, helped shape the research, analysis, manuscript, and contributed to the conceptualization and design of the research.

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