

Migraine induced by hypoxia: an MRI spectroscopy and angiography study

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Migraine with aura is prevalent in high-altitude populations suggesting an association between migraine aura and hypoxia. We investigated whether experimental hypoxia triggers migraine and aura attacks in patients suffering from migraine with aura. We also investigated the metabolic and vascular response to hypoxia. In a randomized double-blind crossover study design, 15 migraine with aura patients were exposed to 180 min of normobaric hypoxia (capillary oxygen saturation 70–75%) or sham on two separate days and 14 healthy controls were exposed to hypoxia. Glutamate and lactate concentrations in the visual cortex were measured by proton magnetic resonance spectroscopy. The circumference of cranial arteries was measured by 3 T high-resolution magnetic resonance angiography. Hypoxia induced migraine-like attacks in eight patients compared to one patient after sham ($P = 0.039$), aura in three and possible aura in 4 of 15 patients. Hypoxia did not change glutamate concentration in the visual cortex compared to sham, but increased lactate concentration ($P = 0.028$) and circumference of the cranial arteries ($P < 0.05$). We found no difference in the metabolic or vascular responses to hypoxia between migraine patients and controls. In conclusion, hypoxia induced migraine-like attacks with and without aura and dilated the cranial arteries in patients with migraine with aura. Hypoxia-induced attacks were not associated with altered concentration of glutamate or other metabolites. The present study suggests that hypoxia may provoke migraine headache and aura symptoms in some patients. The mechanisms behind the migraine-inducing effect of hypoxia should be further investigated.

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Abbreviations: AUC = area under the curve; SpO₂ = capillary oxygen saturation; ¹H-MRS = proton magnetic resonance spectroscopy; MRA = magnetic resonance angiography; NAA = N-acetyl aspartate

Introduction

Migraine is a complex neurological disease affecting 12% of the population, with enormous impact on patients' ability to work and on their family and social life (Lipton *et al.*, 2007). For centuries, physicians have been fascinated by the wide variety of migraine symptoms, and especially by aura symptoms, such as the transient visual and sensory alterations, which may precede headache (Tfelt-Hansen, 2010). To date, no validated model to provoke and investigate migraine with aura under controlled conditions exists. In 1982, Amery hypothesized that hypoxia might trigger migraine attacks (Amery, 1982). Several studies support an association between migraine with aura and hypoxia. Epidemiological studies reported a high prevalence of migraine in high-altitude populations (Arregui *et al.*, 1991, 1994), in particular of migraine with aura, which affected 19% of the adult males (Arregui *et al.*, 1994) compared to 5% at sea level (Russell *et al.*, 1995). Cortical spreading depression is widely accepted as the cause of migraine auras. Cortical spreading depression is characterized by a self-propagating wave of depolarization that spreads across the cerebral cortex followed by hypoperfusion (Olesen *et al.*, 1981; Lauritzen *et al.*, 1982). Hypoxia induces cortical spreading depression in mice *in vivo* (Takano *et al.*, 2007) and in rat brain slices (Mané and Müller, 2012). Exposure to hypoxia increases duration and decreases threshold of cortical spreading depression induced by potassium chloride in mice (Takano *et al.*, 2007). Hypoxia is associated with increased lactate concentration in the brain in healthy volunteers (Edden *et al.*, 2010; Harris *et al.*, 2013) and glutamate concentration in the brain of animals (Zoremba *et al.*, 2007). Interestingly, migraine with aura patients demonstrated increased glutamate (Siniatchkin *et al.*, 2012; González de la Aleja *et al.*, 2013) and lactate (Watanabe *et al.*, 1996; Sándor *et al.*, 2005) concentrations in the brain outside of attacks measured by proton magnetic resonance spectroscopy (¹H-MRS). Increased lactate has been suggested to reflect mitochondrial dysfunction, which may play a role in migraine with aura pathophysiology (Welch *et al.*, 1989; Barbiroli *et al.*, 1990, 1992; Montagna, 1995; Boska *et al.*, 2002; Lodi *et al.*, 2006).

We hypothesized that experimental normobaric hypoxia induces migraine attacks associated with changes in brain glutamate and lactate and with dilatation of cranial arteries in patients with migraine with aura. We conducted a randomized double-blind sham-controlled study and investigated changes in glutamate and lactate concentrations in the visual cortex by ¹H-MRS and circumference of cranial arteries by high-resolution magnetic resonance angiography (MRA). In addition, we investigated healthy volunteers

during hypoxia to compare hypoxic responses of patients to controls.

Materials and methods

Participants were recruited via a Danish website for recruitment of volunteers to health research and via the outpatient clinic at the Danish Headache Centre (Rigshospitalet Glostrup, Copenhagen, Denmark). Patients with migraine with aura suffering from typical aura in every attack, in accordance with the International Classification of Headache Disorders 3 beta version (ICHD-3 beta, 2013), with minimum one attack per month were recruited for the study. We also recruited age (± 3 years) and sex-matched controls without a history of migraine or first-degree relatives with migraine. Exclusion criteria for all participants were any other type of headache (except episodic tension type headache <5 days per month), any somatic or psychiatric disease, smoking, a history of mountaineering training and any daily medication apart from oral contraceptives.

The study was approved by the Ethics Committee of the Capital Region of Denmark (H-4-2012-182) and the Danish Data Protection Agency, and was registered at Clinicaltrials.gov (ID: NCT01896167). All participants provided their written informed consent to participate in the study after detailed oral and written information about the study in accordance with the Declaration of Helsinki of 1964, with later revisions.

Experimental design

In a double-blind, crossover design, the patients were randomly allocated to 180 min of inhalation of the test gas through a mask: normobaric hypoxia [mixture of nitrogen and atmospheric air, capillary oxygen saturation (SpO₂) of 70–75%] or a sham procedure (atmospheric air, Strandmoellen, Denmark) on two separate days with a minimum of 7 days between. The controls were exposed to similar hypoxia on one study day (Fig. 1).

Participants arrived at the laboratory (free of headache) at the same time on each study day (± 2 h). Arrival time for the controls was individually matched to the migraine patients (± 2 h). Participants were not allowed to consume coffee, tea, cocoa, alcohol or other methyl xanthine-containing food or beverages 12 h before the start of the study days. The study was postponed if the participant had had a migraine attack within 5 days or any headache 48 h before the study days. Female participants did not menstruate within 2 days before or after the study days.

The participants were supine and a catheter was inserted in the antecubital vein for blood sampling. We obtained ¹H-MRS, MRA and anatomical T₁ images at baseline, during inhalation (MRA at 120 min, ¹H-MRS at 180 min) and finally ¹H-MRS and T₁ images after inhalation at 240 min (Fig. 1). The participants continuously breathed through the mask

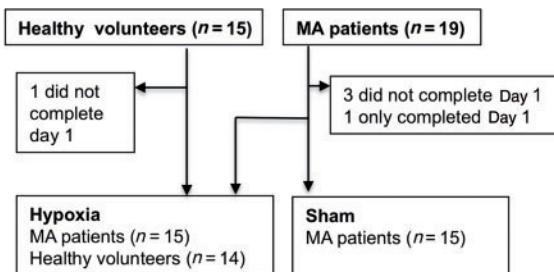
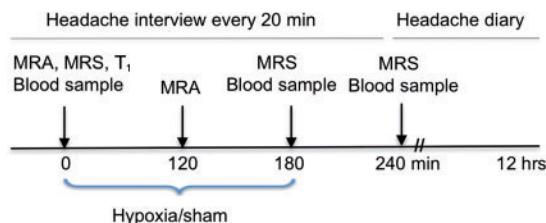
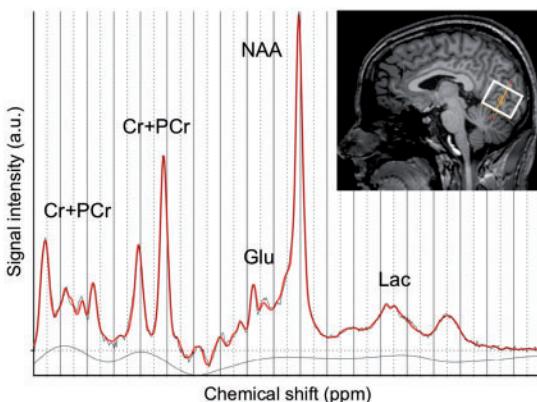
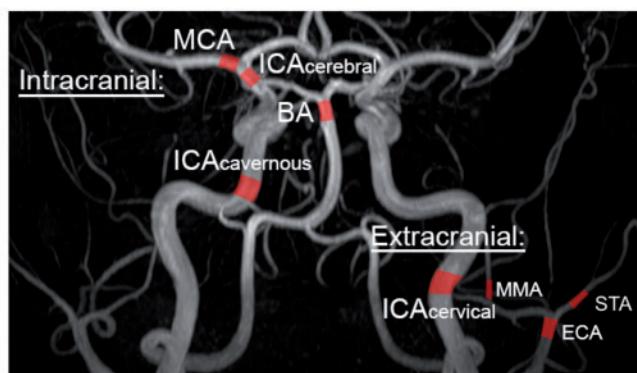
A Study flow chart**B Study design****C Magnetic resonance spectroscopy****D Magnetic resonance angiography**

Figure 1 Study design and MRI methods. (A) Fifteen of 19 patients with migraine with aura completed both study days (12 females/3 males, mean age 28, range 18–46). Three patients withdrew after Day 1 because of discomfort and logistic problems. Three patients were, due to migraine-like attacks, only able to be exposed to 90, 130 and 140 min (Patients 6, 11, 12) of hypoxia and therefore their vital variables and blood samples were excluded for both study days. Fourteen of 15 control subjects completed the study (11 females/3 males, mean age 28, range 20–45). One healthy volunteer withdrew after 70 min of hypoxia because of discomfort. Data from the excluded participants were not used. (B) Study design. (C) Absolute concentrations of glutamate, lactate, NAA and total creatine (Cr + PCr) in the visual cortex were measured by ¹H-MRS. (D) Circumference of each arterial segment marked in red was measured as the mean of 26 slices. The measurement was excluded if it was not possible to assess at least 12 values. If the contour was distorted or small side branches were included in a measurement, we manually corrected the measurement if possible. If not possible the measurement was excluded from each study day. We included four intra- and four extracranial arteries. The exact same segments of each vessel were identified in each scan using the following starting points: middle cerebral artery (MCA) and the cerebral part of the internal carotid artery (ICA_{cerebral}): from their branch off from the main trunk of the ICA; basilar artery (BA): from the point where the basilar artery divides into the two posterior cerebral arteries; cavernous part of the internal carotid artery (ICA_{cavernous}): from the point where the internal carotid artery exits the skull bone to enter the intracranial cavity, before the cavernous sinus; middle meningeal artery (MMA): from the branch off from the main trunk of the maxillary artery, external carotid artery (ECA): from the point where the external carotid artery divides into the maxillary artery and the superficial temporal artery; cervical part of the internal carotid artery (ICA_{cervical}) and the superficial temporal artery (STA): their starting point was identified with the ipsilateral start of the middle meningeal artery as reference. MA = migraine with aura; Glu = glutamate; Lac = lactate.

during 0–180 min including during the MRI scans by the use of extended tubes. The participants were questioned about headache, associated symptoms, adverse events and premonitory symptoms every 20 min until 240 min after the beginning of the inhalation period. If a participant reported headache, this question interval was changed to every 10 min. We monitored SpO₂, ECG, blood pressure, heart rate, and end-tidal CO₂ tension (Veris Monitor, Medrad) at baseline and then every 20 min from 0 to 180 min. We collected blood samples to determine potassium, sodium, haemoglobin, glucose and lactate levels at baseline and after 180 and 240 min (blood gas analyser, Radiometer). After the baseline scan and after 180 min, the subjects were offered a standard small meal (bread with soft cream cheese, grapes, banana and water).

During the first 80 min of inhalation of the test gas, participants could choose to be supine or sitting. One hour after the end of inhalation, the participants were discharged and instructed to complete a validated headache diary for the next 8 h (Fig. 1). All MRI images were analysed blind.

Hypoxia

Hypoxia was induced by an AltiTrainer system (SMTEC) through a 7-m tube, a one-way valve and a tight fitting full-face mask (Hans Rudolph). A physician (N.A.) regulated the concentration of nitrogen and oxygen in the inspired air to obtain and maintain a SpO₂ of ~70–75%. In a blinded fashion the AltiTrainer was either connected to a gas bottle with

atmospheric air (sham day) or nitrogen (100% purity, Strandmoellen) mixed with atmospheric air from the room (hypoxia day). The participants and one investigator (J.B.) were blinded to the content of the inhaled air. SpO₂ was measured continuously using a fingertip pulse oximeter (Veris Monitor, Medrad) and monitored by the unblinded investigator (N.A.) on an external screen in the MRI control room not visible to the blinded investigator (J.B.). The arm and hand on the monitored side were covered by a towel to ensure good perfusion of the fingers. The severity and duration of hypoxia in this study was based on earlier studies and entails no risk in healthy subjects (Pialoux *et al.*, 2009; Wilson *et al.*, 2011; Overgaard *et al.*, 2012).

Headache and migraine-like criteria

The participants were informed of possible headache inducing effects of hypoxia with no information of possible timing and character of symptoms. A blinded investigator (J.B.) obtained data on headache characteristics [intensity, quality (throbbing or pressing), pain location and pain aggravation by physical activity], aura symptoms (visual, sensory or speech symptoms), associated symptoms (nausea, photophobia and phonophobia), and adverse events (palpitations, heat feeling, dizziness and flushing). Headache intensity was recorded on a verbal rating scale (VRS) from 0 to 10, in which 0 is no headache, 1 is a very mild headache (including a feeling of pressing or throbbing pre-pain) and 10 is the worst imaginable headache. Headache ≥ 4 was classified as moderate-to-severe headache intensity. In addition, patients were asked whether headache and aura symptoms mimicked their usual attacks. The participants were also asked to complete a headache diary every hour from 4 until 12 h after the beginning of inhalation of the test gas (Fig. 1) and were allowed to treat headache with common analgesics and their usual migraine medication. Two blinded laboratory technicians (L.E. and W.G.) extracted and double-checked headache data from questionnaires and diaries into Excel data files.

Headache induced by provocation cannot completely fulfil the International Classification of Headache Disorders 3 beta (ICHD-3 beta, 2013) for migraine that requires the migraine attack to be spontaneous. Furthermore, the attack should last at least 4 h if the attack is untreated. In provocation studies participants must be allowed to take treatment although all migraine criteria may not be fulfilled. Most spontaneous migraine attacks develop over hours, with an initiation phase that fulfils only the criteria for tension-type headache. We therefore, as in earlier migraine-provocation studies (Hansen *et al.*, 2010; Schytz *et al.*, 2010), used the following two criteria for a migraine-like attack:

Migraine-like attacks fulfilling either (1) or (2):

- (1) Headache fulfilling criteria C and D for migraine without aura (ICHD-3 beta, 2013).
- (2) Headache described as mimicking usual migraine attack and treated with a triptan.

In the present study, migraine-like attacks were also defined as:

- (3) Attacks fulfilling criteria B–C for migraine with typical aura:
 - (B) One or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal.

(C) At least two of the following four characteristics:

- (i) at least one aura symptom spreads gradually ≥ 5 min, and/or two or more symptoms occur in succession.
- (ii) each individual symptom lasts 5–60 min.
- (iii) at least one aura symptom is unilateral.
- (iv) the aura is accompanied, or followed within 60 min, by headache.

Magnetic resonance spectroscopy

We used a 3.0 T Philips Achieva MRI scanner (Philips Medical Systems) with a 32-element phased-array receiver head coil. ¹H-MRS measured the concentration of glutamate, lactate, N-acetyl aspartate (NAA) and total creatine (i.e. phosphocreatine and creatine) (Fig. 1). A water suppressed point-resolved spectroscopy (PRESS) pulse sequence was used with repetition time 5000 ms; echo time 36.5 ms; voxel size 30 mm \times 35 mm \times 30 mm (31.5 mm³); 128 acquisitions; total duration 13 min 8 s. The water signal was used as internal standard for quantification (Christiansen *et al.*, 1993). The voxel was located in the visual cortex (Fig. 1). Signal from fat has the same frequencies as lactate and could confound quantification of the lactate peak. To avoid signal from subcutaneous fat, the entire voxel was located inside brain tissue. Data post-processing and quantification of the spectra was done with LCModel (Version 6.3-1F). Measurements where lactate were not detected and abnormal spectra were excluded by a blinded investigator (M.V.).

Magnetic resonance angiography

A single-slab 3D time-of-flight (3D TOF) MRA of extra- and intracranial arteries was acquired as described in previous studies (Amin *et al.*, 2013, 2014). MRA data were analysed by LKEB-MRA vessel wall analysis software program (version 6.2007). The investigators (N.A. and F.M.A.) who performed the analyses were blinded to the experimental day and scan session. The intracranial arteries included one extracerebral segment: the cavernous internal carotid artery, and three intracerebral segments: the middle cerebral artery, basilar artery and the cerebral internal carotid artery. The extracranial vessel segments included the external carotid artery, superficial temporal artery, middle meningeal artery and cervical internal carotid artery. For each arterial measurement, we obtained an average of 26 values (i.e. 5-mm long vessel segments) (Fig. 1).

Anatomical T₁ scan

We performed a high-resolution anatomical scan with a 3D T₁-weighted turbo field echo sequence (field of view 256 \times 256 \times 170 mm³; voxel size 1.067 \times 1.067 \times 1.000 mm³; echo time 4.604; repetition time 9.0 ms; echo train length 200; flip angle 8°). All anatomical scans were seen by a radiologist (F.W.) to exclude any pathology.

Statistical analysis

All absolute values are presented as mean \pm standard deviation (SD), except headache scores, ¹H-MRS values and blood samples, which are presented as median values. Angiography data

are presented as percentage changes with a 95% confidence interval (CI). Baseline was defined as t_0 before the start of inhalation.

Sample size was based on previous migraine-provocation studies performed by our group showing migraine incidence of 60–80% after pituitary adenylate cyclase activating peptide-38, calcitonin gene-related peptide, and the nitric oxide donor glyceryl-trinitrate (Schytz *et al.*, 2010).

The endpoints were differences between hypoxia and sham in patients (primary endpoints) and between patients and controls (secondary endpoints) for the following data: (i) incidence in migraine-like attacks and headache during inhalation (0–180 min); (ii) area under the curve (AUC) for headache score during inhalation (0–180 min); (iii) changes from baseline in glutamate, lactate, total creatine, and NAA concentrations in the visual cortex at 180 and 240 min; and (iv) changes from baseline in circumference of the intra- and extracranial arteries between hypoxia and sham at 120 min.

Additional secondary endpoints were differences between hypoxia and sham in patients and between patients and controls for the following data: (i) AUC (0–180 min) for SpO_2 , heart rate, mean arterial pressure, and end-tidal CO_2 tension; (ii) change from baseline of venous blood concentrations of haemoglobin, potassium, lactate and glucose; and (iii) incidence of adverse events.

Incidence of migraine/headache/aura and adverse events were analysed as binary categorical data with McNemar's test to compare hypoxia and sham in patients. For comparison of patients and controls we performed Pearson's chi-square test. We calculated AUC according to the trapezium rule to obtain a summary measure and to analyse the difference in response between hypoxia and sham and between patients and controls. Baseline was subtracted before calculating AUC to reduce within participant variation between sessions. Changes from baseline of ^1H -MRS metabolites, arterial circumference and blood samples, AUC of vital variables and baseline differences of all variables between hypoxia and sham and arterial circumference side-to-side difference, before and after inhalation were compared using the non-parametric Wilcoxon signed rank test. Differences between patients and controls were compared by the Mann-Whitney test.

All analyses were performed with SPSS version 19.0. We made no adjustment for multiple analyses. Five per cent ($P < 0.05$) was accepted as the level of significance.

Results

Fifteen patients with migraine with aura [12 females, mean age 28 (range 18–46), mean body mass index 22 kg/m^2 (range 19–26)] and 14 controls [11 females, mean age 28 (range 20–45), mean body mass index 25 kg/m^2 (range 20–34)] completed both study days (Fig. 1). There were no differences in any variables at baseline between hypoxia and sham days or between patients and controls except the baseline circumference of cervical internal carotid artery, which was larger in controls [16.08 mm (SD 1.03 mm) versus 14.80 mm (SD 1.59 mm), $P = 0.014$].

Migraine

Eight patients (53%) experienced migraine-like attacks during hypoxia inhalation in comparison to one (7%) during sham procedure ($P = 0.039$) and one in the control group (7%) ($P = 0.007$). Three attacks fulfilled the migraine with aura criteria and seven the migraine without aura criteria during hypoxia (Table 1). Furthermore, four patients (27%) experienced a short period of uncharacteristic visual disturbances, three during hypoxia and one after hypoxia (Table 2). During hypoxia median time to onset of migraine-like attacks was 105 min (range 60–180 min) and median duration of the attack was 6 h (range 2–11 h).

One patient reported migraine without aura during sham procedure and 4 h after start of sham procedure the patient reported aura symptoms. Furthermore, two patients experienced migraine without aura-like attacks 5 and 8 h after initiation of sham procedure.

One healthy volunteer experienced migraine-like headache after 180 min hypoxia inhalation (Table 1). Two healthy volunteers experienced a short period of uncharacteristic visual disturbances during hypoxia (Table 2).

Magnetic resonance spectroscopy

In patients, we found no changes of glutamate, total creatine or NAA concentrations in the visual cortex during hypoxia compared to sham ($P > 0.05$). Lactate increased by 61% (CI 13–108%) during hypoxia and by 7% (CI 21–35%) during sham ($P = 0.028$). There were no changes in any of the metabolites at 240 min ($P > 0.05$) (Fig. 2 and Table 3).

In controls, we found no changes of glutamate, total creatine or NAA concentration ($P > 0.05$). Lactate concentration increased by 56% (CI 4–108%) during hypoxia compared to baseline ($P = 0.037$). There were no differences between patients and controls in the change of glutamate, lactate, total creatine or NAA at 180 min ($P > 0.05$) or at 240 min after hypoxia ($P > 0.05$; Table 3).

Magnetic resonance angiography

There was no difference in the change from baseline to hypoxia in arterial circumference of intra- or extracranial arteries between the right and the left side ($P > 0.05$). We therefore used an average of the left and right arteries.

In patients, the circumference of all intracranial arteries increased during hypoxia compared to sham ($P < 0.05$) (Fig. 3A). In controls, the circumference of all intracranial arteries also increased from baseline during hypoxia ($P < 0.05$; Fig. 3A). There was no difference between patients and controls in change of arterial circumference during hypoxia ($P > 0.05$).

In patients, the circumference of all extracranial arteries increased during hypoxia compared to sham ($P < 0.05$), except the circumference of the middle meningeal artery ($P = 0.060$) (Fig. 3B). In controls, the circumference of all

Table 1 Characteristics of migraine-like attacks and headache during inhalation (0–180 min)

Patient ID	Headache characteristics ^a	Associated symptoms ^b	Visual disturbances	Mimics usual migraine	Migraine-like attack onset	Treatment (time)/efficacy ^c
Patients: hypoxia						
1	Right/6/throbbing/+	+ / + / +	No ^d	Yes	80 min	Sumatriptan 100 mg, ibuprofen 600 mg (4 h)/yes
4	Right/7/throbbing / +	+ / - / +	Yes	Yes	150 min	Metoclopramide 20 mg (200 min)/yes Sumatriptan 6 mg, paracetamol 1 g, Dolol® 100 mg (4 h)/yes
6	Left/10/throbbing / +	+ / + / +	Yes	Yes	70 min	Sumatriptan 6 mg (140 min)/yes
7	Bilateral/2/pressing/+	-/-	Yes	Yes	180 min ^e	Metoclopramide 20 mg, ibuprofen 400 mg, paracetamol 1 g (4 h)/ND
8	Bilateral/6/pressing/ +	+ / + / +	No	Yes	130 min	Metoclopramide 20 mg (130 min)/no Ibuprofen 400 mg, paracetamol 1 g (4 h)/no
9	Left/2/pressing/ +	+ / - / +	No	Yes	60 min	
11	Right/6/throbbing / +	+ / - / +	Yes	Yes	130 min	
12	Right/10/pressing/ +	+ / - / +	Yes	Yes	80 min	Sumatriptan 6 mg, paracetamol 1 g (210 min)/yes
Patients: sham						
2	Right/2/pressing/ +	-/- +	None	Yes	110 min	
Controls: hypoxia						
11	Right/1/pressing/ +	-/- +	No	NA	180 min	Paracetamol 1 g (5 h)/yes

^aLocalization/intensity/quality/aggravation by movement.^bPhotophobia/phonophobia/nausea.^cPain relief ≥ 50% within 2 h.^dPatient experienced visual disturbances at 240 min.^ePatient fulfilled the migraine-like criteria for migraine with aura at 180 min and migraine without aura from 200 min.

ND = not determined; NA = not applicable.

extracranial arteries also increased from baseline during hypoxia ($P < 0.05$). Compared to patients, the absolute circumference change of the cervical internal carotid artery in controls during hypoxia was larger [2.38 mm (SD 0.77 mm) versus 1.81 mm (SD 0.44 mm), $P = 0.019$]. However, explorative analysis of the relative circumference changes showed no difference between controls [15% (CI 12–17%)] and patients [12% (CI 12–17%)] ($P = 0.198$). There was no difference between the two groups in the circumference change of the other extracranial arteries ($P > 0.05$).

Vital variables

During hypoxia the participants reached a mean SpO_2 of 72% (SD 4.76%) at a mean inspiratory oxygen content of 11% (SD 1.27%), equivalent to an altitude of ~4700 m (Fig. 4).

In patients, during hypoxia compared to sham the $AUC_{0-180 \text{ min}}$ was higher for heart rate ($P = 0.002$), whereas SpO_2 ($P = 0.002$) and end-tidal CO_2 tension ($P = 0.004$) was lower and there was no difference in $AUC_{0-180 \text{ min}}$ of mean arterial pressure ($P = 0.722$). There was no difference between patients and controls during hypoxia in $AUC_{0-180 \text{ min}}$ for heart rate, SpO_2 , mean arterial pressure or end-tidal CO_2 tension ($P > 0.05$).

Blood samples

Baseline venous blood samples showed normal potassium, sodium and haemoglobin levels on both study days.

In patients, the venous lactate ($P = 0.008$), glucose ($P = 0.035$) and haemoglobin ($P = 0.028$) increased and potassium ($P = 0.021$) decreased during hypoxia compared to sham (Table 3). At 240 min after hypoxia compared to sham, lactate ($P = 0.012$) and glucose ($P = 0.036$) were still increased, whereas no changes of haemoglobin ($P = 0.138$) and potassium ($P = 0.675$) were observed.

There was no difference between the patients compared to controls in the change of haemoglobin, potassium, glucose or lactate during hypoxia ($P > 0.05$) (Table 3). At 240 min after hypoxia, the lactate ($P = 0.016$) and glucose ($P = 0.044$) changes were larger in patients compared to controls.

Headache and adverse events

Thirteen patients experienced headache after hypoxia in comparison to five patients after sham ($P = 0.039$) (Fig. 5 and Supplementary Table 1). $AUC_{0-180 \text{ min}}$ for headache score was higher during hypoxia compared to sham ($P = 0.018$).

Eleven controls experienced headache during hypoxia (Fig. 5). The headaches were predominantly bilateral and pressing (Supplementary Table 2). There was no difference in headache incidence ($P = 0.564$) or AUC for headache score ($P = 0.182$) during hypoxia in patients compared to controls. Explorative analysis revealed that the $AUC_{180-300 \text{ min}}$ for headache score was larger after hypoxia inhalation in patients compared to controls ($P = 0.016$).

In patients during hypoxia compared to sham the incidence of nausea ($P = 0.004$), photophobia ($P = 0.008$), dizziness ($P = 0.002$), and palpitations ($P = 0.031$) were

Table 2 Visual and sensory disturbances

Patient ID	Onset	Duration	GS	Localization	Description	Headache onset	Mimics usual aura	Fulfils aura criteria
Patients: hypoxia								
7	173 min	Visual 30 min	Yes	Central right upper quadrant	Scotoma and flickering	180 min	No ^a	Yes
11	130 min	Visual 130 min	Yes	Central upper quadrants right hemifield	Flickering	120 min	Yes	Yes
12	78 min	Visual (119 min) Sensory (55 min)	Yes	Right hemifield central upper quadrants Fingers right side hand upper arm	Flickering, black spots Numbness and tingling	40 min	Yes	Yes
1	4 h	Visual 10 min	No	Left and right lower quadrant	Blurred vision	60 min	No	Possible
2	170 min	Visual 10 min	No	Diffuse in visual field	'Worms'	170 min	No	Possible
4	80 min	Visual 20 min	No	Central	Blurred vision	40 min	No	Possible
6	80 and 130 min	Visual 2 × 30 min	No	Diffuse in visual field	Blurred distant vision	70 min	Yes, some attacks	Possible
Patients: sham								
2	4 h	Visual 46 min	Yes	Central, right hemifield, left upper quadrant	Scotoma and flickering	40 min	Yes	Yes
Controls: hypoxia								
8	160 min	Visual 10 min	No	Central	Difficulty focusing	100 min	NA	NA
13	60 min	Visual 10 min	No	Diffuse in visual field	Small black spots	120 min	NA	NA

^aPatient's aura is usually a scotoma without flickering in the left side of the visual field.

GS = gradually spreading ≥ 5 min; NA = not applicable.

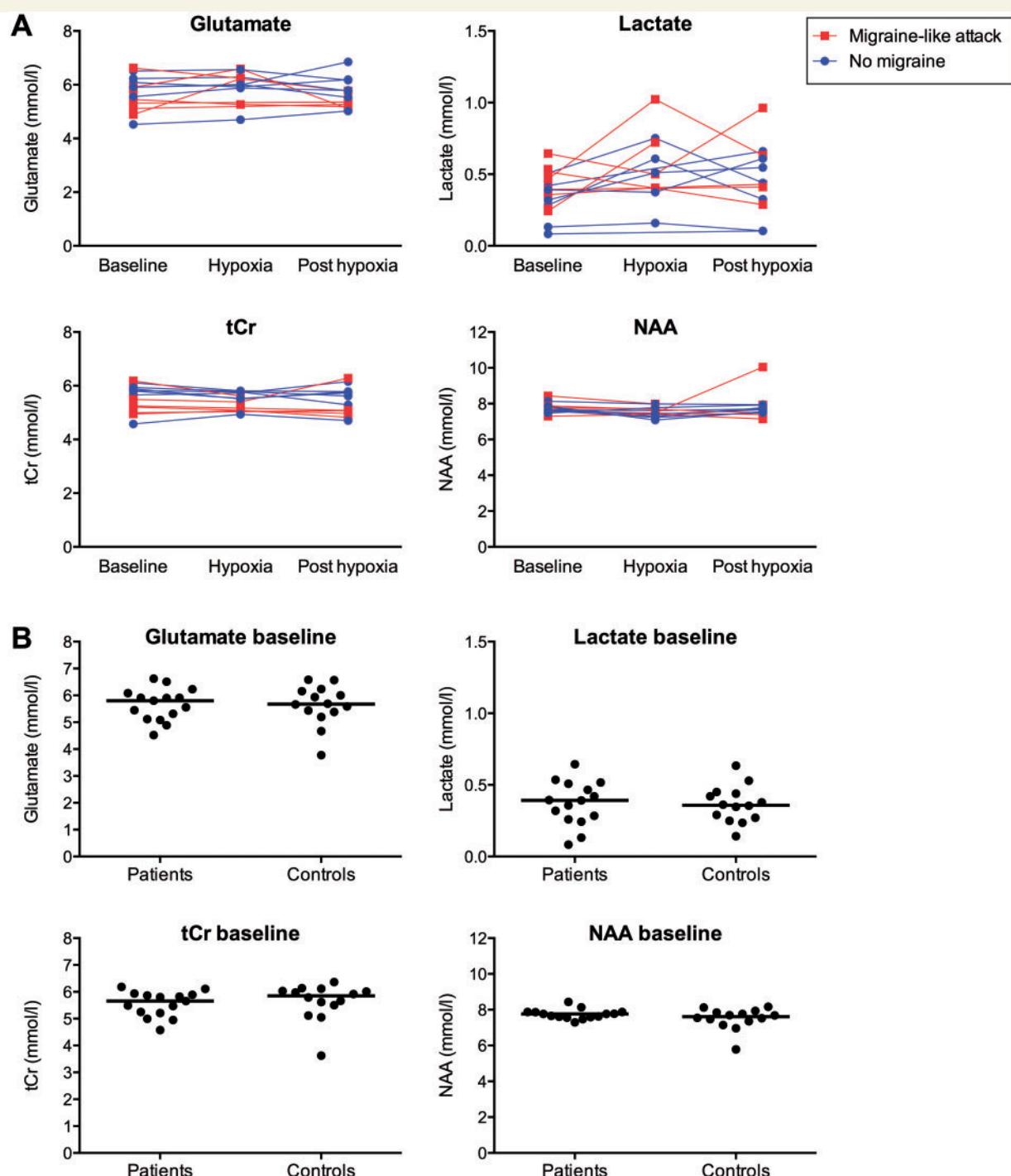


Figure 2 MRS. (A) ^1H -MRS measurements on hypoxia day in patients with migraine with aura (migraine-like attack versus no attack) and (B) at baseline in patients and controls. The flat lines represent median values.

increased. There was no difference during hypoxia compared to sham in incidence of phonophobia, heat sensation or flushing ($P > 0.05$). The incidence of photophobia was higher in patients compared to controls during hypoxia ($P = 0.001$). There was no group difference in incidence of other adverse events during hypoxia ($P > 0.05$).

Discussion

The major finding of this study was that normobaric hypoxia induced migraine in 8 of 15 (53%) patients with migraine with aura (three patients reported migraine with aura, and five patients reported migraine without aura).

Table 3 ^1H -MRS and venous blood samples

Metabolite	Subjects	Baseline (mM)	P	180 min (mM)	P	240 min (mM)	P
^1H-MRS							
Lactate	Controls	0.36 (0.26–0.44)	0.777	0.51 (0.42–0.65)	0.818	0.40 (0.29–0.57)	0.537
	Patients hypoxia	0.39 (0.26–0.51)	0.281	0.51 (0.39–0.74)	0.028	0.43 (0.30–0.63)	0.638
	Patients sham	0.33 (0.23–0.44)		0.39 (0.21–0.52)		0.40 (0.22–0.49)	
Glutamate	Controls	5.68 (5.33–6.18)	0.793	5.83 (5.36–6.06)	0.103	5.90 (5.11–6.20)	0.877
	Patients hypoxia	5.80 (5.12–6.09)	0.177	6.01 (5.88–6.28)	0.374	5.65 (5.21–6.07)	0.937
	Patients sham	5.89 (5.42–6.12)		5.73 (5.55–6.30)		5.71 (5.08–6.32)	
Total creatine	Controls	5.85 (5.41–6.05)	0.275	5.38 (5.09–5.87)	0.586	5.64 (5.24–5.95)	0.918
	Patients hypoxia	5.66 (5.21–6.89)	0.173	5.53 (5.08–5.77)	0.110	5.46 (5.00–5.79)	0.937
	Patients sham	5.62 (5.26–5.98)		5.78 (5.32–5.99)		5.50 (5.31–5.77)	
NAA	Controls	7.61 (7.30–7.87)	0.239	7.60 (6.93–8.18)	0.703	7.73 (7.37–8.05)	0.328
	Patients hypoxia	7.77 (7.58–7.88)	0.053	7.47 (7.29–7.78)	0.131	7.68 (7.49–7.93)	1.0
	Patients sham	7.91 (7.54–8.18)		7.89 (7.60–8.09)		7.76 (7.40–8.16)	
Venous blood samples							
Lactate	Controls	0.83 (0.60–1.21)	1.00	1.18 (1.03–1.39)	0.411	0.80 (0.60–0.99)	0.018
	Patients hypoxia	0.85 (0.59–1.20)	0.593	1.20 (0.70–2.03)	0.008	1.10 (0.68–1.53)	0.012
	Patients sham	0.95 (0.75–1.14)		0.90 (0.58–1.15)		0.80 (0.63–0.90)	
Haemoglobin	Controls	7.90 (7.41–8.46)	0.356	8.43 (7.95–8.80)	0.243	8.33 (7.73–8.68)	0.526
	Patients hypoxia	8.10 (7.80–8.70)	0.366	8.30 (8.00–9.23)	0.028	8.25 (7.88–9.23)	0.138
	Patients sham	8.10 (7.73–8.55)		7.90 (7.90–8.55)		8.05 (7.80–8.70)	
Potassium	Controls	3.80 (3.70–3.96)	0.590	3.43 (3.29–3.60)	0.929	3.50 (3.40–3.75)	0.556
	Patients hypoxia	3.90 (3.70–3.98)	0.812	3.50 (3.29–3.59)	0.021	3.60 (3.58–3.68)	0.675
	Patients sham	3.95 (3.75–4.00)		3.78 (3.68–3.83)		3.63 (3.58–3.71)	
Glucose	Controls	4.78 (4.29–5.11)	0.520	4.80 (4.38–5.34)	0.156	4.98 (4.61–5.43)	0.044
	Patients hypoxia	4.88 (4.55–5.15)	0.333	5.35 (4.78–5.80)	0.035	5.65 (5.25–6.87)	0.036
	Patients sham	5.10 (4.60–5.70)		4.88 (4.54–5.06)		5.00 (4.50–5.85)	

Median concentration (range) at baseline, 180 min and 240 min. P-values are for comparison of baseline values and changes from baseline in patients during hypoxia and after hypoxia compared to sham (Wilcoxon signed rank test) and between patients and controls at baseline, during hypoxia and after hypoxia (Mann-Whitney test). The bold P-values indicate statistical significance. Due to migraine, discomfort, insufficient data quality, n for each spectroscopy measurement was reduced to the following: patients, at 180 min, glutamate, total creatine and NAA: n = 11, lactate: n = 9; patients, at 240 min, all metabolites: n = 12; controls, at 180 min and 240 min, glutamate, total creatine and NAA: n = 13, lactate: n = 11. At 240 min three patients were scanned after medication (Patient 4: 15 min after 20 mg primperan sup; Patient 6: 122 min after 6 mg sumatriptan subcutaneously; Patient 8: 90 min after 20 mg Primperan suppository).

Due to migraine, discomfort, problems with intravenous access and blood gas analyser machine errors, n for each blood samples was reduced to the following: patients, at 180 min and 240 min, lactate and haemoglobin: n = 9, glucose: n = 8, potassium: n = 10. There were no missing values for blood samples from the controls (n = 14). mM = mmol/l.

Hypoxia did not change glutamate levels in the visual cortex, but increased lactate levels and dilated cranial arteries. Furthermore, we found no difference in the metabolic or vascular responses to hypoxia between patients and controls. The migraine-inducing effects of hypoxia may explain similarities between headache characteristics in acute mountain sickness and migraine headache (ICHD-3 beta, 2013) and some efficacy of sumatriptan in acute mountain sickness (Bärtsch *et al.*, 1994; Jafarian *et al.*, 2007). Furthermore, migraine is an independent risk factor for high altitude headache (Mairer *et al.*, 2009; Burtscher *et al.*, 2011).

Previous attempts to trigger aura with self-reported triggers (Hougaard *et al.*, 2013) and known pharmacological migraine triggers have failed (Christiansen *et al.*, 1999; Afridi *et al.*, 2004; Hansen *et al.*, 2010). Few patients reported aura after exposure to light and exercise (11%) (Hougaard *et al.*, 2013), glyceryl trinitrate (0–10%) (Christiansen *et al.*, 1999; Afridi *et al.*, 2004) and calcitonin gene-related peptide (28%) (Hansen *et al.*, 2010). Hypoxia may be directly involved in induction of cortical spreading depression as shown *in vivo* (Takano *et al.*,

2007) and *in vitro* (Mané and Müller, 2012). Furthermore, animal studies show that hypoxia lowers the threshold for cortical spreading depression (Takano *et al.*, 2007) and increases the duration of cortical spreading depression (Takano *et al.*, 2007; Sonn and Mayevsky, 2012). Schoonman *et al.* (2006) exposed a mixed group of migraine patients to 75–80% (SpO_2) hypoxia (obtained SpO_2 data not shown) for up to 5 h and provoked migraine without aura-like attacks in 6 of 14 (43%) patients ($P = 0.197$). The study included seven patients with migraine with aura and hypoxia-provoked migraine without aura-like attacks in three of these seven patients (43%) compared to two after sham (29%). In the present study, we included only patients with migraine with aura ($n = 15$), exposed them to severe hypoxia (mean SpO_2 72%; Fig. 4) and investigated them with ^1H -MRS and MRA. We found that hypoxia provoked migraine ($P = 0.039$), three patients developed migraine aura during hypoxia and a further four of the patients experienced uncharacteristic visual disturbances (Table 2). These uncharacteristic visual disturbances technically fulfilled the International Classification of Headache Disorders 3 beta version criteria B–C for

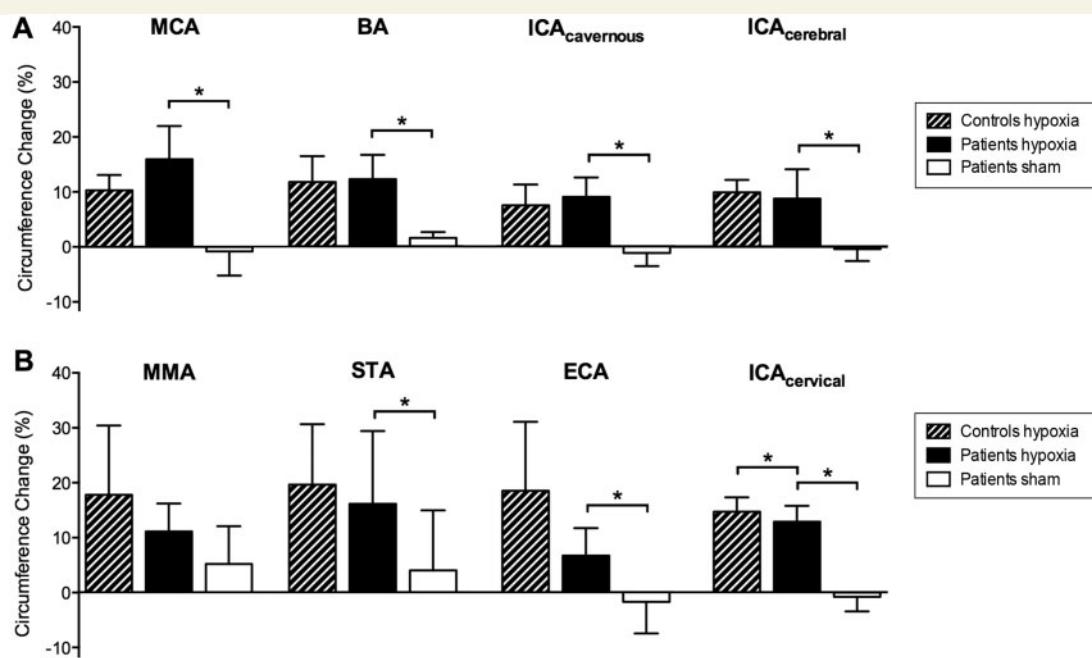


Figure 3 Circumference change of intra- and extra-cranial arteries. Per cent changes (95% CI) from baseline in mean circumference of intracranial (**A**) and extracranial (**B**) arteries after 120 min inhalation. (**A**) There was a significant increase of circumference of all intracranial arteries in patients [middle cerebral artery (MCA), $n = 14$, $P = 0.011$; cerebral internal carotid artery (ICA_{cerebral}), $n = 14$, $P = 0.001$; cavernous internal carotid artery (ICA_{cavernous}), $n = 15$, $P = 0.002$; basilaris (BA), $n = 15$, $P = 0.001$] and in controls (middle cerebral artery, $n = 14$, $P = 0.001$; cerebral internal carotid artery, $n = 14$, $P = 0.001$; cavernous internal carotid artery, $n = 14$, $P = 0.002$; basilaris, $n = 14$, $P = 0.001$). There were no differences between patients and controls in the circumference change during hypoxia (middle cerebral artery, $P = 0.183$; cerebral internal carotid artery, $P = 0.550$; cavernous internal carotid artery, $P = 0.513$, basilaris, $P = 0.743$). (**B**) In patients, the circumference change during hypoxia was larger for all extracranial arteries [external carotid artery (ECA), $n = 14$, $P = 0.016$; cervical internal carotid artery, $n = 10$, $P = 0.002$; superficial temporal artery (STA), $n = 10$, $P = 0.041$] except of the middle meningeal artery (MMA, $n = 12$, $P = 0.060$). In controls, the circumference of all extracranial arteries increased from baseline during hypoxia (external carotid artery, $n = 12$, $P = 0.002$; cervical internal carotid artery, $n = 14$, $P = 0.001$; middle meningeal artery, $n = 14$, $P = 0.002$; superficial temporal artery, $n = 14$, $P = 0.004$). The circumference change of the cervical internal carotid artery during hypoxia in controls [2.38 mm (SD 0.77 mm)] was larger compared to patients [1.81 (SD 0.44 mm), $P = 0.019$]. There was no difference between patients and controls in the circumference change of the other extracranial arteries (external carotid artery, $P = 0.190$; middle meningeal artery, $P = 0.181$; superficial temporal artery, $P = 0.520$). The following data were excluded due to bilaterally distorted contour of the artery segment: patients, middle cerebral artery (Patient 11), cerebral internal carotid artery (Patient 12), external carotid artery (Patient 14), cervical internal carotid artery (Patients 10 and 15), superficial temporal artery (Patients 3 and 10); controls: external carotid artery (Patient 4). Furthermore external carotid artery was excluded in one patient (Patient 7) and one control (Patient 3) because the measured segments were too short bilaterally, and in another control (Patient 5) because of movement artefact. Two patients (Patients 6 and 12) did not complete the middle meningeal artery scan because of migraine. The middle meningeal artery scan of one patient (Patient 7) was excluded because it did not include the relevant artery segments. Error bars represent 95% CI. * P -values < 0.05 for comparison of absolute changes during hypoxia compared to sham in patients and between patients and controls during hypoxia.

migraine with typical aura (ICHD-3 beta, 2013) and were accompanied by migraine-like headache in three of the four patients (Table 1). Interestingly, a case study reported spreading cerebral hypoperfusion during such atypical aura-like symptoms followed by migraine-like headache (Woods *et al.*, 1994). However, we chose to categorize them as ‘possible’ aura, because they lacked the characteristic gradual spread, unilaterality, positive symptoms and did not mimic patients’ usual attacks. Yet, we cannot exclude that these disturbances were atypical auras triggered by hypoxia. Hypoxia may thus induce cortical spreading depression in migraine with aura patients but this likely depends on an individual threshold. The severity of hypoxia seems to be important for the probability to trigger

migraine headache and aura. This is supported by our positive findings conducted at lower oxygen level compared to Schoonman’s study in which none of the patients reported aura or any visual disturbances and the incidence of migraine was not significant (Schoonman *et al.*, 2006). Animal studies showed that the threshold to elicit cortical spreading depression was correlated with the degree of hypoxia (Takano *et al.*, 2007). In addition, the prevalence of acute mountain sickness increases significantly with increasing height (Mairer *et al.*, 2009). Furthermore, increased prevalence of migraine was reported in a high-altitude population at 4300 m (Arregui *et al.*, 1991, 1994) but not in a population at 3380 m (Jaillard *et al.*, 1997). The haemodynamic effects of hypoxia also increase with

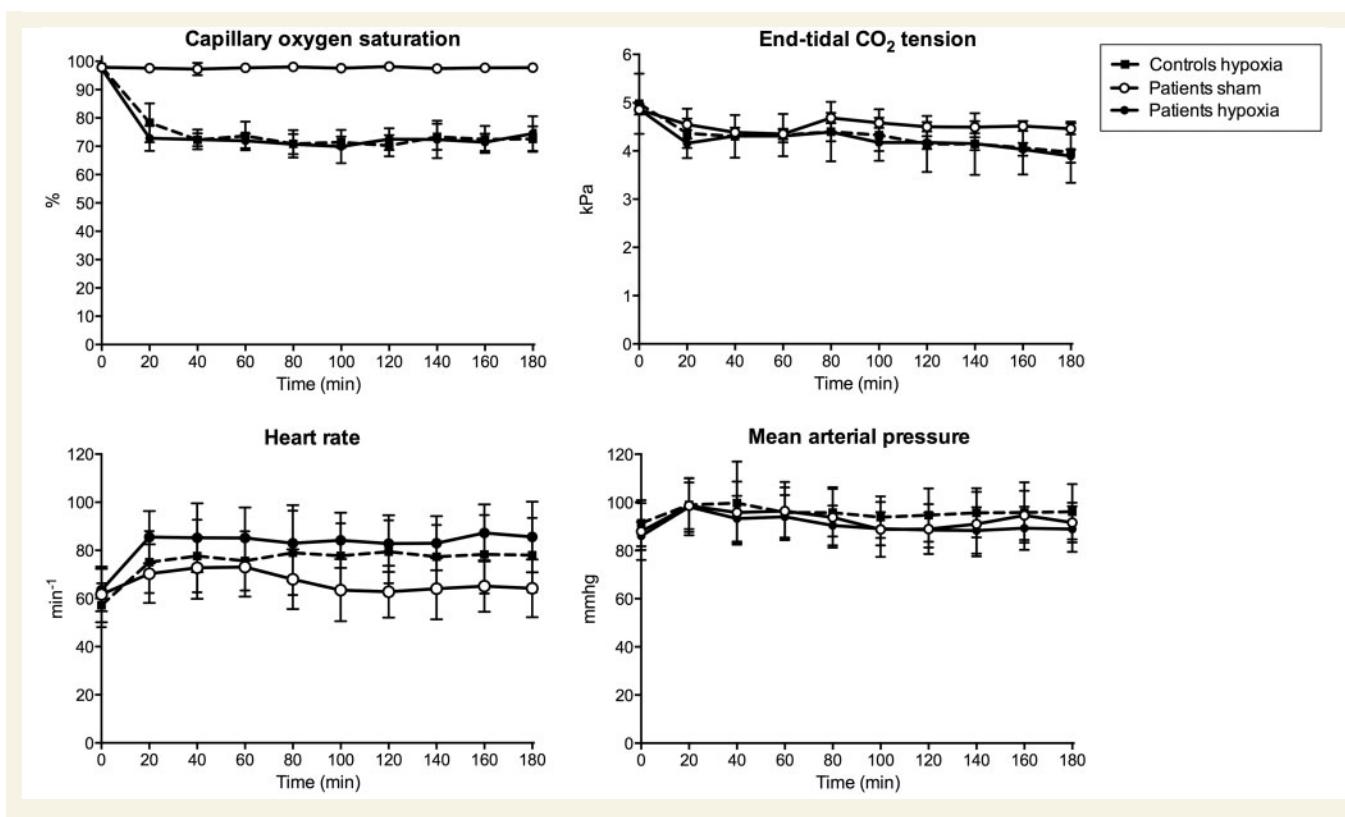


Figure 4 Vital variables during hypoxia and sham procedure. In patients, during hypoxia compared to sham, heart rate was higher ($AUC_{0-180\text{ min}} P = 0.002$) and SpO_2 ($AUC_{0-180\text{ min}} P = 0.002$) and end-tidal CO_2 tension ($AUC_{0-180\text{ min}} P = 0.004$) were lower and there was no difference of $AUC_{0-180\text{ min}}$ of mean arterial pressure ($P = 0.722$). There was no difference between the patients and controls in $AUC_{0-180\text{ min}}$ during hypoxia of heart rate ($P = 0.572$), SpO_2 ($P = 0.700$), mean arterial pressure (0.537) or end-tidal CO_2 tension ($P = 0.837$).

increasing severity of hypoxia (Wilson *et al.*, 2011). In support, Wilson *et al.* (2011) found dilatation of middle cerebral artery at SpO_2 75% but no changes at SpO_2 80%. Thus, even more severe hypoxia and maybe longer duration of the challenge might have caused more migraine auras in the present study but the present level of hypoxia and duration was judged to be what we could ethically accept. Two healthy volunteers also experienced uncharacteristic visual disturbances during hypoxia (Table 2). The question is whether these visual disturbances may be defined as auras. A case report described two attacks of ‘possible aura’ in a healthy male at 5000 m (Jenzer and Bärtsch, 1993). Our controls had no history of migraine or first-degree relatives with migraine and the visual disturbances were described as difficulty focusing/small black spots without accompanying migraine-like headache. Therefore, we consider it unlikely that these symptoms are related to aura.

Possible migraine-inducing mechanisms of hypoxia

Migraine attacks are associated with a relatively small dilatation of the intracranial arteries (Amin *et al.*, 2013). In the present study, we showed that all major intra- and

extracranial arteries dilated after 2 h of normobaric hypoxia. Nitric oxide is an important molecule in migraine pathophysiology (Olesen, 2008) and may play a role in hypoxia-induced migraine attacks and arterial dilatation. In support, Van Mil *et al.* (2002) showed that the ‘hypoxia-induced’ cerebral blood flow increase can be reversed by a nitric oxide synthase inhibitor. This study included eight healthy volunteers that were exposed to a 79% (SpO_2) hypoxia challenge causing a 21% increase in cerebral blood flow. The cerebral blood flow increase was abruptly reversed to baseline level by intravenous administration of the non-specific nitric oxide synthase inhibitor N^G -monomethyl-L-arginine (Van Mil *et al.*, 2002). Similar to hypoxia, the nitric oxide donor glyceryl-trinitrate induces migraine and dilates intra- and extracranial arteries in humans (Tvedskov *et al.*, 2004; Hansen *et al.*, 2007). The migraine-inducing mechanism of nitric oxide involves cyclic guanosine monophosphate (cGMP) signalling, which thus may also be involved in hypoxia-induced migraine, possibly through perivascular sensitization (Olesen, 2008). Adenosine, which is increased in the brain during hypoxia (Winn *et al.*, 1981; Phllis *et al.*, 1987), has also been suggested as a possible mechanism of hypoxic vasodilatation (O'Regan, 2005). In healthy volunteers adenosine induced mild headache and dilatation of superficial temporal artery

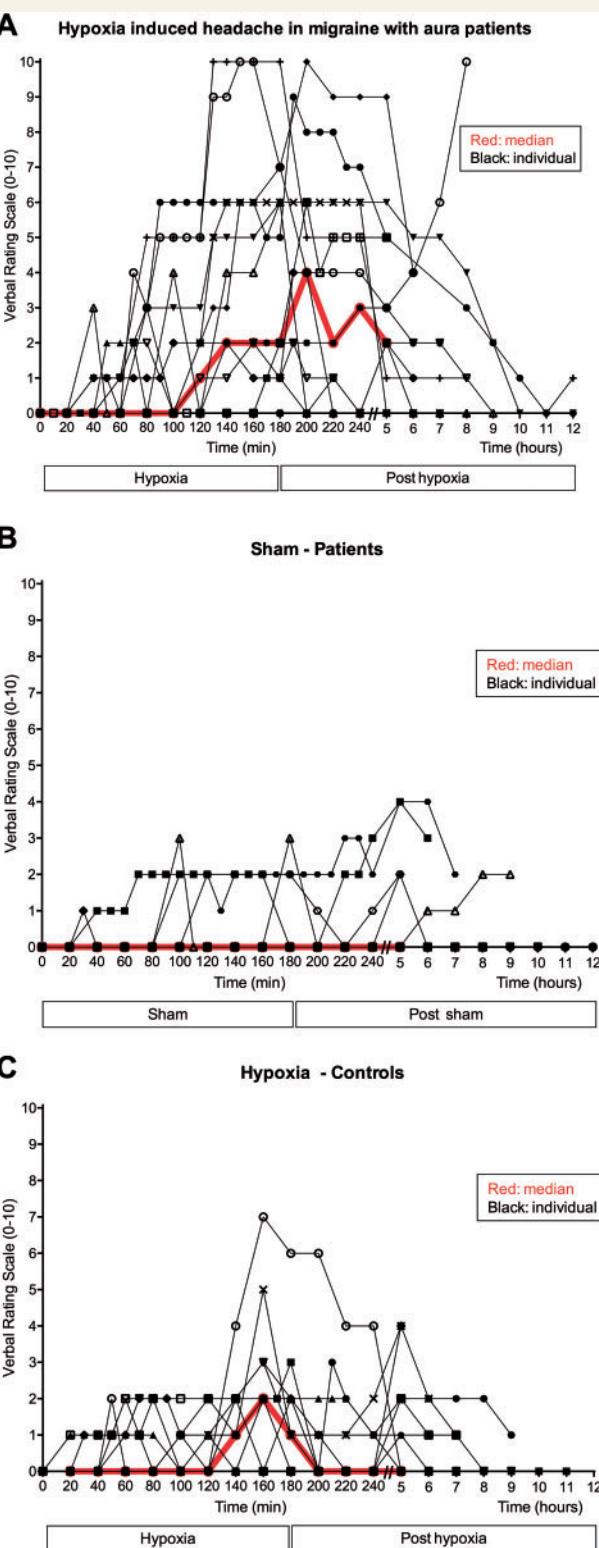


Figure 5 Headache score. Individual and median (red line) headache score after hypoxia (**A**) and sham (**B**) in patients with migraine with aura and after hypoxia in controls (**C**). The median curve is only showed from 0–5 h because most participants went to sleep early after the study and we therefore only have headache scores for all participants from 0–5 h.

(Birk *et al.*, 2005). The possible migraine-inducing effects of adenosine have not been investigated. An arterial supersensitivity to nitric oxide in migraine patients has been described using indirect methods with transcranial Doppler (Thomsen *et al.*, 1993). We therefore found it interesting to investigate if vascular responses to hypoxia in patients differ from controls. Using the direct MRA method we found no difference in changes of the arterial circumference between patients and controls. These findings question the role of arterial dilatation *per se* in provoking migraine attacks. However, we cannot exclude that migraine patients are hypersensitive to vasodilatation, as all known migraine-inducing substances are vasodilators (Schytz *et al.*, 2010).

Glutamate is an important neurotransmitter in migraine pathophysiology (Ramadan, 2014). Topical application of glutamate can trigger cortical spreading depression in animal models (Fikova and Van Harreveld, 1974) and glutamate receptor antagonists can inhibit induction of cortical spreading depression (Lauritzen and Hansen, 1992). Earlier studies have shown conflicting results of cerebral glutamate levels in migraine patients interictally. Gonzalez de la Aleja *et al.* (2013) showed increased glutamate/total creatine ratio in the anterior paracingulate cortex in patients with migraine with aura and increased glutamate in the anterior paracingulate cortex in a mixed group of migraine patients with or without aura. Furthermore, two studies included glutamine measurements and showed interictally increased glutamate + glutamine/total creatine ratio in migraine with aura patients (Siniatchkin *et al.*, 2012) and increased glutamate/glutamine ratio in the visual cortex in a mixed group of migraine with aura and migraine without aura patients (González de la Aleja *et al.*, 2013). In contrast, two studies found no difference in glutamate levels in the visual cortex between patients with migraine with aura and controls (González de la Aleja *et al.*, 2013; Bridge *et al.*, 2015). Similar to these two studies, we found no difference in baseline glutamate in the visual cortex between patients with migraine with aura and controls. To our knowledge, cerebral glutamate levels during hypoxia have not previously been investigated in humans. A microdialysis study showed a >400% increase in glutamate levels in the somatosensory cortex of rats after 30 min exposure to hypoxia (mean inspiratory oxygen content: 6%) (Zoremba *et al.*, 2007). In contrast, a 7T ¹H-MRS rat study showed no glutamate changes in the hippocampus after 48 h of severe hypobaric hypoxia (6700 m). We showed that 3 h of hypoxia induced no changes in glutamate in the visual cortex in patients with migraine with aura or controls. In a hypothesis-generating analysis we further investigated baseline glutamate concentration in patients who later reported migraine-like attacks with and without aura and found no difference (Fig. 2).

Two interictal 1.5 T MRI studies have reported increased cerebral lactate in patients with migraine with aura (Watanabe *et al.*, 1996; Sándor *et al.*, 2005). Sándor *et al.* (2005) found a 31% larger lactate/NAA ratio in the

visual cortex in a small group of patients with migraine with aura ($n = 5$) compared to healthy volunteers ($n = 11$). Similar results were reported by Watanabe *et al.* (1996) in six patients (three had migraine with aura, one basilar migraine, one migraineous infarction, one prolonged aura/migraineous infarction). However, these studies included very small clinical heterogeneous patient groups and lactate is difficult to measure in the brain and high field strength (≥ 3 T) is necessary to obtain a reliable quantification. Two studies investigated patients with migraine without aura by 3 T MRI and found no differences between patients and controls (Reyngoudt *et al.*, 2010, 2011). In the present study, we found no difference in baseline lactate between patients with migraine with aura and controls using 3 T ^1H -MRS. To ensure that our group size was sufficient, we *post hoc* calculated required group size based on earlier standard deviations of lactate concentration at 3 T ^1H -MRS (Edden *et al.*, 2010; Harris *et al.*, 2013). The power calculation showed that 14 subjects in each group would be needed to detect a difference in lactate concentration of 25% at 5% significance level with 90% power. Thus our group size would have been sufficient to detect the difference found in the earlier 1.5 T studies (Watanabe *et al.*, 1996; Sándor *et al.*, 2005). Only two 3 T ^1H -MRS studies have investigated lactate levels during hypoxia in healthy volunteers (Edden *et al.*, 2010; Harris *et al.*, 2013). These studies showed that lactate levels increased 20–39% in the visual cortex during mild ($\text{SpO}_2 = 84\%$) shortlasting (20–30 min) hypoxia in two small groups ($n = 3–6$) (Edden *et al.*, 2010; Harris *et al.*, 2013). Cerebral lactate or total creatine changes in patients with migraine with aura during hypoxia has not previously been investigated. We showed that 3 h of hypoxia induced lactate increase in the visual cortex by 56–61% in patients and controls. Thus, the increase in cerebral lactate seems to be sustained during longer lasting and more severe hypoxia. We also showed that venous lactate concentration increased by 44% in controls and 59% in patients with migraine with aura. Thus, the increase in cerebral lactate may partly be explained by increased transfer of lactate from the blood into the brain during hypoxia. However, it may also originate from increased cerebral lactate production or decreased cerebral consumption (Edden *et al.*, 2010; Overgaard *et al.*, 2012; Harris *et al.*, 2013). In patients, the plasma lactate was increased in the post-hypoxic phase (240 min) compared to sham and controls. The question is whether this reflects mitochondrial dysfunction. Montagna *et al.* (1988) reported increased plasma lactate levels during exercise in four patients with migraine with prolonged aura and Okada *et al.* (1998) found increased interictal plasma lactate levels in a mixed group of 14 migraine patients (three with migraine with aura). The mitochondrial hypothesis for migraine is supported by numerous ^{31}P -MRS studies showing a decreased phosphocreatinine and adenosine triphosphate in the visual cortex of patients with migraine with aura (Welch *et al.*, 1989; Barbiroli *et al.*, 1990, 1992; Montagna, 1995; Boska *et al.*, 2002). ^{31}P -MRS found no

metabolic changes during hypoxia in healthy volunteers (Garde *et al.*, 1995; Vidyasagar and Kauppinen, 2008). In the present study, we did not observe any difference in changes in plasma lactate levels during hypoxia between patients and controls. In addition, our ^1H -MRS data suggest no mitochondrial dysfunction in patients with migraine with aura. In future studies it would be interesting to compare metabolic changes during hypoxia in patients with migraine with aura and healthy controls using ^{31}P -MRS.

In line with earlier studies, we found no difference in baseline NAA or total creatine levels in the visual cortex between patients with migraine with aura and controls (Sándor *et al.*, 2005; Sarchielli *et al.*, 2005; Siniatchkin *et al.*, 2012) and no changes of NAA during hypoxia (Harris *et al.*, 2013).

Interestingly, plasma glucose was increased in the post-hypoxic phase (240 min) in patients compared to sham and controls. The increased plasma glucose in our patients may support earlier studies suggesting abnormal insulin sensitivity in migraine patients (Rainero *et al.*, 2005; Cavestro *et al.*, 2007). However, our study design was not optimal to investigate this aspect, as the participants were not fasting.

Strength and limitations of the study

Our study was performed at high MRI field strength (3 T) and included two relatively large groups: a well-defined group of patients suffering from migraine with visual aura in all attacks, taking no preventive medication, no other illness; and a well-matched control group.

A limitation of ^1H -MRS at 3 T in humans is the differentiation between glutamate and glutamine concentration. This means that the glutamate concentration measured in the present study would to some extent include glutamine. It should also be noted that we exclusively focused on visual cortex and did not investigate glutamate levels in other areas of the brain. In the present study, water signal was used as the internal standard for quantification. Hypoxaemia in the brain could potentially change the water content of the brain and confound the quantification of the metabolites during hypoxia. However, the NAA concentration was also measured with water signal as internal standard and did not change during hypoxia. NAA is a marker of neuronal density and should not be affected by a relatively short period of hypoxia. This indicates that the quantification is similar during normoxia and hypoxia.

MRA is a direct and validated (Amin *et al.*, 2014) method to examine arterial circumference and our results are consistent for the investigated intra- and extracranial arteries. The middle meningeal artery did not increase significantly during hypoxia compared to sham in patients, however a clear trend was observed ($P = 0.060$, Fig. 3B) and there was no difference between the groups ($P = 0.181$).

It would have been interesting to compare lactate and glutamate levels and arterial circumference during hypoxia between those who developed attack and those who did

not. Because of the group size and missing values, such subdivision was not possible. We presented individual ¹H-MRS data in Fig. 2A and MRA data in Supplementary Fig. 1 and found no trend in either direction.

Conclusion

In conclusion, hypoxia induced migraine-like attacks in 8 of 15 patients with migraine with aura, migraine aura attacks in three patients and possible aura attacks in an additional four patients. Thus, hypoxia may be used to provoke migraine-like attacks and aura attacks in a subgroup of patients, allowing us to investigate aura and headache mechanisms under controlled conditions. Similar to other migraine triggers, hypoxia induces arterial dilatation. We found no baseline difference in glutamate and lactate concentration in the visual cortex between patients with migraine with aura and healthy volunteers. Furthermore, both groups showed a similar hypoxia-induced increase in lactate and no change in glutamate. The mechanisms behind hypoxia-induced migraine need to be further investigated, especially the possible role of nitric oxide and metabolic changes that can be measured by ³¹P-MRS. Considering the increased prevalence of migraine in altitude populations, it would be interesting to investigate hypobaric hypoxia either in a decompression chamber or at high altitude to investigate the possible importance of hypobaric pressure. However, our data demonstrated that acute normobaric hypoxia alone is sufficient to induce migraine.

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Supplementary material

Supplementary material is available at *Brain* online.

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Original Article

Efficacy and Safety of Cinnarizine in the Prophylaxis of Migraine in Children: A Double-Blind Placebo-Controlled Randomized Trial



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ABSTRACT

BACKGROUND: In spite of the high occurrence of migraine headaches in school-age children, there are currently no approved and widely accepted pharmacologic agents for migraine prophylaxis in children. Our previous open-label study in children revealed the efficacy of cinnarizine, a calcium channel blocker, in migraine prophylaxis. A placebo-controlled trial was conducted to demonstrate the efficacy and safety of cinnarizine in the prophylaxis of migraine in children. **TRIAL DESIGN:** A double-blind, placebo-controlled, parallel-group study conducted in a tertiary medical center in Tehran, Iran. **METHODS:** Children (5–17 years) who experienced migraines with and without aura, as defined on the basis of 2004 International Headache Society criteria, were recruited into the study. Children were excluded if they had complicated migraine, epilepsy, or a history of use of migraine prophylactic agents. Each participant was randomly assigned to receive cinnarizine (a single 1.5 mg/kg/day dose in children weighing less than 30 kg and a single 50 mg dose in children weighing more than 30 kg, administered at bedtime) or placebo. The frequency, severity, and duration of headaches over the trial period were assessed and adverse effects were monitored. **RESULTS:** A total of 68 children (34 in each group) with migraine were enrolled and 62 participants completed the study. After 3 months of taking cinnarizine or placebo, children in both groups experienced significantly reduced frequency, severity, and duration of headaches compared with baseline measurements ($P < 0.001$). However, compared with 31.3% of children in the placebo group, 60% of children in the cinnarizine group reported more than 50% reduction in monthly headache frequency ($P = 0.023$), suggesting that cinnarizine was significantly more effective than placebo in reducing the frequency of headaches. No serious adverse effects of the medications were observed in the treated children, including no abnormal weight gain or extrapyramidal signs. **CONCLUSION:** Our results indicate that the use of cinnarizine at doses administered in this study is effective and safe for prophylaxis of migraine headaches in children.

Keywords: children, migraine, cinnarizine, placebo, clinical trial

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Introduction

Migraine headaches are among the most common neurological complaints in patients referred to child neurology clinics. Approximately 10% of children and 28% of adolescents experience these headaches. Epidemiologic

studies have revealed that the mean age of onset for migraine headaches is in the elementary school age range.¹ The complex cycle of migraine headaches accompanied by high absenteeism from the stressful environment of schools has a severe impact on the quality of life, possibly leading to the loss of the most productive hours in the daily lives of the affected children. Therefore, development of an effective and safe agent for the prophylaxis of migraine headaches in children is essential for improving the short-term condition and long-term educational and social outlook.^{1–4}

Lifestyle changes and biobehavioral recommendations are among the most frequently advised measures for migraine prophylaxis. However, these approaches are not effective in a large portion of the children suffering from migraine headaches. Therefore, medications are commonly used in children with migraines. In spite of the widespread use of pharmacologic agents, at this time there is no Food and Drug Administration (FDA)-approved treatment for the prophylaxis of headaches in children with migraine.^{1–10} A few prophylactic agents have been suggested by a number of low-quality studies. A recently published meta-analysis found only limited evidence to support the efficacy of topiramate (100 mg/day) in children with migraine.^{3,9} However, studies in adults and children have demonstrated serious adverse effects of topiramate on cognition.^{11–14} Therefore, an effective and safer agent is needed for use in children of school age. Moreover, almost all previous publications have called for better-designed studies that would provide the evidence supporting the efficacy and safety of agents currently considered for migraine prophylaxis in children.^{3,15}

Calcium channel blockers have been demonstrated to be effective in migraine prophylaxis.¹⁶ Cinnarizine is an L-type calcium channel blocker with a number of different proposed pharmacologic effects that may underlie the mechanism of action of its preventive effects on migraine.¹⁷ This agent is inexpensive and has been available since the 1970s in a number of European countries and for more than 15 years in Iran.¹⁶ The efficacy and safety of cinnarizine in the prophylaxis of migraine have been demonstrated in a number of studies.^{16–20} Our group has conducted two clinical trials in adults (one open-label and one double-blind controlled) and one open-label trial in children to demonstrate the efficacy of cinnarizine in the prophylaxis of migraine in both patient populations.^{17–19} However, these studies had major limitations and did not include a placebo-administered control group. Therefore, we performed a double-blind placebo-controlled trial to demonstrate the efficacy and safety of cinnarizine in a population of school-age children.

Material and Methods

Study design and location

We conducted a double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of cinnarizine as a prophylactic medication for headaches in school-age children with migraine. The study was conducted at the Children's Medical Center, a university-affiliated tertiary referral children's hospital in Tehran, Iran. The study was conducted between April 2012 and January 2014. The study design was approved by the ethical board committees of the medical center and Tehran University of Medical Sciences. Written informed consent was

obtained from all patients and their parents. The trial is registered with the Iranian Registry of Clinical Trials, number IRCT201107216907N2.

Patients

Children aged 5–17 years who had migraine with and without aura, according to the 2004 International Headache Society criteria for migraine,²¹ were enrolled into the study. All patients experienced four or more headaches per month for at least 6 months before entry into the study.

Inclusion and exclusion criteria

Patients were excluded from the study if they had complicated or status migraine that required medications other than analgesics, comorbid conditions such as seizures, a history of epilepsy, and if they were previously administered migraine prophylactic agents such as beta blockers, valproate, topiramate, or amitriptyline. Additionally, children with a history of serious adverse reactions to calcium channel blockers, such as cinnarizine, were excluded.

Study phases and randomization

The study was divided into two phases; a prerandomization phase, in which all patients meeting the inclusion criteria and their parents were familiarized with the study, followed by the random assignment of participants to receive either cinnarizine or placebo. The prerandomization phase lasted 4 weeks, whereas the treatment phase lasted 12 weeks. Participants were randomized to cinnarizine or placebo treatment group using a random number table to allocate consecutive patients into quaternary blocks.

Intervention and blinding

Participants in each arm of the study received either cinnarizine or placebo. In the cinnarizine group, the dose of the medication administered was based on body weight. For children weighing less than 30 kg, cinnarizine was administered at a dose of 1.5 mg/kg/day, whereas children who weighed more than 30 kg were administered 50 mg of cinnarizine. Both doses and the placebo formulation were administered as a single dose at 9 pm. All medication was dispensed by the trained staff of the central pharmacy of the medical center. All patients, their parents, interviewing staff, and the staff of the pharmacy of the medical center were unaware of the study arm assignment. Both cinnarizine and placebo formulations were dispensed to the patients in identical envelopes with similar appearance. Cinnarizine and placebo pills were identical in shape, color, and taste. These identical packages and their contents were provided by the laboratory of the School of Pharmacy of the Tehran University of Medical Sciences. The study duration was 4 months, including 4 weeks for the prerandomization phase and 12 weeks for the randomized treatment phase.

Pain measurement scale

To evaluate the duration and intensity of the headaches in each patient in a uniform manner across assessments, we used the Wong-Baker Faces Pain Rating Scale.²² To ensure that the scale was administered correctly, all patients and their parents were instructed by trained interviewing staff during the prerandomization phase on how to correctly assess headache duration and intensity.

Outcome measures

All patients and their parents were asked to maintain a headache diary. They were asked to register all the features of experienced headaches (frequency, intensity, and duration), with the resulting data used as a primary outcome measure. The patients and their parents were asked to register these data daily during both the prerandomization and treatment phases. The interviewing staff collected the data at the end of

the prerandomization phase and at the end of each 4-week interval during the treatment phase.

Adverse effects

Patients and their parents were asked to record all adverse effects experienced during the administration of the medication, especially any sedation or changes in appetite. The patients were also monitored for weight gain and extrapyramidal signs.

Statistics and data analysis

Based on the previous studies, the sample size was calculated with the Type I error $\alpha = 0.05$ and Type II error $\beta = 0.2$.¹⁹ The critical difference in responses between the two groups was considered to be 15%. Assuming the efficacy of cinnarizine to be 68%, based on previously published findings,¹⁹ the necessary sample size was calculated to be at least 34 patients in each treatment group to detect a difference in efficacy and safety with the power of 80%. For each patient randomized to receive either medication or placebo, the median and the mean ($\pm SD$) frequency, intensity, and duration of migraine headaches at the end of each 4-week period were determined. Analysis of variance (ANOVA) was used to evaluate the differences in these parameters between each follow-up visit. For qualitative data, we used Fisher exact test or the Mann-Whitney *U* test, when appropriate. To determine the response rate in each patient, we used the cutoff point of 50% reduction in headache frequency at the end of the study, compared with the prerandomization phase. In all statistical evaluations, $P < 0.05$ was considered significant. To reduce the bias in data analysis, all data were analyzed by a biostatistician who was not aware of the study groups.

Results

A total of 68 children with migraine were enrolled in the study, and 62 participants completed the study. Six children were lost to follow-up (four patients from the cinnarizine group and two patients from the placebo group) because of premature discontinuation of medications or relocation to a city distant from the study center. The baseline characteristics of the children in both groups are summarized in Table 1. Participants in the treatment groups were not significantly different in terms of age, gender, or migraine characteristics.

Efficacy analysis

Analysis of the primary outcome measures demonstrated that both cinnarizine and placebo were effective in controlling headaches (reducing the frequency, severity, and

TABLE 1.
Baseline Characteristics of the Children in the Two Treatment Groups in the Pre-randomization Phase

Characteristics	Cinnarizine, N = 30	Placebo, N = 32
Boys, n (%)	16 (53.3)	11 (34.4)
Girls, n (%)	14 (46.7)	21 (65.5)
Age (yr), mean (SD) [range]	10.7 (2.4) [7-17]	8.9 (1.9) [5-13]
Migraine frequency, headaches/month, median (range)	8 (4-30)	8 (5-30)
Migraine severity, median (range)	8 (6-10)	8 (6-10)
Migraine duration, hr		
1-2 hr	8	13
>2 hr	19	14
>24 hr	3	5

duration), but cinnarizine was significantly more effective in overall headache control (more than 50% reduction in headache frequency) without any serious adverse effects.

Headache frequency

Both cinnarizine and placebo effectively reduced the frequency of headaches. In the cinnarizine group, the median frequency (number of headaches per month) was significantly decreased from eight in the prerandomization phase to five at the end of the first month of treatment, 4.5 at the end of the second month, and four at the end of the third month ($P < 0.001$, Kruskal-Wallis one-way ANOVA by ranks). In the placebo group, median headache frequency (headaches per month) was significantly decreased from 12 in the prerandomization phase to eight at the end of the first month of treatment, 6.5 at the end of the second month, and six at the end of the third month ($P < 0.001$, Kruskal-Wallis one-way ANOVA by ranks). At the end of the third month of treatment, four children in the cinnarizine group were headache-free, but none in the placebo. Compared with 31.3% of children (10 of 32) in the placebo group, 60% of children (18 of 30) in the cinnarizine group reported more than 50% reduction in monthly headache frequency ($P = 0.023$, Pearson chi-square test), suggesting that cinnarizine was significantly more effective than placebo in reducing the frequency of headaches (Table 2).

Headache severity

Both cinnarizine and placebo were effective in reducing the severity of headaches. In the cinnarizine group, median headache severity (severity of headaches during each episode using Pain Scale Rating) was significantly decreased from eight in the prerandomization phase to six at the end of the first month of treatment, to six at the end of the second month, and to four at the end of the third month ($P < 0.001$, Kruskal-Wallis one-way ANOVA by ranks). In the placebo group, median headache severity (severity of headaches during each episode using Pain Scale Rating) was also significantly reduced, from eight in the prerandomization phase to six at the end of the first month of treatment, to six at the end of the second month, and to six at the end of the third month ($P < 0.001$, Kruskal-Wallis one-way ANOVA on ranks). However, the median severity of headaches at the end of the study was significantly lower in the cinnarizine group compared with the placebo group ($P < 0.001$, Mann-Whitney rank sum test; Table 2.)

Headache duration

Cinnarizine was significantly more effective than placebo in reducing the duration of headaches. During the prerandomization phase, 22 of 30 children in the cinnarizine group experienced headaches that lasted more than 2 hours, but at the end of the study, only four of 30 cinnarizine-treated participants had headaches that lasted more than 2 hours, and none experienced headaches that lasted more than 24 hours. In the placebo group, 27 of 32 children had headaches that lasted more than 2 hours during the prerandomization phase. At the end of the study,

TABLE 2.

Reduction in Monthly Migraine Frequency and Severity from Prerandomization Phase to the End of the Randomization Phase

Frequency and severity of headaches during trial phases	Cinnarizine, N = 30	Placebo, N = 32
At prerandomization phase		
Frequency, number per month		
Median (range)	8 (4-30)	8 (5-30)
Mean (SD)	10.4 (6.9)	12.4 (6.6)
P (versus placebo)	0.235	
Severity		
Median (range)	8 (6-10)	8 (6-10)
Mean (SD)	7.8 (1.3)	8.4 (1.4)
P (versus placebo)	0.1	
At the end of the first month of randomization		
Frequency, number per month		
Median (range)	8 (0-15)	12 (2-20)
Mean (SD)	5.4 (3.1)	7.8 (4.4)
P (versus placebo)	0.079	
P (versus prerandomization phase)	<0.001	
Severity		
Median (range)	6 (0-8)	6 (4-10)
Mean (SD)	6 (1.6)	6.4 (1.6)
P (versus placebo)	0.396	
P (versus prerandomization phase)	<0.001	
At the end of the second month of randomization		
Frequency, number per month		
Median (range)	4.5 (0-12)	6.5 (2-16)
Mean (SD)	4.4 (3.1)	7.4 (4)
P (versus placebo)	0.005	
P (versus prerandomization phase)	<0.001	
Severity		
Median (range)	6 (0-8)	6 (4-10)
Mean (SD)	4.8 (2.1)	6.5 (1.6)
P (versus placebo)	0.003	
P (versus prerandomization phase)	<0.001	
At the end of the third month of randomization		
Frequency, number per month		
Median (range)	4 (0-12)	6 (1-20)
Mean (SD)	4 (3)	7.4 (4.9)
P (versus placebo)	0.004	
P (versus prerandomization phase)	<0.001	
Severity		
Median (range)	4 (0-8)	6 (2-10)
Mean (SD)	4.2 (2.4)	6.3 (1.9)
P (versus placebo)	<0.001	
P (versus prerandomization phase)	<0.001	

11 of 32 placebo-treated participants reported experiencing headaches that last more than 2 hours and one of 32 had headaches that last more than 24 hours ($P = 0.042$, Fisher exact test).

Adverse effects

Monitoring of the adverse effects during treatment indicated that cinnarizine was safe. In both cinnarizine- and placebo-treated groups, none of the children developed any serious adverse effects. Three children in the cinnarizine group and one in the placebo group reported mild drowsiness in the early days of treatment. One of the children in the cinnarizine group experienced a weight gain of 2.5 kg at the end of the study necessitating a reduction in dose, and none of the children in the cinnarizine group developed any extrapyramidal signs.

Discussion

In the present study, we have demonstrated that cinnarizine administered over a 3-month period at a dose of 1.5 mg/kg/day in children weighing less than 30 kg and 50 mg/day in children weighing more than 30 kg reduces the frequency and intensity of headaches in children with migraine. Moreover, cinnarizine at these doses elicited no serious adverse effects, causing no significant weight gain or extrapyramidal signs in treated children.

Improved frequency of headaches after cinnarizine administration in children with migraine is demonstrated by the observed significant decrease in median headache frequency. Although a significant reduction in median headache frequency was also observed in the placebo group, a lower number of participants in this group reported greater than 50% reduction in headache frequencies. These results suggest that cinnarizine is significantly more effective than placebo in reducing the frequency of headaches.

Improvement of the intensity and duration of headaches following cinnarizine administration in children with migraine is evident from our observation that the median headache severity of headaches significantly decreased in cinnarizine-treated participants. However, no significant difference was present in the reduction of the headache severity between the cinnarizine- and placebo-treated groups over the trial period. Cinnarizine was significantly more effective than placebo in reducing the duration of headaches, with four children in the cinnarizine group reported to be completely headache-free at the end of the trial.

Calcium channel blockers have been demonstrated to be effective in migraine prophylaxis.¹⁶ Flunarizine is a calcium channel blocker that is sometimes utilized for migraine prophylaxis, but its mechanism of action in migraine is unclear in humans. Studies in rats revealed that flunarizine blocks voltage-gated Na(+) and Ca(2+) currents in cultured cortical neurons as a possible mechanism underlying the preventive effect of flunarizine on migraine episodes.^{23,24} Cinnarizine is an L-type calcium channel blocker and has a number of distinct pharmacologic and physiologic effects that may contribute to the mechanism of its preventive effects on migraine, including inhibition of vascular smooth muscle cell contraction, inhibition of vestibular hair cells stimulation, and anti-histaminergic actions.^{16,17} Rossi et al.¹⁶ were the first to demonstrate the efficacy of cinnarizine in the prophylaxis of migraine headaches by conducting an open-label pilot trial that demonstrated its efficacy and tolerability. In that study, of the 80 recruited patients, 55 indicated a greater than 66% reduction in frequency of headaches. The same study also revealed cinnarizine to be well tolerated, with low incidence and severity of adverse effects. Our group has extensive experience working with this pharmacologic agent, beginning with an open-label trial that revealed the efficacy of cinnarizine in a population of 60 adults with migraine.¹⁸ In a double-blind controlled study by our group, we compared the prophylactic effects of cinnarizine to those of valproate in a group of 125 adults with refractory migraine. Results of this study indicated that cinnarizine is an effective and safe prophylactic agent,

even in severe migraine headaches.¹⁷ Our group also conducted an open-label trial with cinnarizine and compared its efficacy to that of propranolol in a population of children with migraine. In that study, 120 children aged between 6 and 17 years were recruited and 113 of the participating patients completed the trial phases. This study¹⁹ demonstrated a significantly reduced frequency of headaches in both groups. In another study²⁰ conducted in adults, cinnarizine was compared with valproate, and the investigators concluded that these two agents could be appropriate first choices in migraine prophylaxis. Non of the earlier studies, however, were placebo-controlled.

A number of studies and case reports have reported extrapyramidal signs or depression in adult patients who were administered cinnarizine for treatment for vertigo or migraine.^{25–29} However, in our study, none of the participants experienced these adverse effects over the duration of the trial period. The lack of any serious adverse effects in treated children provides evidence that cinnarizine has a good safety profile. However, one cinnarizine-treated participant experienced significant weight gain, necessitating a reduction in dose. Additionally, 3 participants reported mild sedation and drowsiness that resolved without any serious effect on the patients. Importantly, none of the children in the cinnarizine group developed extrapyramidal signs or depression. These observations suggest that cinnarizine is a safe agent for the prophylaxis of migraine headaches in children.

A number of limitations should be considered in interpreting the results of this trial. First, the effect of cinnarizine treatment on the quality of life was not evaluated. A number of studies have previously evaluated the effects of migraine prophylactic agents on the quality of life by measuring school absenteeism and assessing the patients' functioning using the Pediatric Migraine Disability Assessment Scale, with the results suggesting that prophylactic agents improve the quality of life in children.¹⁵ Additionally, although we did not evaluate cognitive function in the participants of the current trial, a recent study indicated that compared with the control group, children with migraine exhibited impairments in some cognitive functions, such as attention, memory, information speed, and perceptual organization.³⁰

In conclusion, our results indicate that cinnarizine administered at bedtime as a single dose of 1.5 mg/kg/day or 50 mg/day in children weighing less than or more than 30 kg, respectively, is effective and safe in the prophylaxis of migraine headaches in children. Because there is currently no FDA-approved agents for the prophylaxis of migraine headaches in children, our results suggest that cinnarizine is a promising compound and should be one of the first choices for further consideration.

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Research Submission

Photophobia and Seasonal Variation of Migraine in a Subarctic Population

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Objective.—To investigate associations between photophobia and seasonal variation of migraine.

Methods.—In this cross-sectional study, migraineurs consecutively recruited were referred to a specialist center located above the Arctic Circle at 68–71 degrees North during a 2.5-year period. Data were obtained through a structured interview.

Results.—In total, 302 migraineurs with a mean (\pm SD) age of 35.5 (\pm 12.6) years were included. Patients who reported seasonal variation of migraine ($n = 90$; 29.8%) also reported more often interictal photophobia than the others (61/90, 67.8% vs 92/212, 43.4%, $P < .0001$). Patients reported sunlight or other bright light to trigger migraine attacks in 74.4% with seasonal migraine (SM) compared with 40.6% in patients with non-seasonal migraine (NSM) ($P < .0001$), but there were similar frequencies of attacks reported to be triggered by sleep, menstruation, and other precipitating factors. After adjusting for migraine with aura, migraine disability, chronic migraine, interictal photophobia, and insomnia, sunlight or other bright light, photophobia was still associated with SM (OR; 3.47, CI [95%]; 1.83–6.59, $P < .0001$).

Conclusions.—Migraineurs in a subarctic area reporting seasonal variation of attack frequency also report increased interictal photophobia independent of other clinical factors. Chronobiological mechanisms and/or increased activity in the visual system may be responsible for this phenomenon.

Key words: migraine, trigger factors, interictal, light, circadian rhythm, photophobia

Abbreviations: BMI body mass index, CAS cranial autonomic symptoms, CI confidence interval, CSD cortical spreading depression, DSM-III Diagnostic and Statistical Manual of Mental Disorders, third edition, HIT-6 headache impact test, ICHD-II International Classification of Headache Disorders, second edition, NSM non-seasonal migraine, OR odds ratio, SD standard deviation, SM seasonal migraine, VAS visual analog scale

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INTRODUCTION

Photophobia is painful or uncomfortable vision by exposure to well tolerated light.¹ Hypersensitivity to light or to other sensory signals is a common symptom in migraine, but the mechanisms behind are complex and not well understood.² A majority of migraineurs experience exacerbation of attacks when exposed to light,³ and photophobia is one of the key diagnostic criteria.⁴ Light intolerance

Conflict of Interest: None.

between migraine attacks has been attributed to increased activity of the visual cortex,⁵ and migraine trigeminal pain increased light-induced activation in the same brain area.⁶ Recently, Noseda et al found that photophobia declined after stimulation with green color as opposed to red and blue colors, demonstrating that retina and its occipital connections plays a role in the biology of migraine photophobia.⁷

Hypothalamic–thalamic projections are probably involved in the evolution of migraine attacks.^{8,9} Neural connections from retina, via hypothalamus, thalamus, and the brain stem to the trigeminal nucleus provide a biological substrate for ictal photophobia.¹⁰ Furthermore, experimental studies show that the posterior thalamus is an important site of action in photophobia.¹¹ Many migraineurs have reduced interictal tolerance to light compared with controls.¹² This may reflect occipital activity and probably also involves the raphe nuclei and the locus coeruleus in the brainstem.^{13,14}

In a survey of 1750 migraineurs, 76% reported that trigger factors precipitated attacks.¹⁵ Menstruation, sleep deprivation, light exposure, weather, stress, missed meals, odors, smoke, and alcohol were common triggers reported by the participants.¹⁵ The mechanisms of how migraine triggers are related to the attacks are incompletely understood, but premonitory symptoms are often attributed to hypothalamic dysfunction.¹⁶ Migraine attacks vary with seasons in our subarctic area located 68–71 degrees North. In this area, the sun is continuously absent (polar night) or present (polar day) in periods of the year. Thus, photophobia can be an important factor in explaining seasonal variation of migraine. A subgroup of migraineurs is especially prone to attacks in this bright arctic season.¹⁷ Assuming an underlying melatonin circadian dysfunction, we hypothesized that photophobia is associated with seasonal migraine (SM). We divided photophobia into susceptibility to light as a trigger factor, interictal and interictal photophobia.

METHODS

Study Population and Location.—The study population in this survey ($n = 302$) is part of a

randomized clinical trial where specialist headache consultations via telemedicine ($n = 150$) were evaluated and compared with traditional consultations ($n = 152$).¹⁸ Sample size in the parent trial was calculated on the assumption of a normal distributed primary binary variable with patient satisfaction with consultation as primary endpoint. By selecting an inferiority limit of 15% and alpha of 0.01 in a 98% confidence interval, 127 participants in each group were required to reach a power of 95%. To maintain sufficient power for a 1-year follow-up analysis, we enrolled 402 headache patients.¹⁸ Migraineurs, all Caucasians, were recruited from referrals in the electronic application system of the Department of Neurology in Tromsø University Hospital located at 69.4 degrees North. Volunteers who fulfilled the inclusion criteria were continuously enrolled over two seasonal cycles (from 30 September 2012 to 30 March 2015). Altogether, 557 headache patients were referred for second opinion and screened for study participation in this period.

In this geographical area, daylight declines rapidly during autumn until the second half of November when the sun disappears and remains below the horizon line until the end of January. After a 2-month period with limited daylight (polar night), the sun gradually returns and culminates in a 2-month “midnight-sun” – period lasting from second half of May when it is continuously present above the horizon line (polar day). The angle of the sun relative to the horizon line depends on the latitude where people stay, and the balance between darkness and brightness is, therefore, not homogeneous. The inclusion criteria were: (1) both sexes, aged 16–65 years, (2) migraine with aura (1.2), without aura (1.1), and chronic migraine (1.5.1) according to the International Classification of Headache Disorders, second edition (ICHD-II),⁴ and (3) subjects having good command of Norwegian. Patients with other primary headaches or suspected secondary headaches, and those with concomitant neurological diseases were excluded. Headache reported ≥ 15 days per month and use of painkillers or triptans ≥ 15 days per month was defined as possible medication-overuse headache (MOH) (ICHD-II R1, 8.2.6). The Regional Medical Ethics Committee approved

the study, and all participants signed a consent form before study entrance.

Data Collection.—The patients were interviewed by one of the authors (KIM, SIB). All data were recorded using a structured administrative form and then transferred to an electronic database. Consequently, there is no missing data. We recorded age, sex, marriage or common-law partner, education in years, employment, and sick leave due to migraine, concomitant diseases, alcohol, and current smoking. Before each interview, a nurse measured weight and height of patients, and body mass index (BMI) was calculated (kg/m^2). The presence of chronic neck and shoulder pain were assessed by the following question: “Did you have neck and/or shoulder pain continuously lasting at least 3 month during the last 12 month?” (“Yes,” “No”). Insomnia was screened for and classified by Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III).¹⁹ Age at the disease onset, disease duration, number of migraine attacks per month, and whether patients experienced photophobia and phonophobia during attacks were recorded. Use of painkillers (over-the-counter- and prescription analgesics) and triptans where categorized into “daily,” “three times per week or more,” “1-2 times per week,” “less than once per week,” “less than every second week.” Use of preventive drugs against migraine was specified.

We asked the patients: “Do you have seasonal variation of migraine?” (“Yes,” “No”), and if so, “do migraine attacks occur more frequently in the polar day season, in the transition to polar day season, in the polar night season, or in the transition to polar night season?” The seasonal data are categorized as shown in Table 3. Assessment of photophobia included questions about sunlight or other bright light as trigger factor, as well as ictal and interictal hypersensitivity to light. Questions to characterize light hypersensitivity were: “Do you experience light hypersensitivity between attacks” (“Yes,” “No”) and/or “during attacks”? (“Yes,” “No”). Trigger factors indicating circadian misalignment (“too little sleep,” “too much sleep,” “attack onset during night”), menstruation, and common exogenous triggers¹⁵ (“sunlight or other bright light,” “stress,” “weekends,” “physical activity,” “food and

beverage,” and “alcohol”) were recorded. All triggers were asked for in the following way: “Do stress/sunlight or other bright light/physical activity, etc., commonly trigger a migraine attack?” and “Do migraine attacks commonly occur during nights/weekends?” (“Yes,” “No”). We also recorded shift-work. Headache impact test (HIT-6)²⁰ and visual analogue scale (VAS)²¹ were used to assess impact of headache.

Statistical Analysis.—Data were analyzed with SPSS software version 23 (IBM Inc, Armonk, NY, USA). Descriptive data are presented as mean and standard deviation (SD) or numbers and frequencies. To compare frequencies (dichotomous data), χ^2 -tests were performed. Independent two-tailed *t*-test was used for comparison of means between the groups. By logistic regression, possible confounders known to be associated with seasonal migraine reported in the literature²² were tested and adjusted for with seasonal light hypersensitivity as dependent variable and age, sex, migraine with aura, interictal light hypersensitivity, HIT-6, and chronic headache as independent variables. Odds ratio (OR) with 95% confidence interval (CI) was calculated. Age and sex were tested for separately. Subgroup analysis in patients who reported more attacks in the polar day season as compared with the polar night season was performed to further investigate the relationship between photophobia and variation in seasons. The level of significance was set at 5%.

RESULTS

In this sample, 302 patients with migraine and a mean (\pm SD) age of 35.5 years (\pm 12.6) fulfilled the criteria, and were included in the study. Of them were 66 men (21.9%), and 236 women (78.1%). Mean age in men was 38.7 years (\pm 13.3) and 34.6 years (\pm 12.2) in women ($P = .018$). About 90 (29.8%) of 302 participants reported seasonal variation of migraine (SM) attacks and 212 (70.8%) did not (non-seasonal migraine; NSM). The gender distribution was similar in the two groups. More than half of the patients in both the SM and the NSM group had five migraine attacks or more per month (Table 2), and the mean overall HIT-6 score was 64.9 (\pm 5.2). There was no

Table 1.—Demographic and Clinical Data in Seasonal Migraine (SM) and Non-Seasonal Migraine (NSM)

Variables	SM (N = 90)	NSM (N = 212)	P value
Females, n (%)	66 (73.3)	170 (80.2)	.223
Age, years, mean (SD)	34.5 (13.5)	35.8 (12.1)	.413
Education, years (SD)	13.5 (2.9)	13.8 (3.0)	.390
Shift work, n (%)	14 (15.6)	41 (19.3)	.515
Work compensation, n (%)	42 (46.7)	93 (43.9)	.705
BMI, kg/m ² , mean (SD)	27.1 (5.3)	27.0 (5.2)	.899
Current smokers, n (%)	9 (10.0)	39 (18.4)	.083
Alcohol ≥ 3 times/week, n (%)	5 (5.6)	6 (2.8)	.310
Insomnia, n (%)	32 (35.6)	63 (29.7)	.344
Hypertension, n (%)	10 (11.1)	11 (5.2)	.082
Chronic neck/shoulder pain, n (%)	41 (45.6)	108 (50.9)	.451

difference in burden of migraine between the two groups (Table 2). Painkillers were used ≥15 days per month in 40.0% with SM and 45.8% in the others (Table 2). Similar proportions of participants in the SM and NSM groups had chronic headache and possible MOH (Table 2). Background variables

and migraine related variables where otherwise indifferent between the two groups (Tables 1 and 2).

Of the total group, 90 (29.8%) reported seasonal variation of migraine attacks, 153 (50.7%) sunlight or other bright light as a migraine trigger

Table 2.—Migraine Characteristics in Seasonal Migraine (SM) and Non-Seasonal Migraine (NSM)

Variables	SM (N = 90)	NSM (N = 212)	P value
Migraine in family*, n (%)	50 (55.6)	112 (52.8)	.724
Migraine with aura, n (%)	38 (42.2)	68 (32.1)	.113
Onset of migraine, age (SD)	19.7 (10.7)	22.6 (12.9)	.014
Duration of migraine, years (SD)	15.4 (12.3)	14.4 (12.3)	.535
Migraine days last month, n (%)			
0-7	23 (25.6)	46 (22.2)	.278
8-14	21 (23.3)	45 (21.2)	.432
≥15	46 (51.1)	120 (56.6)	.226
Attacks ≥5 per month, n (%)	56 (60.0)	135/212 (63.7)	.603
VAS score 0-10, mean (SD)	6.9 (2.2)	7.2 (2.0)	.311
HIT-6, mean (SD)	64.8 (4.7)	64.9 (5.9)	.819
Ictal photophobia, n (%)	79 (87.8)	168 (79.2)	.102
Interictal photophobia, n (%)	61 (67.8)	92 (43.4)	<.0001
Phonophobia, n (%)	67 (74.4)	142 (67.0)	.222
Prophylactic medication, n (%)	18 (20.0)	31 (14.6)	.306
Use of over-the-counter painkillers, n (%)	78 (86.7)	189 (89.2)	.558
Use of prescribed painkillers, n (%)	23 (25.6)	62 (29.2)	.577
Use of painkillers ≥15 days/month, n (%)	36 (40.0)	97 (45.8)	.214
Use of triptans, n (%)	59 (65.6)	91 (42.9)	<.0001
Use of triptans ≥15 days/month	17 (18.9)	29 (13.7)	.451
Possible MOH**	30 (33.3)	70 (33.0)	.480

BMI = body mass index; VAS = visual analog scale; HIT-6 = headache impact test-6; MOH = medication overuse headache; SD = standard deviation.

*Migraine in parents and/or children.

**Migraineurs reporting ≥15 headache days per month and/or use of triptans ≥15 days/month and use of painkillers ≥15 days/month.

Table 3.—Seasonal Variation of Migraine in a Subarctic Area Relative to SM and the Total Study Group [Numbers (%)]

Seasons	SM (n = 90)	Total (n = 302)
Polar day season	59 (65.6)	59 (19.5)
Polar day season	39 (43.3)	39 (12.9)
Transition to polar day season	20 (22.2)	20 (6.6)
Polar night season	31 (34.4)	31 (10.3)
Polar night season	28 (31.1)	28 (9.3)
Transition to polar night season	3 (3.3)	3 (1.0)
All seasons	90 (100)	90 (29.8)

SM = seasonal migraine.

factor and 153 (50.7%) reported interictal photophobia. Interictal photophobia was more often reported in SM than NSM (Table 2). Frequency of reported intraictal photophobia did not differ between the groups (Table 2). Among those with SM, increased migraine attack frequency in the polar day season was more common than in the polar night season, while 20/90 (22.2%) reported increased attack frequency in the transition to the light season (Table 3). Nocturnal and menstrual attacks, as well as weekend migraine, did not differ significantly (Table 4). Overall, stress (163/302; 54%) was the most common trigger factor for migraine attacks followed by sunlight or other

bright light (147/302; 48.7%) and sleep deprivation (82/302; 27.2%). Sunlight or other bright light was reported to be a more frequent migraine trigger in the SM group (Fig. 1). Also, interictal photophobia was more common in SM (Fig. 2). Of 59 with more frequent migraine attacks in the polar day season or in the transition period to the polar day season, 52 (88.1%) reported sunlight or other bright light as a common trigger factor compared with 15/31 (48.4%) in those with more attacks in the dark season (Fig. 3). These patients also reported more frequently interictal photophobia (Fig. 4). Those with more frequent migraine attacks in the polar day season or in the transition period to the polar day season ($n = 59$) had more frequently ictal photophobia than 31 migraineurs reporting increased attack frequency in the polar day season or in the transition period to the polar night season (56/59; 94.9% vs 23/31; 74.2%) ($P = .007$). Insomnia and sleep deprivation as trigger factors were not associated with SM.

Almost 50% of SM with more attacks in the polar night season reported sunlight or other bright light to trigger migraine attacks and interictal photophobia (Figs. 3 and 4). In a multivariate model, interictal photophobia, age, sex, migraine with aura, HIT-6, and chronic migraine were included in the list of independent variables (Table 5). After adjusting for these variables, sunlight or other

Table 4.—Factors Reported to Trigger Attacks in Seasonal Migraine (SM) and Non-Seasonal Migraine (NSM)

Precipitating factors	SM (N = 90)	NSM (N = 212)	P value
Any trigger factor, n (%)	83 (92.2)	164 (77.4)	.002
Sunlight or other bright light, n (%)	67 (74.4)	86 (40.6)	<.0001
Stress, n (%)	52 (57.8)	111 (52.4)	.449
Sleep deprivation, n (%)	21 (23.3)	61 (28.8)	.397
Excessive sleep, n (%)	12 (13.3)	18 (8.5)	.211
Sleep deprivation + excessive sleep, n (%)	11 (12.2)	16 (7.5)	.130
Attack start during night, n (%)	5 (5.6)	9 (4.2)	.765
Menstruation, n (%) women	14/66 (21.2)	36/170 (21.2)	.866
Food and beverage, n (%)	12 (13.3)	23 (10.8)	.558
Alcohol, n (%)	14 (15.6)	18 (8.4)	1.000
Physical activity, n (%)	4 (4.4)	12 (5.7)	.785
Weekend migraine, n (%)	17 (18.9)	29 (13.7)	.293

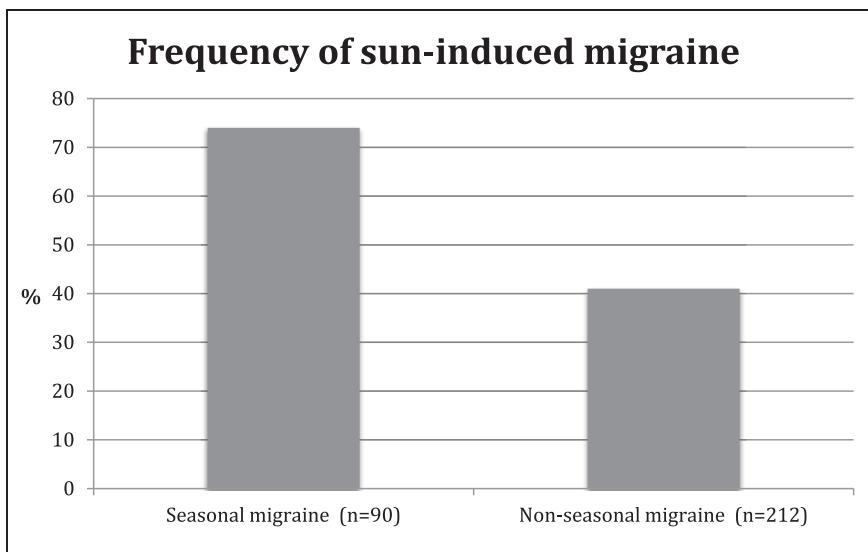


Fig. 1.—Frequency of sunlight or other bright light reported as a migraine trigger factor in seasonal migraine compared with non-seasonal migraine ($P < .0001$).

bright light as a trigger remained significantly associated with SM (OR; 3.47, CI (95%); 1.83-6.59, $P < .0001$) (Table 5).

DISCUSSION

The present study documents that almost 30% of migraineurs in a subarctic geographical area referred to specialist for second opinion reported seasonal variation of migraine attacks. Patients in the SM group reported more often sun or bright light to trigger migraine attacks, and more frequently interictal photophobia than the NSM group. The SM subgroup with more frequent attacks in the polar day season

reported more often ictal photophobia than those with more attacks reported in the polar night season. SM was not associated to sleep, menstrual-related migraine, functional disability insomnia, migraine aura, chronic migraine, or MOH. However, it is worth noticing that there were more patients with migraine with aura in the group of patients with SM than in NSM, though not significant (42% vs 32%).

In a previous study, 21% of migraine patients consulted by specialist in the same subarctic area reported seasonal variation of headache.²³ The present study confirms that a subset of migraineurs experiences seasonal periodicity of migraine. An

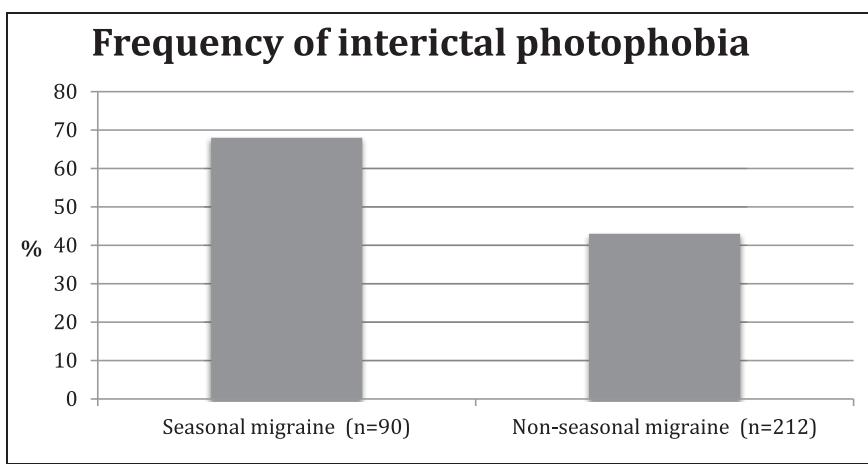


Fig. 2.—Frequency of reported interictal photophobia in seasonal migraine compared with non-seasonal migraine ($P < .0001$).

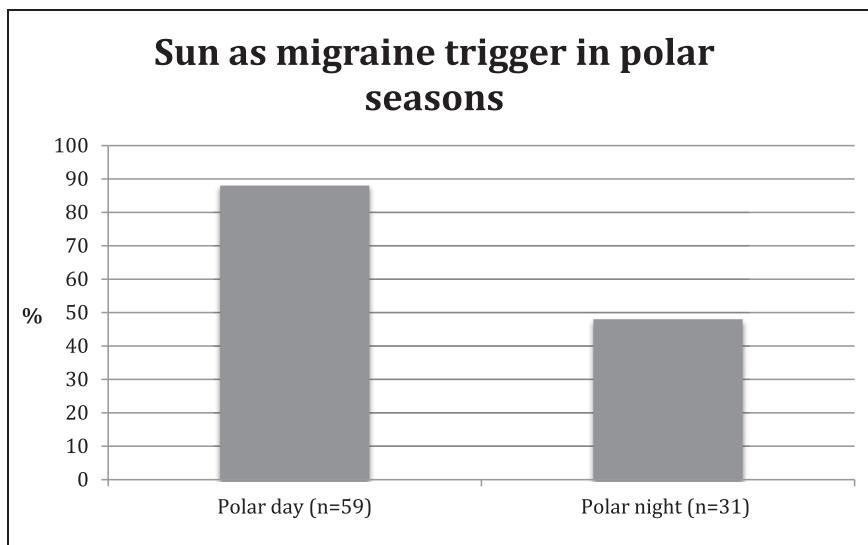


Fig. 3.—Frequency of reported sunlight or other bright light as a trigger factor in polar day season compared with polar night season ($P < .0001$).

important question is to what extent this phenomenon is due to external factors, involves the visual system and/or reflects melatonin circadian dysfunction.

Stress and sunlight/bright light were the two most frequently reported trigger factors in this population, in line with other studies.^{15,24} Intense light precipitated migraine attacks in 74.6% in a previous study above the arctic circle which is identical to the present study.¹⁷ Migraine attacks in the polar day season, prospectively recorded via diaries, were

associated with number of hours with sunshine registered at the nearby meteorological station in a 10% subset of the population, but other meteorological variables did not predict migraine attacks.²⁵ The threshold for light-induced discomfort is markedly reduced in migraineurs (about 500 lux) than controls (23,000 lux).¹² The trigger mechanisms is not well understood, but cortical activity such as cortical spreading depression (CSD) may hypothetically play a role.²⁶ One possible link may be the connection with aura since aura is associated with

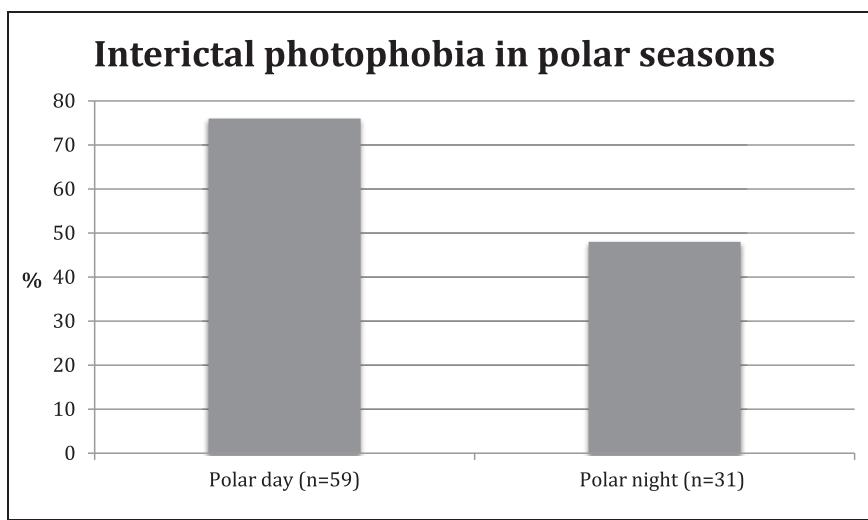


Fig. 4.—Frequency of reported interictal photophobia in polar day season compared with polar night season ($P < .0001$).

Table 5.—Adjusted Odds Ratio (OR) with 95% Confidence Interval (CI) for Sunshine or Bright Light as Migraine Trigger Associated with Seasonal Migraine

	OR (95% CI)	P value
Seasonal migraine	3.47 (1.83-6.59)	<.0001
Age	1.01 (.99-1.04)	.191
Sex	1.85 (.97-3.52)	.064
Insomnia	.81 (.46-1.43)	.456
Interictal light hypersensitivity	.64 (.34-1.20)	.161
Migraine with aura	.80 (.46-1.41)	.497
Chronic migraine	.84 (.50-1.46)	.540
HIT-6	1.01 (.96-1.07)	.721

HIT-6 = headache impact test-6.

CSD, although not demonstrated in this study.²⁷ In a Danish study of 179 migraineurs with aura, light precipitated >50% of the attacks in 48%. Another subgroup analysis showed an even more consistent trigger impact for sunlight.²⁴ Despite the small numbers, the study suggested that “bright light” is more valid as an external trigger factor than “light.” In contrast, Hougaard et al, showed that migraine attacks occurred in only a minority of patients being provoked with self-reported trigger factors.²⁸ We have previously reported an association between SM and migraine with aura, but the seasonal migraine periodicity disappeared when removing insomnia-related attacks, indicating a biological link between migraine with aura and insomnia which raises the question of hypothalamic involvement.²²

Neurophysiological studies in attack free periods demonstrated that EEG activity developed within 36 hours prior to migraine attacks. Increased trigger sensitivity and photophobia correlated with higher EEG theta power and depressed photic responses indicating interictal cortical activity.²⁹ On the other hand, Denuelle et al demonstrated in a PET study that light stimulated the cerebral cortex during attacks and not between attacks, illustrating the neural complexity of visual symptoms in migraine.¹⁰ Additionally, treatment with a serotonin agonist alleviated photophobia indicating brainstem involvement in photophobia.³⁰ Additionally, the light/dark and dark/light transitions were important

external factors influencing the 5-HT levels in dorsal raphe nucleus.³¹ In parallel, 22.2% in the SM group reported increased attack frequency in the transition to polar day season and 3.3% in the transition to polar night season in our study suggesting that periodically change in ambient light plays a role. Another finding that may be significant in understanding SM is that pain perception threshold declines in migraineurs following light stimulation.³² However, atmospheric light intensity has not been measured systematically in the polar light/night periods and no study has related ambient polar light to migraine. Neither is there any knowledge about why some migraineurs report light-associated migraine attacks in the polar night period.

Half of the patients in the present study had chronic migraine, 1/3 possible MOH, and mean HIT-6 score was almost 65, all documenting a high headache burden. Whether this is representative for this geographic area or is due to referral practice, lacks of headache specialists or suboptimal treatment are not known. Another question to address is whether headache burden and use of medication vary with seasons. The present survey is not optimally designed to give the answers, but patients in our clinical practice have reported less severe headache when using preventive treatment only in the polar day season.³³ Subsequently, 769 Korean migraineurs without aura reported SM in 104 (13.5%) of the participants.³⁴ These patients had more cranial autonomic symptoms, photophobia, phonophobia, neck pain, and intolerance to physical activity, weekend migraine, and functional disability than others.³⁴

The seasonal variation of interictal photophobia in addition to the pre-attack light sensitivity may be due to abnormal hypothalamic activity. Experimentally, GABA-ergic inhibition of posterior hypothalamus stimulated sympathetic outflow and thereby reduced light activity in ocular neurons.³⁵ A previous PET study showed increased hypothalamic blood flow during migraine attacks documenting a contribution of hypothalamus in the pathophysiology of migraine.³⁶ Furthermore, attenuation of the pupillary light reflex, as documented both in the wake of migraine attacks³⁷ and in the interictal

phase of cluster headache³⁸ has been suggested as a hypothalamic compensatory mechanism due to increased locus coeruleus-activity. In view of that, SM may represent a state with increased hypothalamic dysfunction as reflected in the Korean study where they found increased cranial autonomic symptoms (CAS) in patients who reported seasonal variation.³⁴ Unfortunately, the frequency of CAS in the present cross-sectional was not evaluated. More research to clarify the clinical phenotype of SM is needed. The true nature of photophobia in migraine has not been studied. Does it induce pain, exacerbate pain, or is it just simply an uncomfortable dazzle or other unpleasant visual experience?

Limitations to the study include difficulties in defining pre-ictal light as a migraine trigger from interictal photophobia and onset of migraine attack itself with presence of ictal photophobia because we used a non-validated questionnaire to define triggers. Consequently, we have no information about exposure time and latency to attack onset.²⁴ Comparisons of studies reporting trigger factors are difficult to perform due to variable study designs and definitions.³⁹ Additionally, the tendency to overestimate or underestimate impact of trigger factors in retrospective studies should be taken into account.⁴⁰ Furthermore, it is difficult to separate the effect of sunlight or other bright light exposure from the impact of seasonal variation in this retrospective designed study. By face-to-face interview, we avoided missing data and improved the internal validity, but could possibly not eliminate recall-bias. We acknowledge the explorative nature of this study, and the risks of statistical type I and type II-failures in a sample originally powered for another purpose. Especially subgroup-analysis may be underpowered. On the other hand, inclusion of 302 migraineurs from a pool of totally 557 eligible headache patients referred from general practitioners for second opinion over 2.5 years, strengthen the external validity of the study. In the absence of validated SM classification, we based the definition of SM solely on self-reported seasonal variation of migraine ("Yes"/"No") without setting standards for migraine frequency. This may have overestimated SM.

CONCLUSION

This study demonstrated an association between seasonal variation of migraine and photophobia manifested as attacks triggered by sunlight and hypersensitivity to light between attacks. The seasonal variation of photophobia with more light intolerance in those with attacks confined to the polar day as compared with the polar night season is consistent with a circadian rhythmicity of the disease. Future studies should investigate the relationship between photophobia and attack frequency in migraineurs living in a subarctic area. Whether continuous exposure to light over time or switching between light and dark periods possibly interferes with the biology of migraine is another question to address.

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Hypoxia triggers high-altitude headache with migraine features: A prospective trial

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Abstract

Background: Given the high prevalence and clinical impact of high-altitude headache (HAH), a better understanding of risk factors and headache characteristics may give new insights into the understanding of hypoxia being a trigger for HAH or even migraine attacks.

Methods: In this prospective trial, we simulated high altitude (4500 m) by controlled normobaric hypoxia ($F_iO_2 = 12.6\%$) to investigate acute mountain sickness (AMS) and headache characteristics. Clinical symptoms of AMS according to the Lake Louise Scoring system (LLS) were recorded before and after six and 12 hours in hypoxia. O_2 saturation was measured using pulse oximetry at the respective time points. History of primary headache, especially episodic or chronic migraine, was a strict exclusion criterion.

Findings: In total 77 volunteers (43 (55.8%) males, 34 (44.2%) females) were enrolled in this study. Sixty-three (81.18%) and 40 (71.4%) participants developed headache at six or 12 hours, respectively, with height and SpO_2 being significantly different between headache groups at six hours ($p < 0.05$). Binary logistic regression model revealed a significant association of SpO_2 and headache development ($p < 0.05$, OR 1.123, 95% CI 1.001–1.259). In a subgroup of participants, with history of migraine being a strict exclusion criterion, hypoxia triggered migraine-like headache according to the International Classification of Headache Disorders (ICHD-3 beta) in $n=5$ (8%) or $n=6$ (15%), at six and 12 hours, respectively.

Interpretation: Normobaric hypoxia is a trigger for HAH and migraine-like headache attacks even in healthy volunteers without any history of migraine. Our study confirms the pivotal role of hypoxia in the development of AMS and beyond that suggests hypoxia may be involved in migraine pathophysiology.

Keywords

High-altitude headache, migraine, hypoxia, SpO_2 , acute mountain sickness

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Introduction

With increasing numbers of people who experience high altitude comes a demand for an awareness of the presentations and knowledge of the syndromes including treatment options for altitude-related illness. High-altitude headache (HAH) is the most prominent symptom of acute mountain sickness (AMS) and has been defined by the International Headache Society as headache, usually bilateral, aggravated by exertion and caused by ascent above 2500 meters (1,2). Nevertheless, the underlying pathophysiological mechanisms and even more the potential risk factors are still poorly understood. Current pathophysiological theories include the elevation of intracranial pressure, alteration of brain oxygen consumption, impaired

glucose metabolism, free radical production and increased cerebral blood flow. Each of these factors is discussed as a proposed mechanism underlying HAH (3–8).

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Most data on the clinical presentations, features and predictors of HAH derive from observational studies in the field (9–11). The interpretation of the pathophysiological processes behind HAH is limited because of the complexity of confounding factors such as great exertion, inadequate fluid and food intake, sleep deprivation, environmental factors (i.e. temperature, humidity), comorbidities and history of primary headaches.

Thus, assessment of headache features and other important pathophysiological markers might help to clarify the pathophysiological relevance of hypoxia on HAH development. These markers could include arterial oxygen saturation (SpO_2) that should, however, be measured during strictly standardized, passive normobaric hypoxia exposure to avoid confounding factors.

Recent studies have shown that a migraine attack can be triggered or become more pronounced by high altitude; however, only in patients with history of migraine (4,10). It is possible that migraine-like headache could be triggered by profound hypoxia simulating high altitude. However, thus far this has never been investigated prospectively in a large cohort of migraine-naïve individuals. On the other hand, recent papers speculate on hypoxia triggering cortical spreading depression secondarily promoting migraine headache attacks (12,13).

This prospective study investigates the influence of controlled normobaric hypoxia (i.e. simulated high altitude of 4500 m) on the development of AMS and headache characteristics in a large cohort of healthy volunteers. We hypothesized that hypoxia is the major trigger for AMS and HAH but also may induce a migraine-like headache in a sub-proportion, even in volunteers without history of primary headaches.

Materials and methods

Participants

A detailed description of the study protocol has been published recently (14).

In brief, participants were recruited by advertisements on the homepage of the Austrian Alpine Association and by information via the mailing list of the University of Innsbruck. Exclusion criteria included cardiovascular, respiratory, neurological and psychiatric diseases, episodic or chronic migraine and chronic headache (defined as any headache occurring on more than 15 days per month). In addition, smoking, pregnancy, permanent residence at altitudes exceeding 1000 m, an overnight stay at altitudes >2500 m in the previous month, or exposure above 2500 m two weeks prior to the 12-hour hypoxic exposure were also exclusion criteria. At enrollment all individuals had a face-

to-face interview with a headache specialist excluding all those with history of migraine.

Participants were instructed to abstain from all anti-inflammatory medication and nutritional supplements for two weeks prior to the exposure and from alcohol starting the day before the experiment. Caffeine was not allowed on the day of the exposure. All participants gave their written informed consent prior to the participation in the study. The study was carried out in conformity with the ethical standards laid down in the 2008 Declaration of Helsinki and was approved by the ethics committee of the Medical University of Innsbruck.

Procedures

Participants were passively exposed at a fraction of inspired oxygen (F_1O_2) of 12.6% in our hypoxic chamber in Innsbruck at 600 m (corresponding to a simulated altitude hypoxia of 4500 m, partial pressure of inspired oxygen (P_1O_2) = 83.9 mmHg) for 12 hours. Room temperature and humidity were kept constant at 22–24 °C and 23–27%, respectively. Prior to entering the hypoxic chamber all participants were examined, including a medical routine check. A pregnancy test was performed in all women prior to the 12-hour hypoxic exposure. During the simulated hypoxia exposure, the same food (i.e. brown bread, cheese, boiled ham, cucumber, banana, apple, cookies and chocolate) and drinks (water and apple juice) were provided and could be consumed as the patient desired. Most of the time participants were seated but some activities (e.g. standing, walking and stretching) were also performed. Recumbent position or sleeping was not allowed. Measurements, described in detail in the following sections, were performed before, during and/or after the session.

Measurements and instruments

The Lake Louise scoring system (LLS) was used to assess the incidence and severity of AMS (2). It is a self-assessment questionnaire including five symptom complexes (headache; gastrointestinal symptoms like anorexia, nausea or vomiting; fatigue and/or weakness, dizziness and/or light headedness; and difficulty sleeping); scores range from 0 to 3. The participants self-rated their status: 0 for no discomfort, 1 for mild, 2 for moderate and 3 for severe symptoms. The symptom complex “difficulty sleeping” was not taken into account because participants did not stay overnight in the hypoxic chamber. AMS was diagnosed whenever the symptom headache was present in combination with at least one other symptom. A total score of ≥ 3 signified either mild disease or AMS at an early stage, while a score ≥ 4 was used to recognize a more severe

disease state (5). The LLS at the point when leaving the chamber was taken to distinguish between AMS+ and AMS-. SpO₂ was measured before hypoxia by pulse oximetry (Onyx II 9550, Nonin, Plymouth, MI, USA) (i.e. before entering the high-altitude chamber) and at 6 (i.e. in the high-altitude chamber) and 12 (i.e. in the high-altitude chamber) hours, respectively.

Detailed headache characteristics were evaluated before hypoxia (i.e. before entering the high-altitude chamber) and at six and 12 hours (i.e. in the high-altitude chamber) respectively, using a standardized questionnaire evaluating all migraine and HAH features according to the International Classification of Headache Disorders, third edition beta (ICHD-3 beta) (1). Additionally, we asked for headache characteristics (pulsating, pressing, burning, stabbing, dull or other), neck stiffness, factors improving (fluids, stand up, resting, avoiding light, avoiding noise or other) or worsening headache (movement, exertion, stand up, stretching, coughing, nausea, cold, light, noise or other).

Statistical analysis

This study tested the hypothesis that simulated exposure to hypoxia triggers headache. Metric variables (age, height, SpO₂ at six hours, SpO₂ at 12 hours, visual analog scale (VAS 0–100) at six hours, VAS 0–100 at 12 hours, onset of headache) were compared using Mann-Whitney *U* test.

A univariate analysis between headache groups (headache versus non-headache) including demographic (age, height, sex) and clinical parameters (SpO₂) was conducted in a first step. A binary logistic regression analysis with dichotomized outcome (i.e. headache yes versus no) at both outcome endpoints (i.e. six hours and 12 hours) was applied to analyze predictors for headache. Only variables with significant

difference in the univariate approach (i.e. height and SpO₂) were included in this model.

The accuracy of SpO₂ levels to differentiate between headache yes versus no was evaluated by the receiver operating characteristic (ROC) analysis.

Data analyses were performed with the use of the SPSS statistical software package (SPSS version 22, IBM) and Prism 6 (GraphPad Inc, 2014). A *p* value of less than 0.05 (two tailed) was considered to indicate statistical significance. Results are expressed as mean ± standard deviation (SD), 95% confidence interval (CI), odds ratio (OR) or median + interquartile range (IQR).

Results

In total 77 healthy volunteers were consecutively enrolled in this study. Baseline characteristics and dichotomized outcome parameters are given in detail in Table 1. Sixty-three (81.18%) and 40 (71.4%) volunteers had developed headache at six or 12 hours, respectively. Twenty-one individuals had left the hypoxic chamber between six and 12 hours because of the high severity of AMS symptoms. All headache symptoms resolved within 24 hours post-exposure. Only height and SpO₂ were significantly different between headache groups at six hours (*p* < 0.05, Table 1). Clinical characteristics of headache including pain localization, quality and accompanying symptoms were evaluated for both time points (Table 2). Two or more migraine features including unilateral location, pulsating quality, moderate or severe pain intensity and aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) tested positive for *n* = 17 (27%) and *n* = 17 (43%) at six and 12 hours, respectively. Complete migraine criteria according to ICHD-3 beta also included at least one

Table 1. Distribution of baseline characteristics and arterial oxygen saturation using pulse oximetry (SpO₂) at simulated high altitude (4500 m).

Patient characteristic	Headache at six hours			Headache at 12 hours		
	Yes, <i>n</i> = 63	No, <i>n</i> = 14	<i>p</i> value	Yes, <i>n</i> = 40	No, <i>n</i> = 16	<i>p</i> value
Age years, median (IQR)	24 (6)	24 (3.5)	0.791	24 (6)	24 (2.5)	0.523
Height cm, median (IQR)	173 (13)	179 (9.75)	0.048	173.5 (11.75)	178.5 (15.5)	0.182
Sex female (%)	30 (88.2)	4 (11.8)	0.243	15 (75)	5 (25)	0.763
Sex male (%)	33 (76.7)	10 (23.3)		25 (69.4)	11 (30.6)	
AMS LL ≥ 4	40 (90.9)	4 (9.1)		21 (91.3)	2 (8.7)	
SpO ₂ , median (IQR)	81.8 (6.5)	84.9 (7.9)	0.031	84.5 (9.7)	87 (8.5)	0.543
VAS Scale, median (IQR)	25 (20)			20 (42)		

Data are presented as median and IQR, statistical differences were compared using Mann-Whitney *U* test. AMS: acute mountain sickness; LL: Lake Louise scale; IQR: interquartile range; VAS: visual analog scale ranging from 0 to 100.

Table 2. Clinical features and characteristics of headache at simulated high altitude (4500 m).

Characteristic	N	% of headache
Number of patients with headache at six hours	63	
Onset of headache, minutes ± SD	189.8 ± 98	
Localization		
Left	31	49.20%
Frontal	37	58.70%
Occipital	14	22.20%
Right	34	54.00%
Character		
Pulsating	16	25.40%
Pressing	33	52.40%
Burning	1	1.60%
Stabbing	9	14.30%
Dull	12	19.00%
Other	12	19.00%
Neck stiffness	10	15.90%
Worsening through		
Movement	21	55.30%
Exertion	3	7.90%
Stand up	15	39.50%
Stretching	5	13.20%
Nausea	1	2.60%
Cold	2	5.30%
Light	8	21.10%
Noise	5	13.20%
Other	9	23.70%
Improvement through		
fluids	21	58.30%
Stand up	10	27.80%
Avoiding light	4	11.10%
Avoiding noise	3	8.30%
Other	17	47.20%
Number of patients with headache at 12 hours	40	
Localization		
Left	20	50.00%
Frontal	22	55.00%
Occipital	10	25.00%
Right	25	62.50%
Character		
Pulsating	13	32.50%
Pressing	14	35.00%
Burning	1	2.50%
Stabbing	8	20.00%

Table 2. Continued.

Characteristic	N	% of headache
Dull	10	25.00%
Other	7	17.50%
Neck stiffness	8	20.00%
Worsening through		
movement	19	76.00%
Exertion	5	20.00%
Stand up	11	44.00%
Stretching	8	32.00%
Coughing	2	8.00%
Nausea	1	4.00%
Cold	2	8.00%
Light	6	24.00%
Noise	7	28.00%
Other	6	24.00%
Improvement through		
fluids	6	25.00%
Stand up	1	4.20%
Resting	1	4.20%
Avoiding light	4	16.70%
Avoiding noise	5	20.80%
Other	17	70.80%

Data are presented as absolute numbers (N) and percentage of respective headache groups.

of the following: 1) nausea and/or vomiting or 2) photophobia and phonophobia were still positive in $n = 5$ (8%) or $n = 6$ (15%), at six and 12 hours, respectively (1). No statistical significant differences in baseline characteristics (sex, age, height, SpO₂ at baseline) or under hypoxia (SpO₂, headache intensity and onset of headache) could be detected in a univariate model between participants with or without migraine-like headache.

No statistical significant differences in baseline characteristics (sex, age, height, SpO₂ at baseline) or under hypoxia (SpO₂, headache intensity and onset of headache) could be detected in a univariate model between females with or without use of oral contraceptives.

None of the participants reported an aura symptom

Results of the 21 individuals who terminated early at six hours were included only in the six-hour analysis. Baseline characteristics were not significantly different (age, height) with the exception of sex ($p = 0.02$). In this subpopulation start of headache symptoms was significantly earlier (138 versus 210 minutes, $p = 0.002$), headache intensity more severe (45 versus 27, $p = 0.01$) and SpO₂ lower (81 versus 84, $p = 0.048$) than in those who

(continued)

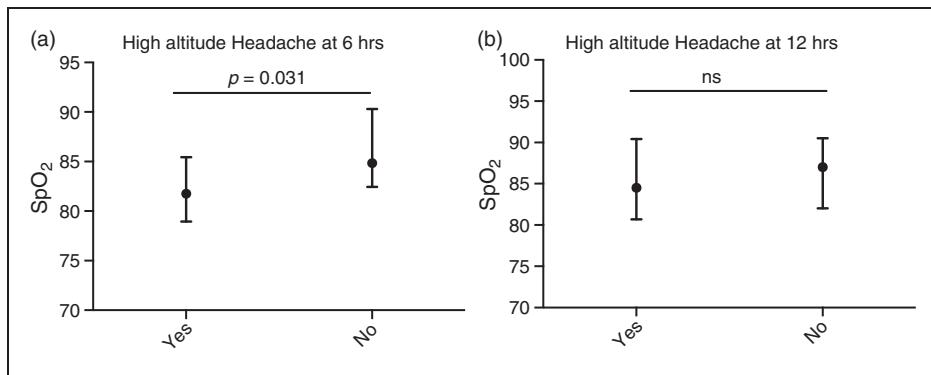


Figure 1. Distribution of arterial oxygen saturation between headache groups (SpO₂).

(a) Six hours.

SpO₂ was measured using pulse oximetry. Data are presented as median + interquartile range. Statistical differences were compared using Mann-Whitney U test.

(b) 12 hours.

SpO₂ was measured using pulse oximetry. Data are presented as median + interquartile range. Statistical differences were compared using Mann-Whitney U test.

continued until 12 hours. Only one of those 21 participants fulfilled migraine-like headache criteria.

SpO₂. No baseline differences were detected comparing SpO₂ at baseline between the headache groups. SpO₂ was significantly lower in the headache group at six hours ($p < 0.05$) (Figure 1). The binary logistic regression model adjusted for height revealed SpO₂ as a significant predictor for headache at six hours (OR 1.123, 95% CI 1.001–1.259, $p < 0.05$). The ROC showed an area under the curve (AUC) of 0.698 (95% CI 0.555–0.840) for SpO₂ at six hours.

Discussion

The main results of this prospective study were that simulated high altitude by hypoxia ($F_iO_2 = 12.6\%$, $\cong 4500\text{ m}$) triggers profound headache in more than 80 % of healthy volunteers without a history of primary headaches. Furthermore, we found that SpO₂ predicts headache. Additionally, a proportion of headache patients fulfilled migraine attack criteria under induced hypoxia.

HAH is defined as headache, usually bilateral and aggravated by exertion, caused by ascent above 2500 m (1). Approximately 10%–25% of un-acclimatized individuals who ascend to 2500 m will develop HAH (2). With an 80% headache rate in our study, the incidence is surprisingly high, but comparable to results published for altitudes of 4500 m and above (15,16). Interestingly, of the known risk factors for the development of HAH (rapid ascent, young age, exertion, history of altitude illness, migraine and genetic predisposition) only young age, history of altitude illness and rapid ascent are likely to explain the high HAH rate in

our study population, considering history of primary headache, especially episodic or chronic migraine were an exclusion criterion (4,10,11). Furthermore, during simulated high altitude, individuals were not exposed to exertion and fluid and food intake was not limited. Keeping this in mind, our headache rate of greater than 80% is even more impressive, underlining the pivotal role of hypoxia as the most potent trigger for HAH.

The cause of high-altitude headache is still elusive. In our prospective study we minimized potential triggers and risk factors to rapid ascent to 4500 m by induced hypoxia (F_iO_2 of 12.6%) (4). Pulse oximetric measurements of SpO₂ were normal in all participants before exposure but were evaluated to be significantly lower in HAH individuals at six hours. Furthermore, in the binary logistic regression model lower SpO₂ was associated with headache ($p < 0.05$). ROC analysis for SpO₂ and occurrence of headache revealed an AUC of 0.698. Taken together our results propose a predominant role of hypoxia in the pathophysiology of HAH.

The International Headache Society defines HAH as headache, usually bilateral and aggravated by exertion, with mild to moderate intensity (1). Interestingly, in our population more than a quarter of individuals developed a migraine-like headache with moderate to severe pain intensity, unilateral location, pulsating quality, aggravation by physical activity and nausea (Table 3) (1). This finding is of the utmost interest since we strictly excluded volunteers with a history of migraine with or without aura. It is unclear if low atmospheric pressure and hypoxia trigger migraine on their own or if they simply trigger HAH and migraine-like headache (17,18). It is well established that hypoxia or even normobaric hypoxia can trigger migraine attacks in patients with a history of migraine

Table 3. (a) Migraine-like headache features at six hours using modified ICHD-3 beta (1).

Migraine features at six hours	n = 63
Headache has at least two of the following characteristics	
1. Unilateral location	
2. Pulsating quality	
3. Moderate or severe pain intensity	
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)	
During the headache at least one of the following:	
1. Nausea and/or vomiting	
2. Photophobia and phonophobia	
(b) Migraine-like headache features at 12 hours using modified ICHD-3 beta (1).	
Migraine features at 12 hours	n = 40
Headache has at least two of the following characteristics	
1. Unilateral location	
2. Pulsating quality	
3. Moderate or severe pain intensity	
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)	
During the headache at least one of the following:	
1. Nausea and/or vomiting	
2. Photophobia and phonophobia	

ICHD-3 beta: International Classification of Headache Disorders, third edition beta.

(10,19,20). However, our experiment was conducted under strictly controlled normobaric hypoxia, suggesting that merely hypoxia triggers a migraine-like headache in a proportion of individuals without a history of primary headache. The reason behind this is still elusive: A recent publication could not find a relationship between the change (hypoxia versus normoxia) in cerebral nitrite (NO_2) or calcitonin gene-related-peptide (CGRP) exchange and AMS or headache scores (21). If hypoxia triggers cortical spreading depression/depolarization as proposed by some authors and secondarily promotes migraine-like headache, has to be investigated on the basis of our results (12,13).

Not surprisingly, those 21 participants who terminated early after the six-hour examination suffered from more severe headache with early onset and showed significantly lower SpO_2 values at six hours. The exclusion of those participants from the 12-hour analysis may explain the loss of significance regarding SpO_2 at this time point. Interestingly, only one person from this subgroup fulfilled migraine-like headache features.

To the best of our knowledge, this is the first report on this observation in a prospective study, possibly adding to our pathophysiological concept of migraine and HAH in a large sample. However, future studies

will have to reproduce and further elaborate on this, while also including biomarker sampling and prospective therapeutic intervention.

Limitations

Our study was conducted prospectively but without a control group. However, we do not believe that including a control group would add to the understanding of HAH, since being exposed only to a room without hypoxia would not trigger headache, nor would blinding of volunteers be feasible. Given the young mean age of our study population, we might have included individuals who will develop episodic migraine in future years. Another important limitation is that caffeine intake was not allowed on the days of the experiment. Therefore, we cannot fully rule out that at least a small proportion of patients may have suffered from caffeine-withdrawal headache.

Conclusion

In conclusion, the present findings confirm that hypoxia is substantially involved in the development of AMS. Furthermore our data suggest that hypoxia may also trigger migraine-like headache attacks in

healthy volunteers without any history of episodic or chronic migraine. Thus, we believe that elements we provided should be implemented in new official HAH diagnosis criteria.

Furthermore, the role of hypoxia in migraine pathophysiology must be investigated in future trials.

Key findings

- The present findings confirm that hypoxia is substantially involved in the development of acute mountain sickness (AMS).
- Our data suggest that hypoxia may also trigger migraine-like headache attacks in healthy volunteers without any history of episodic or chronic migraine.
- Furthermore, the role of hypoxia in migraine pathophysiology must be investigated in future trials.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Research Submission

Age But Not Sex Is Associated With Efficacy and Adverse Events Following Administration of Intravenous Migraine Medication: An Analysis of a Clinical Trial Database

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Background.—Migraine prevalence is associated with both sex and age. Differences in efficacy of parenteral migraine medication administration based on the sex and age of the patient have not been explored in the published literature.

Objective.—The objective was to determine whether sex and age are associated with short-term headache relief, sustained headache freedom, or adverse medication effects in data collected during 3 emergency department (ED)-based acute migraine comparative efficacy trials.

Methods.—Data were combined from 3 studies in which patients who presented to an ED with acute migraine were randomized to one of the following intravenous medication regimens: (1) metoclopramide combined with diphenhydramine; (2) metoclopramide combined with diphenhydramine and dexamethasone; (3) metoclopramide alone; (4) ketorolac; or (5) valproate. In each of these studies, (1) short-term efficacy (patient description of the headache as “mild” or “none” 1 hour after medication administration); (2) sustained efficacy (patient description of the headache as “none” within 2 hours of medication administration and no headache recurrence for 24 hours post ED discharge); and (3) the frequency of any adverse medication effects within 24 hours of medication administration was determined. For each of the medication regimens studied, efficacy and adverse event rates were compared between men vs women and the older vs the younger half of patients. Multivariate logistic regression models were constructed in which sex and age were maintained in the model as well as variables representing each of the medication regimens patients received.

Results.—A total of 884 patients were included in this analysis (140 men and 744 women). The median age was 35 years. After controlling for age and medication received, female sex was not associated with short-term efficacy (OR 0.98 [95% confidence interval (CI): 0.66, 1.46]), sustained efficacy (OR 0.72 [95%CI: 0.45, 1.15]), or adverse events (OR 1.14 [95%CI: 0.77, 1.71]). Age >36 years, however, was associated with short-term efficacy (OR 0.66 [95%CI: 0.49, 0.88]), sustained efficacy (OR 0.50 [95%CI: 0.34, 0.73]), and adverse events (OR 1.36 [95%CI: 1.02, 1.82]).

Conclusion.—Sex was not associated with response to parenteral acute migraine medication. Age was associated with both efficacy and adverse events.

Key words: migraine, emergency department, sex, age

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Migraine, one of the most prevalent neurological disorders worldwide and a leading cause of functional disability,¹ is 3 times more common in women than men.² Women also experience greater symptomology, higher headache-related disability,

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and greater healthcare resource utilization than men.^{3,4} The mechanisms for sex-based differences in this disease are incompletely understood. Sex hormones modulate nociceptive processing within the trigeminovascular pathway.⁵ High levels of estrogen increase nociception while testosterone is antinociceptive. Male to female transsexuals suffer from migraine at the same frequency as women,⁶ while female to male transsexuals have decreased rates of chronic pain.⁷ Neuroanatomical differences between male and female migraineurs have been described as well.⁸ Finally, psychosocial expectations based on gender and disparate coping strategies may also contribute to burden of illness.⁹ Despite established sex-based differences in migraine impact, little is known about sex-based differences in response to treatment.

Migraine is also an age-dependent disease. Prevalence increases with every decade until the fourth decade of life and then gradually declines.⁴ Although some of this prevalence peak may be attributed to the hormonal fluctuations associated with reproductive stage of a woman's life, men demonstrate a similar prevalence peak in the fourth decade.⁴ Age-related changes in migraine nociception are yet to be explored in the published literature.

Typically, clinicians treating a patient with acute migraine will not consider sex when choosing a parenteral therapeutic agent. Age is used to determine probability of serious adverse medication effects, but as with sex, is not used to predict response to medication. The goal of this analysis is to determine if sex- and age-based differences exist in response to acute parenteral medication. We focused our analysis on migraineurs presenting to an emergency department (ED) who received an intravenous medication regimen. Using combined data from 3 ED-based acute migraine clinical trials, we determined if a patient's sex or age is associated with short-term headache relief, sustained headache freedom, or adverse medication effects.

MATERIALS AND METHODS

Overview.—This is an analysis of de-identified data gathered during 3 ED-based randomized comparative efficacy trials of different migraine medica-

tions. These studies compared several medications, doses, and combinations of medications with established efficacy in migraine, including: metoclopramide, an antiemetic dopamine antagonist; ketorolac, a nonsteroidal anti-inflammatory drug; dexamethasone, a corticosteroid; and valproate, an antiepileptic. The antiemetic dopamine antagonists are used in two-thirds of all migraine visits to US EDs.¹⁰ Ketorolac is used in one-third of visits.¹⁰ Dexamethasone is used in 5% of ED migraine visits, usually as adjunct therapy.¹⁰ Valproate is used infrequently but often is discussed in the headache literature.¹¹ In each of these clinical trials, patients presenting to an ED with acute migraine were randomized to treatment with one or a combination of the intravenous medications listed above. The goal of this analysis was to determine if sex and age are associated with efficacy or adverse events. The Albert Einstein College of Medicine institutional review board approved this study.

Materials.—The 3 studies that provided data for this analysis enrolled patients between 2005 and 2013 (Appendix Table A1).^{11–13} To participate, patients were required to have an acute headache that fulfilled all International Classification of Headache Disorders, 2nd edition, migraine without aura criteria except duration of headache (patients were not excluded for prolonged duration of headache), nor were they required to have had more than one similar previous headache.¹⁴ These migraine clinical trials used similar inclusion and exclusion criteria (Appendix Table A1) and enrolled patients with nearly identical socio-demographic characteristics (Appendix Table A2). Given the similarity of both the methodology and population demographics, there was sufficient homogeneity to combine the data from these 3 studies for the purpose of this analysis (Appendix Tables A1 and A2). Altogether, 884 patients were enrolled.

In the first study, an examination of the efficacy of dexamethasone as an adjunctive agent, all subjects received metoclopramide 20 mg IV + diphenhydramine 25 mg IV. The diphenhydramine was included to minimize akathisia, a common side effect of parenteral metoclopramide administration.¹² Half the subjects also received dexamethasone 10 mg IV while

the other half received intravenous placebo. Subjects who reported insufficient relief after 1 hour were administered a second dose of metoclopramide 20 mg IV + diphenhydramine 25 mg IV. There was no difference between the arms in the frequency of sustained headache freedom, the primary outcome, although dexamethasone was of benefit on some secondary outcomes.

The second study was a metoclopramide dose finding study. Patients were randomized to receive 10, 20, or 40 mg of IV metoclopramide.¹³ In this study, all research subjects also received diphenhydramine 25 mg IV. This study was a negative study, with no clinically or statistically significant difference in outcome among the 3 treatment arms.

The third study was a randomized comparison of metoclopramide 10 mg IV vs ketorolac 30 mg IV vs valproate 100 mg IV.¹¹ In this study, valproate was shown to be substantially less efficacious than either of the other 2 agents, with a trend toward superiority of metoclopramide over ketorolac.

In each of these randomized controlled trials (RCTs), we assessed pain levels at baseline, and 1 and 2 hours after medication administration, as well as by telephone 24–48 hours after ED discharge. We also assessed medication side effects at each of the same time points. Pain levels were assessed using a standard ordinal scale, on which patients described their pain as “none,” “mild,” “moderate,” or “severe.” At each time point, patients were also asked if they had developed any new symptoms potentially attributable to the investigational medication.

Outcomes of Interest.—For the purpose of the present analysis, we considered 2 efficacy outcomes and one safety (adverse events) outcome. The short-term outcome was short-term headache relief, defined as obtaining a headache level of “mild” or “none” within 1 hour of the medication.¹⁵ The second efficacy outcome was sustained headache freedom, obtained by patients who reported a headache level of “none” in the ED and who remained headache free for at least 24 hours after ED discharge. The third outcome targeted side effects, defined as the development of any additional symptoms at any time post medication administration and prior to the follow-up phone call.

Predictor Variables.—Sex (male or female) and age were our primary predictor variables. For the primary analysis, age was dichotomized at the median into an older and younger half. In a secondary analysis, we also consider age (in years) as continuous data. Because migraine with aura is considered a distinct migraine subtype,¹⁶ we also determined whether visual or other sensory symptoms preceding the acute headache modified any of the associations between age or sex and the 3 outcomes of interest. Patients were considered to have aura if they reported a positive response to either of the following questions: (1) Some people have changes in their vision with their headache. BEFORE YOUR HEADACHE BEGAN, did you see things like spots, stars, lights, zig-zag lines or heat waves? (2) Some people have changes in their skin sensation with their headache. BEFORE YOUR HEADACHE BEGAN, did you have numbness or tingling in your face or arms?

Medication Covariates.—We grouped medication regimens into the following categories:

1. Metoclopramide + diphenhydramine: This included patients who received any dose of metoclopramide in the metoclopramide dose finding study in addition to patients randomized to metoclopramide + diphenhydramine + placebo in the dexamethasone study. We felt comfortable aggregating these patients into one group for analysis because there were no differences in outcomes among the various metoclopramide doses.¹³
2. Metoclopramide + diphenhydramine + dexamethasone: This included patients randomized to the dexamethasone arm of the dexamethasone study.
3. Metoclopramide alone: This included patients randomized to the metoclopramide arm of the metoclopramide/ketorolac/valproate study.
4. Ketorolac: This included patients randomized to the ketorolac arm of the metoclopramide/ketorolac/valproate study.
5. Valproate: This included patients randomized to the valproate arm of the metoclopramide/ketorolac/valproate study.

Analysis.—Baseline characteristics, including age, race/ethnicity, presence of aura symptoms, duration of headache, and severity of headache are reported

Table 1.—Baseline Characteristics

Characteristic	Sex		Age	
	Male (n = 140)	Female (n = 744)	≤35 years (n = 442)	≥36 years (n = 441)
Age, years, median (IQR)	35 (27, 46)	36 (27, 44)	28 (27, 28)	46 (45, 46)
Race/ethnicity (%)				
Latino	94 (68)	539 (73)	303 (69)	330 (75)
Black	33 (24)	162 (22)	112 (25)	83 (19)
Asian	1 (1)	4 (1)	2 (1)	3 (1)
White	6 (4)	21 (3)	14 (3)	13 (3)
Other	4 (3)	15 (2)	10 (2)	9 (2)
Missing	2	3	1	3
Headache duration, hours, median (IQR)	48 (30, 66)	49 (30, 66)	48 (24, 96)	58 (24, 96)
Aura (%)†	45/138 (33)	308/735 (42)	175/434 (40)	178/439 (41)
Baseline nausea (%)	58/140 (41)	412/738 (56)	219/439 (50)	250/438 (57)
“Severe” headache at baseline (%)	83/140 (59)	515/743 (69)	281/441 (64)	316/440 (72)
Used migraine medication prior to ED presentation (%)	93/139 (67)	505/743 (68)	299/437 (68)	299/439 (68)

†Patients were considered to have aura if they reported a positive response to either of the following questions: (1) Some people have changes in their vision with their headache. BEFORE YOUR HEADACHE BEGAN, did you see things like spots, stars, lights, zig-zag lines, or heat waves? and (2) Some people have changes in their skin sensation with their headache. BEFORE YOUR HEADACHE BEGAN, did you have numbness or tingling in your face or arms?

as medians with interquartile ranges or proportions. Bivariate associations between the 2 predictor variables and the 3 outcomes of interest are reported as proportions with 95%CI. Multivariate logistic regression models were constructed to determine whether medication administered or the predictor variables themselves modified the association between age and sex and the outcomes of interest. In each model, sex, age, and dummy variables representing the medications administered were entered and retained in the model regardless of whether or not they were associated with the dependent variable. For the primary analysis, we dichotomized age at the median so that we could compare the older half of patients to the younger half of patients. As a secondary analysis, we included age in the regression models as a continuous variable. We determined the impact of aura on our primary predictor variables (age and sex) by adding aura to the regression models to see if it altered the relationship between the predictor variables and the outcomes in a meaningful way. Results of the regression models were reported as

odds ratios with 95%CI. Odds ratios were considered statistically significant if the 95%CI did not cross 1. Differences between sexes or age groups were considered statistically significant if the 95%CI did not cross 0.

RESULTS

Aggregated data from the 3 original studies included a total of 884 participants (Table 1). There were no differences between the sexes in age, race, duration of headache, or presence of aura. Women were more likely to be nauseated (56% vs 41%, 95%CI for difference of 14%: 5, 23%) and to report severe pain at baseline (69% vs 59%, 95%CI for difference of 10%: 1, 19%). Patients ≥36 years were more likely to be nauseated (57% vs 50%, 95%CI for difference of 7%: 1, 14%) and to report severe pain at baseline (72% vs 64%, 95%CI for difference of 8%: 2, 14%) than patients younger than 36 years.

Overall, men and women were comparably likely to report short-term and sustained headache

Table 2a.—Efficacy and Safety Outcomes by Sex and Age

Outcome	Men (n/N) (%)	Women (n/N) (%)	Difference (95%CI) and P value	Adults ≤35 years (n/N) (%)	Adults ≥36 years (n/N) (%)	Difference (95%CI) and P value
One hour headache relief	93/139 (67)	486/734 (66)	1% (-8, 9%), P = .87	303/433 (70)	275/439 (63)	7% (1, 14%), P = .02
Sustained headache freedom	28/140 (20)	115/732 (16)	4% (-3, 11%), P = .21	90/438 (21)	53/433 (12)	8% (3, 13%), P < .01
Adverse events	41/140 (29)	241/744 (32)	-3% (-11, 5%), P = .47	125/442 (28)	157/441 (36)	-7% (-13, -1%), P = .02

improvements and adverse events, while patients ≥36 years were less likely than younger patients to respond favorably to headache medication and were more likely to report adverse events (Tables 2a, 2b, and Appendix Table A3). When analyzed by response to specific medication regimens, we did not observe statistically significant differences between men and women (Table 3a). Most of the discrepancy in efficacy outcomes between patients ≥36 years and younger patients can be explained by differential response to metoclopramide regimens (Table 3b). The higher rate of adverse events

in older patients was due primarily to a disparity in response to dexamethasone (Table 4).

Results of multivariate logistic regression modeling are depicted in Tables 5a and 5b. The association between age and all outcomes of interest was not influenced meaningfully by sex, while the lack of association between sex and the outcomes of interest was not influenced by age.

Aura was not associated with any of the outcomes. Including it in the models did not influence any of the predictors in a meaningful way (Appendix Table A4). Similarly, including in the models

Table 2b.—Efficacy and Safety Outcomes by Sex, Stratified by Age

Outcome	Men (n/N) (%)	Women (n/N) (%)	Difference (95%CI) and P value for men vs women
One hour headache relief			
Age ≤ 35	49/70 (70)	254/363 (70)	0% (-12, 12%), P = 1.00
Age ≥ 36	43/68 (63)	232/371 (63)	1% (-12, 13%), P = .91
Difference (95%CI) and P value for younger vs older participants	7% (-9, 22%), P = .40	7% (1, 14%), P = .03	
Sustained headache freedom			
Age ≤ 35	18/71 (25)	72/367 (20)	6% (-5, 17%), P = .27
Age ≥ 36	10/68 (15)	43/365 (12)	3% (-6, 12%), P = .50
Difference (95%CI) and P value for younger vs older participants	11% (-3, 24%), P = .12	8% (3, 13%), P < .01	
Adverse events			
Age ≤ 35	16/71 (23)	109/371 (29)	7% (-4, 18%), P = .24
Age ≥ 36	25/68 (37)	132/373 (35)	1% (-11, 14%), P = .83
Difference (95%CI) and P value for younger vs older participants	-14% (-29, 1%), P = .07	-6% (-13, 1%), P = .08	

Table 3a.—Short-Term and Sustained Efficacy Outcomes of Men and Women Listed for Each Medication Regimen

Medication	One Hour Headache Relief			Sustained Headache Freedom		
	Men (n/N) (%)	Women (n/N) (%)	Difference, (95%CI), P value	Men (n/N) (%)	Women (n/N) (%)	Difference, (95%CI), P value
Metoclopramide + diphenhydramine	50/66 (76)	270/376 (72)	4% (-7, 15%), P = .51	19/67 (28)	65/372 (17)	11% (-1, 22%), P = .04
Metoclopramide + diphenhydramine + dexamethasone	15/19 (79)	68/85 (80)	-2% (-23, 19%), P = .92	3/19 (16)	23/86 (27)	-11% (-30, 8%), P = .32
Metoclopramide alone	11/18 (61)	59/90 (66)	-4% (-29, 20%), P = .72	4/18 (22)	8/91 (9)	13% (-7, 34%), P = .10
Ketorolac	9/17 (53)	51/93 (55)	-2% (-28, 24%), P = .89	1/17 (6)	16/92 (17)	-12% (-25, 2%), P = .23
Valproate	8/19 (42)	38/90 (42)	0% (-25, 24%), P = .99	1/19 (5)	3/91 (3)	2% (-9, 13%), P = .68

variables with baseline between-group discrepancies did not meaningfully influence our hypothesized predictors (Appendix Table A5).

LIMITATIONS

Several limitations should be noted. First, the aggregated study cohort was unbalanced due to the well-known differential prevalence of migraine in men and women.³ This imbalance leads in turn to a

loss of power in the sex analysis due to the paucity of men with migraine available for enrollment. Because only slightly more than 15% of participants were men, small effect sizes associated with sex may have been missed. However, these data appear to be sufficiently robust to detect meaningful differences.

Second, we did not record female participant's phase of menstrual cycle, stage of life, or use of

Table 3b.—Short-Term and Sustained Efficacy Outcomes of Adults Older and Younger Than 36 Listed for Each Medication Regimen

Medication	One hour headache relief			Sustained headache freedom		
	Adults ≤35 years (n/N) (%)	Adults ≥36 years (n/N) (%)	Difference, (95%CI), P value	Adults ≤35 years (n/N) (%)	Adults ≥36 years (n/N) (%)	Difference, (95%CI), P value
Metoclopramide + diphenhydramine	159/197 (81)	161/245 (66)	15% (7, 23%), P < .01	49/199 (25)	35/240 (15)	10% (3, 18%), P < .01
Metoclopramide + diphenhydramine + dexamethasone	47/55 (85)	36/49 (73)	12% (-3, 27%), P = .13	20/56 (36)	6/49 (12)	23% (8, 39%), P < .01
Metoclopramide alone	43/61 (70)	27/47 (57)	13% (-5, 31%), P = .16	8/63 (13)	4/46 (9)	4% (-8, 16%), P = .51
Ketorolac	29/61 (48)	30/48 (63)	-15% (-4, 34%), P = .12	10/60 (17)	7/48 (15)	2% (-12, 16%), P = .77
Valproate	25/59 (42)	21/50 (42)	0% (-18, 19%), P = .97	3/60 (5)	1/50 (2)	3% (-4, 10%), P = .40

Table 4.—Adverse Events by Sex and Age Listed for Each Medication Regimen

Medication	Any adverse events					
	Men (n/N) (%)	Women (n/N) (%)	Difference between men and women (95%CI), P value	Adults ≤35 years (n/N) (%)	Adults ≥36 years (n/N) (%)	Difference between age groupings (95%CI), P value
Metoclopramide + diphenhydramine	19/67 (28)	138/381 (36)	-8% (-20, 4%) <i>P</i> = .21	65/201 (32%)	92/247 (37%)	-5% (-14, 4%) <i>P</i> = .28
Metoclopramide + diphenhydramine + dexamethasone	9/19 (47)	34/87 (39)	8% (-16, 33%) <i>P</i> = .51	16/57 (28%)	27/49 (55%)	-27% (-45, -9%) <i>P</i> < .01
Metoclopramide alone	4/18 (22)	20/92 (22)	0% (-20, 21%) <i>P</i> = .96	11/63 (17%)	13/47 (28%)	-10% (-26, 6%) <i>P</i> = .20
Ketorolac	5/17 (29)	28/93 (30)	-1% (-24, 23%) <i>P</i> = .95	20/61 (33%)	13/48 (27%)	6% (-12, 23%) <i>P</i> = .52
Valproate	4/19 (21)	21/91 (23)	-2% (-22, 18%) <i>P</i> = .85	13/60 (22%)	12/50 (24%)	-2% (-18, 13%) <i>P</i> = .77

exogenous hormones because we did not envision this analysis when we designed the randomized trials. Therefore, we are unable to comment on whether these additional data would have influenced our results. In experimentally induced pain

studies in humans, phase of menstrual cycle has been associated with sensitivity to painful stimuli.¹⁷

Also, we included patients in the original studies if the acute headache duration was greater than 72 hours, less than 4 hours, or if the patients had

Table 5a.—Results of Multivariate Regression Modeling With Age Dichotomized at the Median

	One hour headache relief OR (95%CI)	Sustained headache freedom OR (95%CI)	Adverse medication effects OR (95%CI)
Demographic variables			
Sex (female relative to male)	0.98 (0.66, 1.46)	0.72 (0.45, 1.15)	1.14 (0.77, 1.71)
Age (≥ 36 relative to ≤ 35 years)	0.66 (0.49, 0.88)	0.50 (0.34, 0.73)	1.36 (1.02, 1.82)
Medications administered			
Metoclopramide + diphenhydramine + dexamethasone relative to metoclopramide alone	2.19 (1.18, 4.09)	2.79 (1.31, 5.92)	2.44 (1.34, 4.43)
Metoclopramide + diphenhydramine relative to metoclopramide alone	1.50 (0.96, 2.36)	2.12 (1.11, 4.07)	1.86 (1.14, 3.06)
Ketorolac relative to metoclopramide alone	0.64 (0.37, 1.11)	1.55 (0.70, 3.45)	1.55 (0.84, 2.86)
Valproate relative to metoclopramide alone	0.40 (0.23, 0.69)	0.31 (0.10, 0.99)	1.05 (0.55, 1.98)

The following variables were entered and included in this model: sex, age (dichotomized), and 4 “dummy” variables representing the medications the patients received. Aura had a negligible impact on this model (Appendix Table A4). Similarly, nausea and duration of headache, variables that were discrepant between the groups at baseline, had a minimal impact on the model (Appendix Table A5).

Table 5b.—Results of Multivariate Regression Modeling With Age in Years as a Continuous Variable

Variable	Short-term headache relief OR (95%CI)	Sustained headache freedom OR (95%CI)	Adverse medication effects OR (95%CI)
Demographic variables			
Sex (female relative to male)	0.96 (0.64, 1.44)	0.71 (0.44, 1.14)	1.16 (0.77, 1.73)
Age, per year	0.98 (0.96, 0.99)	0.97 (0.95, 0.98)	1.01 (1.00, 1.03)
Medications administered			
Metoclopramide + diphenhydramine + dexamethasone relative to metoclopramide alone	2.16 (1.16, 4.03)	2.73 (1.28, 5.79)	2.47 (1.36, 4.49)
Metoclopramide + diphenhydramine relative to metoclopramide alone	1.50 (0.96, 2.36)	2.10 (1.09, 4.04)	1.88 (1.15, 3.09)
Ketorolac relative to metoclopramide alone	0.61 (0.35, 1.07)	1.53 (0.69, 3.40)	1.58 (0.85, 2.90)
Valproate relative to metoclopramide alone	0.38 (0.22, 0.65)	0.29 (0.09, 0.93)	1.08 (0.57, 2.04)

The following variables were entered and included in this model: sex, age (continuous), and 4 “dummy” variables representing the medications the patients received.

fewer than 5 similar lifetime headaches. Thus, this study population is mixed and includes patients with migraine with and without aura and probable migraine with and without aura. However, neither aura nor duration of headache meaningfully modified the association between the predictor variables and the outcomes of interest (Appendix Table A5).

Another limitation is that we performed multiple similar analyses, thereby increasing the risk of type 1 error. For both sex and age, we determined whether there was an association with short-term headache relief, sustained headache freedom, and adverse medication events – thus we performed 6 primary analyses. This concern is the greatest for the association between age and adverse medication events, where the results are statistically significant, but not robustly so. This association in particular should be viewed with skepticism until validated in subsequent work.

Finally, our data were collected predominantly from an underserved population in the Bronx, NY. Although validity is not compromised by the demographics of this population, generalizability of these data to populations drawn from other socioeconomic strata and catchment areas is necessarily limited.

DISCUSSION

In this analysis of nearly 900 patients gathered from 3 acute migraine randomized clinical trials performed over a 9-year period, sex was not associated with short-term headache relief, sustained headache freedom, or adverse events. Age, however, was associated with both short-term and sustained efficacy as well as adverse events.

Regarding the lack of association between sex and migraine outcomes, we identified similar data from the outpatient setting. In a post hoc analysis of pharmaceutical data, men and women demonstrated comparable rates of short-term and sustained headache relief after oral triptans.¹⁸ However, other investigators reported that women experience migraine recurrence after successful treatment with oral triptans more frequently than men.^{19,20} We were not able to replicate this latter finding in our analysis of sustained headache response, which incorporates the potential for headache recurrence. In the broader arena of acute pain, men and women did not demonstrate any substantial differences in response to either 400 mg of oral ibuprofen²¹ or placebo²² after molar extraction surgery. Sex-based comparisons of opioids for acute pain have provided heterogeneous data.²³ When

aggregated, these data do not demonstrate sex-based differences in response to opioids among general pain patients.

In our multivariate models, age was inversely associated with efficacy and directly associated with propensity for adverse events. However, analyzing these data by specific treatment demonstrates a more nuanced truth. Bivariate analyses performed for each medication type revealed that older adults were less likely to respond to combinations of metoclopramide and diphenhydramine. Age-associated disparities in efficacy were not apparent with either ketorolac or valproate. Because the bulk of our data come from patients who received metoclopramide, these data do not necessarily translate to other medication classes. The clinical relevance of these findings is uncertain because while adults older than 35 years may be less likely to respond to metoclopramide regimens, it is not clear that they are any more likely to respond to alternate treatment regimens. Therefore, one should not reject metoclopramide in adults older than 35 years based solely on these data.

As with efficacy, the association between age and adverse effects is mostly attributable to reactions to one medication, in this case, dexamethasone. Adults older than 35 years experienced an adverse event rate of more than 50% when receiving dexamethasone. Because the benefit of dexamethasone for patients with acute episodic migraine is relatively modest,²⁴ clinicians may wish to avoid administering this medication to these patients.

We can hypothesize a variety of explanations for age-related disparities in medication efficacy. Age-related alterations in pharmacodynamics may impact drug bioavailability. Alternatively, the explanation for reduced efficacy may lie within nociceptive pathways. Experimental induced pain studies have indicated that endogenous pain modulation declines with age, affecting the middle-aged as well as the elderly.^{25,26} Our data suggest that middle-aged migraine patients may indeed respond differently to headache, and its treatment, than younger patients. Finally, one can hypothesize an explanation based on psychological response to investigational medication. Middle-aged adults with migraine were less likely to respond to oral placebo

in outpatient triptan trials than younger adults.²⁷ Thus, these data may not represent a difference in true efficacy at all, but rather a diminished expectation of treatment benefit.

We were unable to find other clinical data that addressed the association between age and response to acute parenteral migraine medication. As with sex, other investigators have reported that middle-aged adults were more likely than younger adults to report recurrence of headache after using an oral triptan.²⁸ This finding was not supported in our assessment of sustained outcomes, which included the potential for headache recurrence.

Several other findings are worth highlighting. First, there was a very large predominance of women enrolled in these clinical trials. These data are consistent with population-based data, which demonstrate that among young and middle-aged adults, women are more than 3 times as likely to suffer from migraine as men,⁴ and 30% more likely to visit an ED for migraine.³ Second, as has been reported in other settings, women were slightly more likely to report severe pain and nausea at baseline.⁶ These findings support data indicating that women experience migraine differently than men.³ We are the first to report that older adults are more likely than younger adults to report severe headache and nausea at baseline.

There have been multiple calls in the headache, general pain, and emergency medicine literature for clinically oriented, sex-based analyses of response to treatment.^{29–31} Age-based disparities in response to intravenous migraine medication have never been reported. We intended this analysis to address these gaps in current knowledge. By aggregating data from similar studies, we were able to include data from a sufficient number of men so that a meaningful sex-based analysis could be performed. Future work should investigate sex- and age-based response to other parenteral migraine medications, including migraine-specific agents such as sumatriptan and dihydroergotamine.

In conclusion, in this analysis of aggregated data from nearly 900 ED migraine patients, we did not identify sex-based differences in response to parenteral acute migraine medication. Age was associated with both efficacy and adverse events.

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APPENDIX A. SUPPLEMENTARY DATA

Table A1.—Descriptions of the 3 Studies That Were Pooled to Create the Dataset

Study (year of publication)	Interventions (N)	Location	Inclusion criteria	Exclusion criteria
Study 1 (2007)	Arm A: Metoclopramide 20 mg IV + Diphenhydramine 25 mg IV + Dexamethasone 10 mg IV (106) Arm B: Metoclopramide 20 mg IV + Diphenhydramine 25 mg IV + Placebo (99)	4 EDs in New York City	Adult patients with ICHD2 migraine without aura, migraine with aura, probable migraine with or without aura (Probable migraine was included only if the acute headache lasted between 2 and 4 hours or 72 and 168 hours)	Patients were excluded if the attending emergency physician intended to perform a lumbar puncture in the ED. Patients were also excluded for persistent objective focal neurologic deficits, temperature greater than 100.3°, pregnancy, lactation, or allergy or intolerance to any of the study medications. Patients could only enroll once
Study 2 (2011)	Arm A: Metoclopramide 10 mg IV + Diphenhydramine 25 mg IV (113) Arm B: Metoclopramide 20 mg	1 ED in the Bronx, NY	Adult patients younger than 70 with ICHD2 migraine. If the acute headache met all migraine criteria, with the exception of	Patients were excluded if they had a secondary headache (an “organic” headache), if the patient was to receive a lumbar puncture in the ED, or if they had a maximum

Table A1.—Continued

Study (year of publication)	Interventions (N)	Location	Inclusion criteria	Exclusion criteria
Study 3 (2014)	IV + Diphenhydramine 25 mg (118) Arm C: Metoclopramide 40 mg IV + Diphenhydramine 25 mg IV (118) Arm A: Valproate 1 g IV (110) Arm B: Metoclopramide 10 mg IV (110) Arm C: Ketorolac 30 mg IV (110)	1 ED in the Bronx, NY	prolonged duration (>72 hours) or insufficient duration (<4 hours), it was included in the study Adult patients who presented to the ED with acute migraine or acute probable migraine headache as defined by ICHD2 were eligible for participation. Patients with acute probable migraine were only eligible if their reason for not meeting full migraine criteria was insufficient number of total lifetime headaches (5) or prolonged duration of headache (>72 hours)	documented temperature greater than 100.3°F, a new objective neurologic abnormality, allergy or intolerance to a study medication, previous enrollment, or pregnancy Patients were excluded for secondary headache or if they were to receive a lumbar puncture in the ED. Patients were also excluded for a temperature of ≥ 100.4°F, a new objective neurologic abnormality, seizure disorder, concurrent use of an investigational medication, pregnancy, lactation, previous enrollment, or for allergy, intolerance, or other contraindication to any of the investigational medications, including hepatic dysfunction, peptic ulcer disease, or concurrent use of immunosuppressives or a monoamine oxidase inhibitor

Table A2.—Characteristics of Participants in Each of the 3 RCTs Included in This Analysis

Study (year of publication)	Age in years (SD)	Female (%)	Race/ethnicity (%)	Used any medication to treat headache prior to ED presentation (%)	Median baseline pain score on 0 to 10 scale (IQR)
Study 1 (2007)	36 (10)	85	Asian 1 Black 24 Latino 69 White 4 Other 2	71	8 (7, 10)
Study 2 (2011)	38 (11)	84	Asian 1 Black 21 Latino 68 White 3 Mixed 5 Other 3	63	9 (7, 10)
Study 3 (2014)	35 (11)	84	Asian 1 Black 22 Latino 66 White 2 Mixed 7 Other 2	72	9 (8, 10)

Table A3.—Outcomes Divided Into 5-Year Age Increments

Age (years)	One hour headache relief % (N)	Sustained headache freedom % (N)	Adverse events % (N)
18–22	63 (64)	22 (67)	24 (67)
23–27	74 (156)	25 (155)	33 (158)
28–32	74 (132)	19 (133)	25 (134)
33–37	63 (120)	13 (121)	30 (122)
38–42	66 (130)	11 (128)	34 (132)
43–47	61 (119)	15 (117)	34 (119)
48–52	67 (78)	13 (77)	47 (78)
53–57	49 (37)	11 (37)	38 (37)
≥58	62 (34)	12 (34)	24 (34)

Table A4.—The Influence of “Aura” on Outcome—Results of the Regression Models When Aura Is Included as a Variable in the Model

Variable	One hour headache relief OR (95%CI)	Sustained headache freedom OR (95%CI)	Adverse medication effects OR (95%CI)
Demographic variables			
Sex (female relative to male)	1.01 (0.68, 1.51)	0.73 (0.49, 1.17)	1.12 (0.75, 1.67)
Age (≥ 36 relative to ≤ 35 years)	0.66 (0.49, 0.89)	0.49 (0.34, 0.72)	1.37 (1.02, 1.83)
Medications administered			
Metoclopramide + diphenhydramine + dexamethasone relative to metoclopramide alone	2.30 (1.23, 4.33)	2.70 (1.26, 5.76)	2.50 (1.37, 4.55)
Metoclopramide + diphenhydramine relative to metoclopramide alone	1.47 (0.94, 2.32)	2.05 (1.06, 3.95)	1.92 (1.17, 3.16)
Ketorolac relative to metoclopramide alone	0.64 (0.37, 1.11)	1.54 (0.69, 3.42)	1.53 (0.83, 2.83)
Valproate relative to metoclopramide alone	0.40 (0.23, 0.69)	0.30 (0.09, 0.97)	1.03 (0.55, 1.96)
Migraine symptoms			
Aura	0.87 (0.64, 1.18)	0.71 (0.48, 1.05)	1.27 (0.94, 1.71)

Table A5.—The Influence of Disparate Baseline Variables on Outcome—Results of the Regression Models When “Baseline Nausea” and “Headache Duration” Are Included as Variables in the Model

Variable	One hour headache relief OR (95%CI)	Sustained headache freedom OR (95%CI)	Adverse medication effects OR (95%CI)
Demographic variables			
Sex (female relative to male)	1.04 (0.69, 1.59)	0.85 (0.51, 1.41)	1.16 (0.78, 1.74)
Age (≥ 36 relative to ≤ 35 years)	0.70 (0.51, 0.95)	0.54 (0.36, 0.80)	1.37 (1.03, 1.83)
Medications administered			
Metoclopramide + diphenhydramine + dexamethasone relative to metoclopramide alone	2.21 (1.17, 4.17)	2.49 (1.16, 5.35)	2.51 (1.37, 4.59)
Metoclopramide + diphenhydramine relative to metoclopramide alone	1.46 (0.91, 2.33)	2.08 (1.07, 4.06)	1.91 (1.16, 3.15)
Ketorolac relative to metoclopramide alone	0.58 (0.33, 1.01)	1.38 (0.61, 3.11)	1.56 (0.84, 2.87)
Valproate relative to metoclopramide alone	0.37 (0.21, 0.64)	0.30 (0.09, 0.97)	1.05 (0.56, 2.00)
Variables added to the model due to baseline between-group discrepancies			
Nausea	0.57 (0.42, 0.78)	0.69 (0.47, 1.02)	1.01 (0.76, 1.36)
Duration of headache			
24–48 hours vs 0–24 hours	0.52 (0.33, 0.83)	0.62 (0.33, 1.19)	1.01 (0.65, 1.58)
48–72 hours vs 0–24 hours	1.07 (0.67, 1.72)	1.53 (0.91, 2.57)	1.05 (0.69, 1.60)
>72 hours vs 0–24 hours	0.92 (0.63, 1.34)	0.77 (0.47, 1.26)	1.13 (0.79, 1.61)



PACAP27 induces migraine-like attacks in migraine patients

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Abstract

Introduction: Pituitary adenylate cyclase-activating polypeptide (PACAP) is found in two functional isoforms, namely PACAP38 and PACAP27. The migraine-inducing properties of PACAP38 are well studied. However, it is not known whether the lesser-known and under-studied protein isoform, PACAP27, can also induce migraine attacks. Here, we studied the effect of human PACAP27 infusion on induction of migraine in a provocation model.

Methods: In a crossover study, 20 migraine without aura patients were randomly assigned to receive human PACAP27 (10 picomol/kg/min) or saline (placebo) infusion over 20 min. We recorded the migraine and associated symptoms.

Results: All patients completed the study. PACAP27 provoked migraine-like attacks in 11 patients (55%) and two developed attacks after placebo (10%) ($p = 0.022$). The headache intensity and duration after PACAP27 was significantly greater compared to placebo ($p = 0.003$).

Conclusion: PACAP27 triggers migraine attacks without aura. These novel data strengthen the role of PACAP and its receptors in migraine pathogenesis.

Keywords

Pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal polypeptide, migraine, headache, flushing, cyclic adenosine monophosphate

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Introduction

The novel multifunctional neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) is highly conserved and found in two major isoforms: PACAP38 and PACAP27 (1,2). PACAP38 is the major isoform (3) and the lesser-known and under-studied isoform, PACAP27, is an amidated form of PACAP38, representing 10% of total PACAP in the body (4). PACAP isoforms and vasoactive intestinal polypeptide (VIP) are member of the secretin peptide superfamily (1). PACAP27 shows 68% homology in amino acid sequences with VIP (1). PACAP isoforms and their receptors are expressed in anatomical structures related to migraine (5,6), specifically in the trigeminal ganglion (7–9), perivascular nerve fibers and trigeminal nucleus caudalis (TNC) (10,11).

Interestingly, both isoforms have many similarities; however, some pharmacological differences have been reported (11–17). PACAP38's migraine-provoking properties are well established (18–21). In contrast, VIP provoked no migraine in one study (22) and

migraine attacks in few patients in another study (19). PACAP isoforms and VIP share three G-protein-coupled receptors (GPCRs), namely PAC₁, VPAC₁, and VPAC₂ (4). PACAP isoforms bind with PAC₁R with higher affinity (15) and activate the receptor approximately 1000-fold greater than that of VIP (2). PACAP38 provocation studies in migraine patients suggested PACAP or the PAC₁ receptor as a possible novel target for migraine prevention (18,23).

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PACAP isoforms share several key pharmacological features, particularly their equipotent high affinity to the PAC₁ receptor (24), yet PACAP27's migraine-provoking properties have not been studied. Thus, we hypothesised that PACAP27 would provoke migraine-like attacks and induce flushing in a similar manner to PACAP38 in patients. To investigate this, we designed a double-blind crossover, placebo-controlled study using intravenous infusion of human PACAP27 in migraine without aura patients. Additionally, we used laser speckle contrast imaging to quantify and assess the effect of PACAP27 on the facial microvasculature.

Material and methods

Migraine without aura patients of both sexes were recruited via forsoegsperson.dk, a website for recruitment of volunteers to clinical research. All patients were invited by phone for further screening at the Rigshospitalet-Glostrup. All migraine patients were interviewed and physically examined by a trained physician (HG). Inclusion criteria were: age 18–60 years old; a minimum of two migraine without aura attacks per month as defined according to the ICHD-3 (beta) criteria (25). All female patients were allowed to take oral contraceptives. Exclusion criteria were: any medical conditions (except tension-type headache under five days per month and migraine without aura).

The Capital Region Ethics Committee of Denmark (H-17016232) approved the study protocol and the study was registered at Clinicaltrials.gov (ID: NCT03471039). In accord with the Declaration of Helsinki 2013 version, informed consent was obtained after oral and written information were provided. The study was performed between January 2018 and August 2018.

Experimental design

In a placebo-controlled study, 20 patients were randomly allocated to receive infusion of human PACAP27 (10 picomol/kg/min) (Bachem AG, Bubendorf, Switzerland) or placebo (saline) over 20 min in a double-blinded fashion on two different experiment days separated by a minimum of one week. This concentration was chosen based on earlier studies with PACAP38 that showed this dose induces migraine-like attacks and is well tolerated (18,19,21). A balanced randomisation was performed by the Capital Region Central Pharmacy to allocate patients equally to receiving infusion of PACAP27 or saline (placebo) on the first study day.

The experiment was canceled if the patient reported a migraine attack within 5 days, had taken any analgesics, or experienced headache two days prior to the experiment. Twelve hours before the start of the

experiment, all patients were prohibited from consuming alcohol, cocoa, tea, coffee and caffeine, and smoking. Pregnancy tests were conducted on female patients on both study days.

Patients were placed in a supine position and a venous catheter was inserted into the right or left antecubital vein for PACAP27 or placebo infusion. The study was conducted in a temperature and light (dimmed) controlled lab at the same time of day ±1 h. After a rest, the baseline values were recorded in the following order: a) A well-validated headache questionnaire was used to record headache/migraine intensity and characteristics; b) an electrocardiogram was obtained; c) facial flushing was measured using a speckle contrast imager (moorFLPI, Moor Instruments, Devon, UK); d) mean arterial blood pressure (MAP) and heart rate (HR) were measured. After assessment of all baseline measurements, the infusion of PACAP27 was initiated from 0–20 min (Figure 1). All recordings were repeated every 10 min until 120 min. The study was completed after 2 hours and the patients were discharged from the hospital with a headache questionnaire to fill in every hour for 13 h post infusion. Patients were instructed to use their usual migraine medication as needed after completion of the experiment.

Migraine-like attack criteria

According to the ICHD-3 (26), migraine attacks are spontaneous and last a minimum of 4 hours, if untreated. A migraine attack typically evolves slowly, and it may take hours before the criteria are met. However, in migraine provocation studies, the participants must be allowed to take rescue medication if needed. Therefore, as previously described, well-validated criteria for experimentally induced migraine-like attacks were used (27).

Headache and associated symptoms

The headache and migraine-associated symptoms, including premonitory symptoms, were recorded in the following order using a standard questionnaire: Nausea, vomiting, photophobia, phonophobia, unusual fatigue, craving, yawning, thirst, mood swings, facial flushing and difficulty in concentrating. We used a numerical rating scale (NRS) from 0 to 10 to obtain headache and migraine pain intensity, as published previously (28).

Facial skin blood flow

We measured blood flow intensity and fluctuation using the laser speckle contrast technique (moorFLPI, Moor Instruments, Devon, UK) as previously described (29–31). The contrast imager was manually optimised and placed 30 cm perpendicularly above the face of the

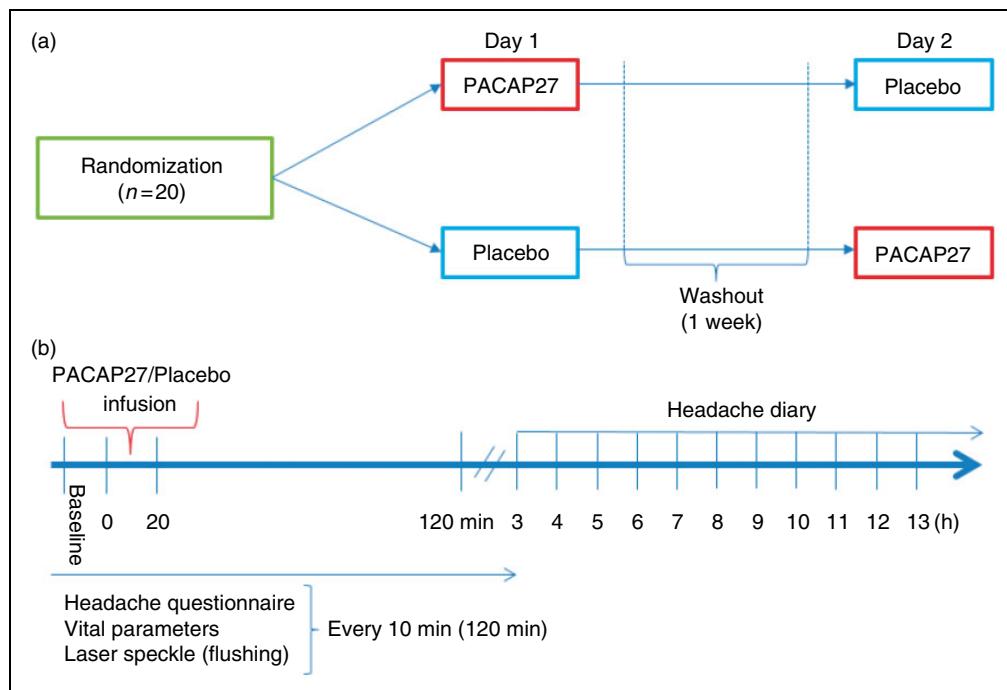


Figure 1. (a) Study design diagram. (b) Work flow chart of the methodological procedures during hospital phase (0–120 min) and post-hospital phase (3–13 hours).

patients. The laser speckle contrast imager measured facial skin blood flow automatically every 10 seconds. Approximately 1 minute before each of the chosen measurement time points, the patients were instructed to remain still for a minute. All patients were instructed to stay still in a supine position with closed eyes during the measurements.

Statistics and data analysis

All data are presented as mean \pm standard deviation (SD) except the headache intensity scores, which are presented with individual data sets and median score. Furthermore, data shown in percentage changes are presented with a 95% confidence interval (CI).

We have calculated the sample size by determining the risk of type 1 error at 5% and defined a power at 80%. According to the study protocol, the type 2 error was fixed at 20%. Therefore, we estimated a requirement to include 20 patients in the study. In accordance with the trapezium rule (32), we applied the area under the curve (AUC) as a summary measure for analysing the difference in response between PACAP27 and placebo. We have set the difference between incidence of migraine headache and AUC for headache score (0–13 h) between PACAP27 and placebo as the primary endpoints of the study. The differences in secondary endpoints were in AUC (0–120 min) for facial skin blood flow, HR and MAP. Prior to the experiment

initiation, the baseline was defined at time t_0 . In order to limit within-participant variation between experiment days, the baseline values were subtracted before calculating AUC. The non-parametric Wilcoxon signed rank test was used to compare AUC and baseline differences of all variables between PACAP27 and placebo. The Mann-Whitney test was used to test for period and carry-over effects for all baseline variables.

All statistical analyses were carried out using SPSS version 23.0 (Chicago, IL, USA) and no adjustments were made for multiple analyses. Five percent ($p < 0.05$) was accepted as the level of significance.

Results

Twenty patients completed both days of the experiment. The mean age of patients was 29 (range 18–52 years) and mean weight was 70 kg (range 52–91 kg). We tested the baseline values of MAP and HR ($p > 0.05$) for carry-over or period effect. Laser speckle data from seven patients were blindly excluded from analysis due to technical issues and artifacts.

Migraine-like attacks and associated symptoms

Eleven patients (55%) reported migraine-like attacks after PACAP27 infusion while only two patients reported this after placebo (10%) ($p = 0.022$). Median time for initiation of migraine-like attacks was 3 h

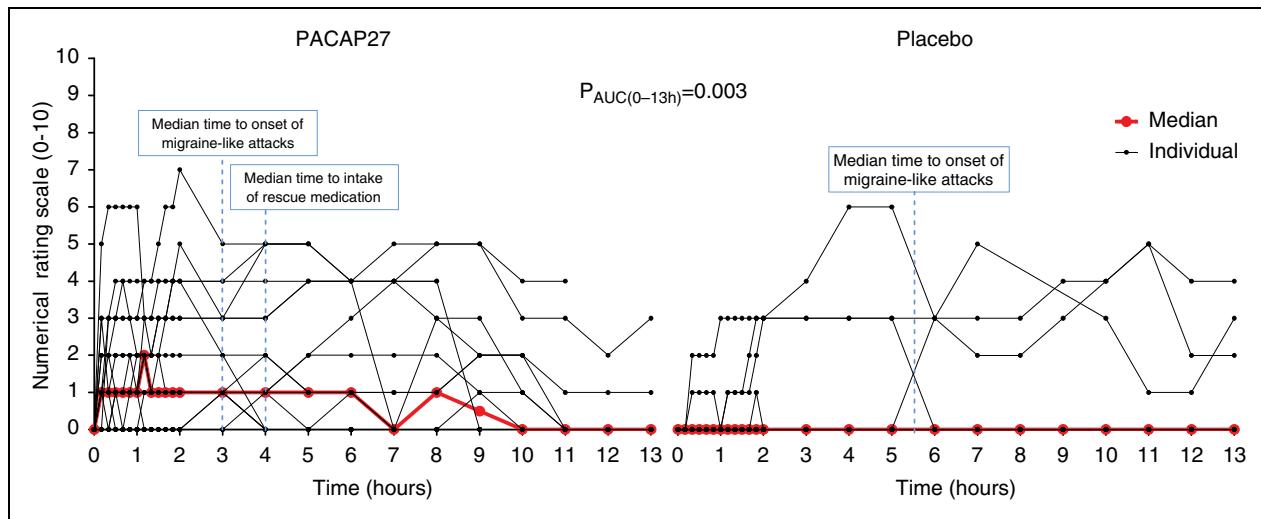


Figure 2. Individual (black lines) and median (red line) headache intensity. The median peak headache score was 2.5 (range 0–7) after PACAP27 compared to 0 (range 0–5) after placebo.

(range 30 min – 7 h) and median time for headache onset was after 10 min (range 10 min – 3 h). Furthermore, the headache intensity score AUC_{0-13h} was larger after PACAP27 compared to placebo ($p=0.003$) (Figure 2). The peak headache intensity score was 2.5 (range 0–7) and the median headache duration was 2 h (range 10 min – 7 h) after PACAP27 and 0 (range 0–6) and 3 h (range 20 min – 11 h) after placebo.

The incidence of the migraine-associated symptoms nausea ($p=0.016$), photophobia ($p=0.039$) and fatigue ($p=0.008$) was significant after PACAP27 compared to the placebo day. The time to onset of nausea after PACAP27 infusion was 4 h (range 2–13 h), corresponding to the median time for onset of migraine-like attack (3 h) (Figure 3). We found no difference in incidence of phonophobia ($p=0.125$). Table 1 shows migraine and headache-associated symptoms and characteristics.

Vital signs and facial skin blood flow

PACAP27 induced increased facial skin blood flow ($p=0.001$) (Figure 4). The $AUC_{0-120\text{ min}}$ for HR was higher after PACAP27 compared to placebo ($p<0.001$). $AUC_{0-120\text{min}}$ for MAP ($p=0.305$) was unchanged (Figure 5).

Headache and adverse events

Eighteen out of 20 patients reported headache after PACAP27 infusion, with a median headache duration of 7 h (range 1–13 h) compared to six out of 20 after placebo (median 5.5 h, range 20 min – 13 h).

PACAP27 induced palpitation, heat sensation and flushing in all patients ($p<0.001$). Forty-five percent of patients experienced fatigue after PACAP27

compared to 5% after placebo ($p=0.008$). (Figure 2, Table 2). We found no difference in incidence of other adverse events ($p>0.05$).

Discussion

This study presents novel data on PACAP27-provoked migraine-like attacks in patients with migraine without aura. The headache and migraine-eliciting properties of PACAP27 (10 picomol/kg/min) were similar to the effect of PACAP38 infusion (10 picomol/kg/min) (18). Table 3 summarises incidence of recorded variables in the present study compared to previously published variables after PACAP38 (18) infusion in migraine without aura patients. Both PACAP isoforms induced delayed migraine-like attacks with similar median onset time (PACAP27: 3 h, PACAP38: 4 h). The incidence of autonomic symptoms such as palpitation, heat sensation and long-lasting flushing were also similar in both studies. The incidence of nausea was numerically higher after PACAP27 (40%) compared to after PACAP38 (17%), but *post hoc* analysis revealed no difference. The blinding of the present study might have been compromised by PACAP27 induced autonomic symptoms including flushing, heat sensation and palpitations. However, we used a double-blind crossover study design to avoid methodological errors.

PACAP is a potent local and systemic vasodilator across several species, and both isoforms dilate intra-cerebral and meningeal arteries with the same potency in animal models (24). In contrast to PACAP38, the vasorelaxant effect of PACAP27 shows regional differences, with a larger effect on the middle cerebral artery (MCA) and anterior cerebral arteries compared to the basilar artery in animals (33). In migraine (19) and

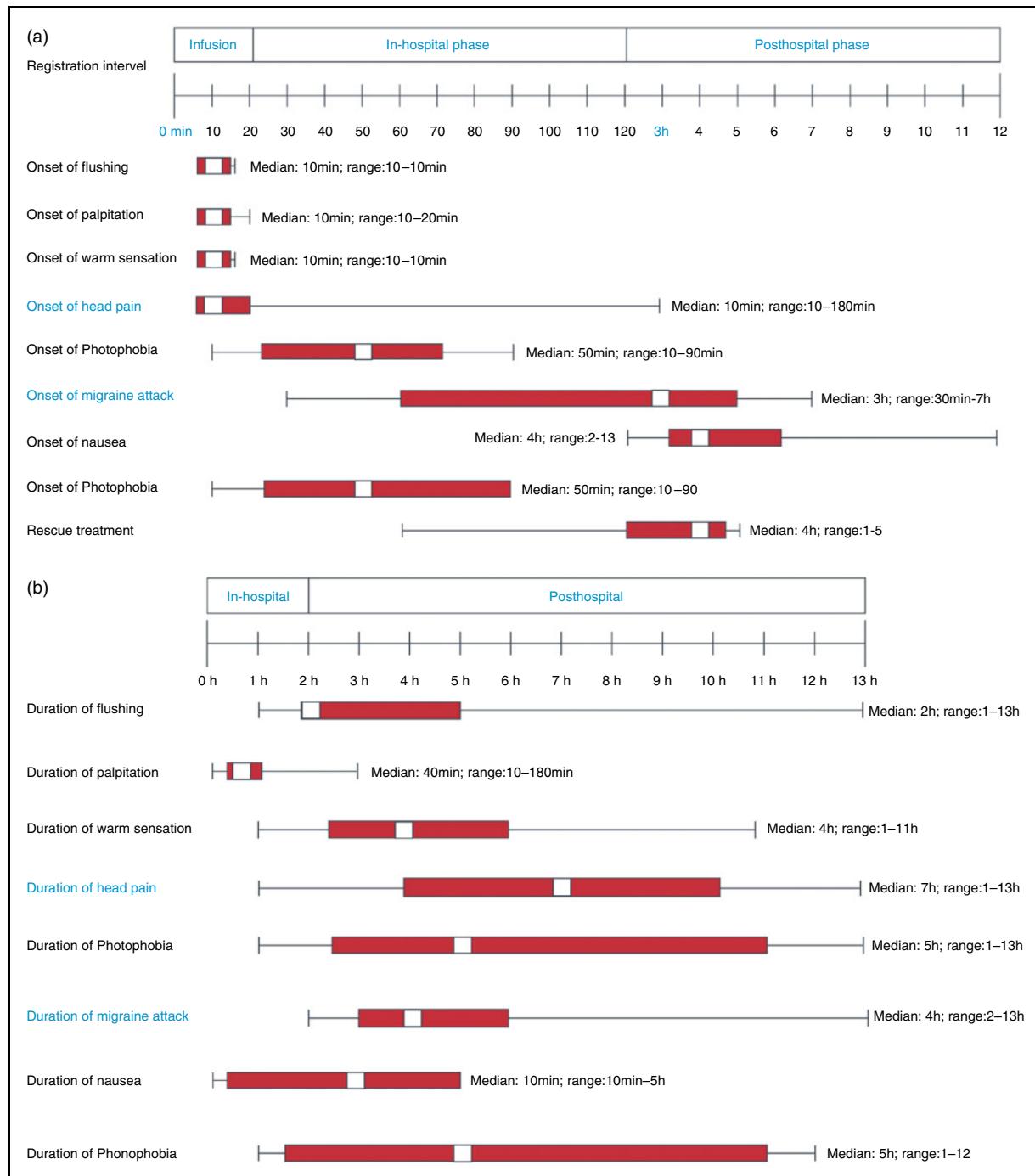


Figure 3. PACAP27-induced migraine associated symptoms and adverse events. (a) Onset time of each parameter. (b) Duration of each parameter. White box: Median. Red box: percentile 25–75%.

healthy participants (34), PACAP38 caused a prolonged dilatation (>2 h) of extracranial arteries. We assessed facial skin blood flow intensity and showed that PACAP27 induced sustained dilatation of facial vasculature for up to >2 h (Figure 4). Three patients in the placebo group reported flushing in the post-hospital phase (3–13 h), including the two patients that developed migraine. However, we found no

flushing in these patients during the hospital phase (0–2 h). To our knowledge, this is the first study to quantify facial flushing induced by a vasoactive peptide in migraine patients. Laser speckle can independently verify any hemodynamic change in facial vasculature. Therefore, we propose that future migraine studies should look at correlation between facial flushing intensity and migraine induction.

Table 1. Characteristics of headache and associated symptoms in migraine without aura patients after PACAP27 and placebo (0–13 h).

Patient		Peak headache (Duration of headache)	Headache characteristics ^a	Associated symptoms ^b	Mimics usual migraine	Migraine-like attacks (onset) ^c	Treatment (time)/efficacy ^d
1	Spontaneous PACAP27	30 min (3 h)	Right/5/pres/+	+/-/+	Yes	Yes (1 h)	Inj. Sumatriptan 6 mg (60)/Yes
	Placebo		None	-/-/-			
2	Spontaneous PACAP27	11 h (12 h)	Bilat/5/throb/+	+/-/+	Yes	Yes (4 h)	Rizatriptan 10 mg (4)/Yes
	Placebo		Right/6/throb/-	-/+/-			
3	Spontaneous PACAP27	20 min (30 min)	Right/8/throb/+	+/-/+	No	No	None
	Placebo		Bilat/2/pres/-	-/-/-			
4	Spontaneous PACAP27	7 h (1 h)	Right/5/throb/+	+/-/-	Yes	Yes (7 h)	None
	Placebo		Right/8/pres/+	+/-/+			
5	Spontaneous PACAP27	90 min (6 h)	Right/6/throb/+	-/-/+	No	No	None
	Placebo		Diffus/4/pres/-	-/-/-			
6	Spontaneous PACAP27	11 h (12 h)	Diffus/5/pres/+	-/-/-	No	No	Paracetamol 1 g (11 h)/Yes
	Placebo		Left/1/throb/-	+/-/+			
7	Spontaneous PACAP27	10 min (3 h)	Right/8/throb/+	+/-/+	No	Yes (30 min)	None
	Placebo		Bilat/1/throb/+	-/+/-			
8	Spontaneous PACAP27	7 h (6 h)	Right/8/pres/+	+/-/+	No	No	None
	Placebo		Bilat/5/pres/+	-/-/-			
9	Spontaneous PACAP27	1 h (5 h)	Right/8/throb/+	+/-/+	Yes	Yes (7 h)	None
	Placebo		Bilat/5/throb/+	+/-/+			
10	Spontaneous PACAP27	2 h (10 h)	Bilat/3/throb/+	-/-/-	Yes	No	None
	Placebo		Right/8/throb/+	+/-/+			
11	Spontaneous PACAP27	110 min (10 min)	Right/5/pres/+	-/+/-	Yes	Yes (3 h)	Sumatriptan 100 mg (3 h)/Yes
	Placebo		Bilat/1/pres/-	-/-/-			
12	Spontaneous PACAP27	2 h (5 h)	Bilat/5/throb/+	+/-/+	Yes	Yes (4 h)	Sumatriptan 50 mg (4 h) / NA
	Placebo		Bilat/5/throb/+	-/+/-			
13	Spontaneous PACAP27	5 h (9 h)	Top/2/pres/-	+/-/+	Yes	No	None
	Placebo		None	-/-/-			

(continued)

Table I. Continued.

Patient		Peak headache (Duration of headache)	Headache characteristics ^a	Associated symptoms ^b	Mimics usual migraine	Migraine-like attacks (onset) ^c	Treatment (time)/efficacy ^d
14	Spontaneous		Left/5/throb/+	+/-/+			
	PACAP27	4 h (13 h)	Left/5/pres/+	+/-/+	No	Yes (70 min)	None
	Placebo	20 min (1 h)	Left/1/pres/-	-/-/-	No	No	None
15	Spontaneous		Right/8/throb/pres/+	+/-/+			
	PACAP27	10 min (2 h)	Right/2/pres/-	-/-/-	Yes	No	None
	Placebo	None					
16	Spontaneous		Bilat/8/throb/+	+/-/+			
	PACAP27	70 min (13 h)	Right/2/throb/+	-/-/-	Yes	No	None
	Placebo	None					
17	Spontaneous		Bilat/8/throb/pres/+	+/-/+			
	PACAP27	5 h (8 h)	Bilat/4/pres/+	+/-/-	Yes	Yes (5 h)	*Treo 550 mg (5 h)/No
	Placebo	None					
18	Spontaneous		Bilat/8/throb/+	+/-/+			
	PACAP27	30 min (6 h)	Right/4/throb+pres/+	+/-/-	Yes	Yes (30 min)	None
	Placebo	None					
19	Spontaneous		Bilat/5/throb/+	+/-/-			
	PACAP27	3 h (4 h)	Right/1/throb/-	+/-/-	Yes	Yes (3 h)	None
	Placebo	None					
20	Spontaneous		Bilat/8/throb/+	-/+/-			
	PACAP27	4 h (6 h)	Bilat/2/pres/-	-/-/-	No	No	Paracetamol 1 g/(4 h)/Yes
	Placebo	6 h (9 h)	Bilat/6/pres/+	-/-/+	Yes	Yes (4 h)	Paracetamol 1 g + Ibuprofen 200 mg (4 h) / Yes

^aLocalization/intensity/quality (throb = throbbing; pres = pressing)/aggravation (by cough during in-hospital phase and by movement during out-hospital phase).

^bNausea/photophobia/phonophobia.

^cMigraine-like attacks are defined according to criteria described in methods.

^dPain freedom or pain relief ($\geq 50\%$ decrease of intensity) within 2 h.

*Acetylsalicylic acid 500 mg and caffeine 50 mg.

Distinct downstream signaling features of the PACAP isoforms are reported (15). Both PACAP isoforms increase cyclic adenosine monophosphate (cAMP) production, while only PACAP38 activated extracellular signal regulated kinase (ERK) in glia cells (15). It has been suggested that PACAP38 is more neuroprotective compared to PACAP27 (16). In an *in vivo* rat study, intrathecal administration of PACAP27 was able to suppress C-fiber-evoked flexion reflex at lower doses than PACAP38 (6). This study suggested that PACAP27 might be a more potent neurotransmitter or neuromodulator in c-fiber signaling than PACAP38. However, the role of PACAP27 in nociceptive signaling and cerebral hemodynamics in humans should be further studied.

Possible mechanisms behind PACAP27 induced migraine-like attack

In the present study, PACAP27 induced migraine-like attacks in 55% of patients, similar to migraine induction after PACAP38 (58–75%) (18–20,35). We found that the incidence of the migraine-associated symptom nausea was numerically higher after PACAP27 compared to PACAP38. This might be due to the longer plasma half-life of PACAP27 (45 min) compared to PACAP38 (less than 5 min) (36). The migraine-inducing action of PACAP27 may originate from several different anatomic sites, as the PACAP isoforms and their receptor are expressed in trigeminovascular structures such as the trigeminal ganglion (7–9),

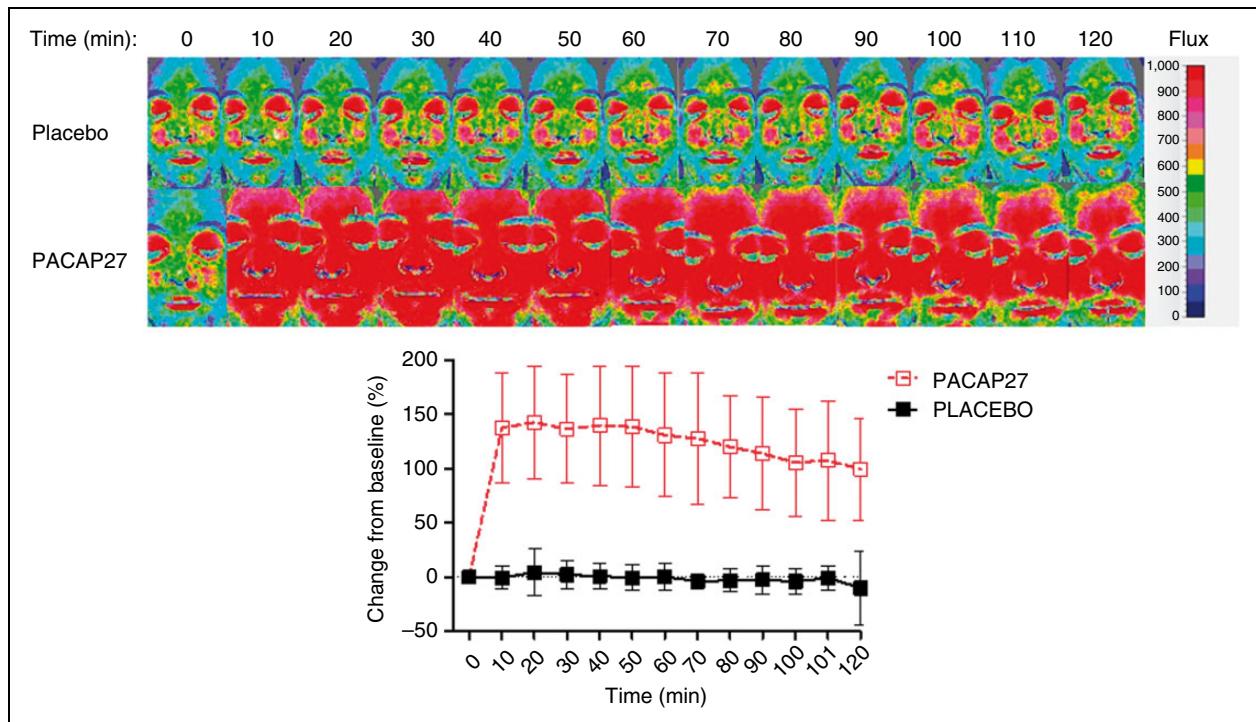


Figure 4. Facial skin blood flow changes after PACAP27 and placebo (0–120 min) shown in percentage change ($n=13$) and direct flux measurement of an individual patient. The complete data sets (PACAP/placebo days) of seven patients were excluded due to movement artifacts, facial hair and other technical issues.

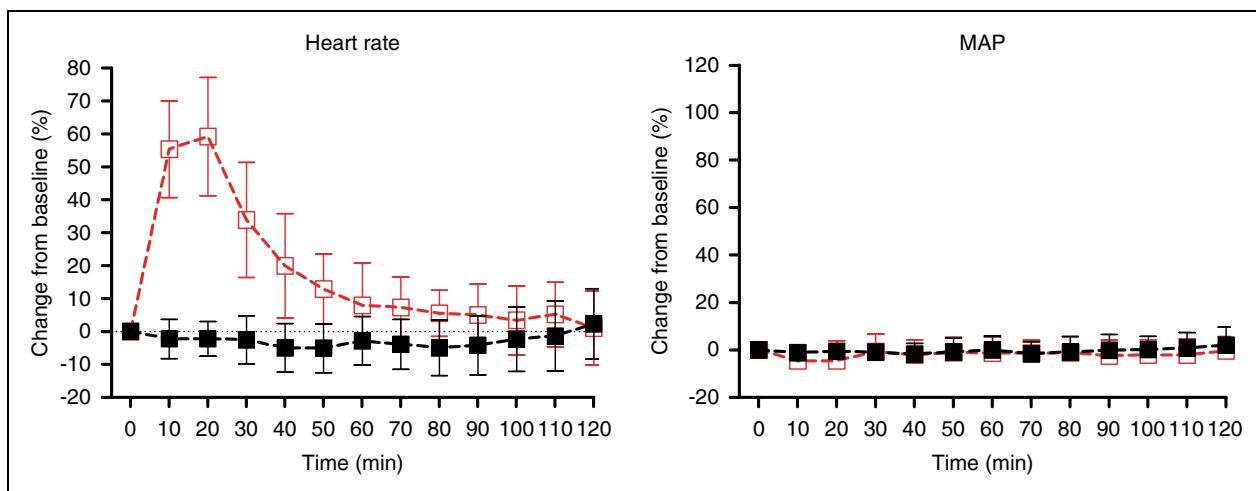


Figure 5. Percentage change from baseline of heart rate and MAP after infusion of PACAP27 (red) and placebo (black).

perivasculär nerve fibers and TNC (10,11). Experimental human migraine models suggested that the PACAP38 migraine-provoking properties might be mediated via the PAC₁ receptor (18), which in turn might lead to delayed sensitisation of the central trigeminovascular neurons (37). It is not known if PACAP27 sensitises central trigeminovascular neurons. In rats, PACAP

isoforms were elevated in the trigeminal nucleus caudalis upon electrical stimulation of the trigeminal ganglion or by intraperitoneal glyceryl trinitrate injection (11). This suggests that PACAP27 may be involved in central pain processing. PACAP27 activates the PAC₁ receptor with similar affinity to PACAP38 (4). The first study of the monoclonal anti-PAC₁ receptor antibody

Table 2. Incidence of adverse events 0–13 h after PACAP27 or placebo.

Adverse events	PACAP27	Placebo	p-value
Palpitation	20	2	<0.001
Flushing	20	3	<0.001
Heat sensation	20	2	<0.001
Nausea	8	1	0.016
Neck stiffness	9	3	0.109
Difficulty concentrating	6	2	0.125
Fatigue	9	1	0.008
Thirst	5	1	0.219

The following adverse events were reported by a few participants: After PACAP27, urge to yawn ($n = 1$), hunger ($n = 1$); after placebo, urge to yawn ($n = 1$) and hunger ($n = 1$).

Table 3. Comparison of variables between PACAP27 and PACAP38.

Variables	PACAP27 (n = 20)	PACAP38 (n = 12)
Headache ^a	90	92
Migraine ^a	55	58
Palpitation	100%	100%
Flushing	100%	100%
Heat sensation	100%	100%
Nausea	40%	17%
Heart rate ^b	59%	70%
Systolic blood pressure ^b	4.5%	6.7%
Diastolic blood pressure ^b	-11.6%	-14.4%

^aHeadache and migraine incidence in percentage.

^bMean change from baseline.

in migraine prevention has been completed (NCT03238781), but data have not yet been reported. Interestingly, a recent study reported a new humanised monoclonal anti-PACAP antibody that was highly selective to PACAP isoforms (38). Future studies will

clarify whether anti-PACAP or its receptors are effective in migraine prevention.

The VPAC₁ and VPAC₂ receptors' role in migraine pathophysiology is not well studied. Both PACAP isoforms can activate VPAC₁ and VPAC₂ receptors (4). Activation of PACAP receptors stimulates cAMP accumulation in smooth muscle cells (1,2). PACAP isoforms increase cAMP at a similar rate (15,39). Furthermore, the activation of VPAC₁ leads to anti-inflammatory processes (40,41), whereas VPAC₂ stimulation induces peripheral vasodilation (42). However, VIP, which has the same affinity to VPAC₁ and VPAC₂ receptors as PACAP isoforms, did not provoke migraine in one study (22) and induced a minimal headache in healthy volunteers (43). This calls into question the role of VPAC₁₋₂ receptors in migraine induction.

It has been suggested that mast cell degranulation in the dura mater (12) may be attributed in migraine pathogenesis (44) and may in part explain the long-lasting vasodilatation caused by PACAP38 (34). PACAP27 is a weak dural mast cell degranulator compared to PACAP38 (12). PACAP27 releases histamine from skin mast cells more effectively than PACAP38 (45). Pretreatment with antihistamine (mepyramine) prevented migraine-like attacks induced by infusion of histamine in migraine without aura patients (46). A recent study reported that pretreatment with H₁-antihistamine and an anticholinergic drug (Clamastine) was unable to prevent PACAP38-induced migraine. This study suggests that mast cell degranulation or histamine release might not play a major part in PACAP38-induced migraine (47).

Conclusion

PACAP27 induced migraine-like attacks in migraine without aura patients with similar incidence rate to PACAP38. These data reinforce PACAP and its receptors' role in migraine pathogenesis and the therapeutic potential of targeting PACAP or its receptors for novel migraine treatment.

Key findings

- PACAP27 induced migraine-like attacks in 55% of patients.
- PACAP27 provoked prolonged headache in 90% of patients.
- PACAP27 increased facial blood flow and heart rate.

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Behavioral treatment for migraine prophylaxis in adults: Moderator analysis of a randomized controlled trial

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Abstract

Background: While growing evidence suggests the efficacy of various behavioral approaches to the preventive treatment of migraine, it remains largely unclear which behavioral interventions are indicated for which type of patient. This exploratory study aimed to identify moderators for the outcome between migraine-specific cognitive-behavioral therapy and relaxation training.

Methods: In this secondary analysis of an open-label randomized controlled trial, the data of $N = 77$ adults (completer sample) with migraine (mean age = 47.4, $SD = 12.2$, 88% female), who were allocated to either migraine-specific cognitive-behavioral therapy or relaxation training, was examined. Outcome was the frequency of headache days at the 12-month follow-up. We analyzed baseline demographic or clinical characteristics and headache-specific variables (disability, emotional distress, trigger sensitivity and avoidance, pain acceptance, self-efficacy) as candidate moderators.

Results: Higher headache-related disability (assessed via the Headache Impact Test, HIT-6, $B = -0.41$ [95% CI: -0.85 to -0.10], $p = .047$), higher anxiety (assessed via the subscale Anxiety of the Depression, Anxiety and Stress scales, DASS-A, $B = -0.66$ [95% CI: -1.27 to -0.02], $p = .056$), and the presence of a comorbid mental disorder ($B = -4.98$, [95% CI: -9.42 to -0.29], $p = .053$), moderated the outcome in favor of migraine-specific cognitive-behavioral therapy.

Conclusion: Our findings contribute to an individualized treatment selection and suggest that preference for complex behavioral treatment (migraine-specific cognitive-behavioral therapy) should be given to patients with high headache-related disability, increased anxiety, or a comorbid mental disorder.

Study Registration: Original study registered in the German Clinical Trials Register (<https://drks.de/search/de>; DRKS-ID: DRKS00011111).

Keywords

Migraine, prophylaxis, randomized controlled trial, behavioral treatment, moderators, therapeutic indication

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Introduction

Psychological or behavioral factors are assumed to affect the course of migraine (1,2). For example, the experience of stress is considered to be a major trigger of migraine attacks (3,4). Comorbid mental disorders such as depression or anxiety disorders are associated with higher headache activity and disability (5). Thus, behavioral treatments have a central role among the non-pharmacological prophylactic interventions (6). The term “behavioral treatment” encompasses different categories of interventions. Common treatment categories in behavioral migraine prophylaxis are (a) patient

education and lifestyle counseling, (b) relaxation training, (c) biofeedback, and (d) cognitive-behavioral therapy (7). Other categories are (e) mindfulness-based (8) and (f)

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exposure-based approaches (trigger management) (9). Given the different interventional categories, two fundamental questions remain unanswered (10,11). The first question is whether and if so, which behavioral interventions are overall superior compared to others in the preventive treatment of migraine. The second question is which behavioral interventions are indicated for which type of patient. The current German medical guideline on the treatment of migraine attacks and migraine prophylaxis recommends supplementing pharmacological therapy with non-pharmacological, behavioral therapy (such as relaxation or cognitive-behavioral therapy as a standard approach). In the case of remarkable migraine-related disability and/or comorbid mental disorders, pain-specific behavioral therapy should be applied as an escalation of the standard behavioral approach (12). Beyond these recommendations, the empirical evidence for a differentiated indication or individual selection of behavioral treatments (“precision therapy”) in migraine should be advanced, particularly since clinical characteristics and treatment response in migraine patients are heterogeneous (11,13). Also, it is not yet clear whether a combination of several interventions is superior to single behavioral approaches.

In our randomized controlled trial (RCT), the efficacy of a multimodal, migraine-specific cognitive-behavioral therapy (miCBT) was compared with relaxation training (RLX) only (14). Both treatments led to a statistically similar reduction of headache activity, disability, and emotional distress, and neither treatment was superior to the other overall (14). This secondary analysis aimed to investigate which type of patient benefits more from miCBT than RLX and to explore demographic, clinical, and headache-related moderators of treatment outcome. Considering the existing guideline, disability and comorbidity are included as potential moderators.

Methods

Study design and participants

This study is a secondary analysis of an open-label RCT (14). The first stage of this trial comprised three conditions (miCBT, RLX, and a waiting-list control group, WLC). Eligible participants were randomly assigned with a 1:1:1 ratio to miCBT, RLX, or the WLC. The second stage (four- and 12-month follow-up) comprised two conditions (miCBT, RLX) since the participants, who successfully passed the WLC by providing a post measurement, were randomly assigned to the miCBT- or RLX-condition (1:1 ratio, Figure 1). The treatment was carried out at the psychotherapy

outpatient clinic of the Department of Psychology (University of Mainz, Germany). The protocol was approved by the competent Ethics Committee of the State Chamber of Medicine in Rhineland-Palatinate, Germany, reference number 837.291.16 (10610). All participants gave their written informed consent.

Participants were recruited via several newspaper articles, social media, and one TV clip as well as through the distribution of flyers in local medical practices (general practitioners, neurologists, pain therapists). Eligible participants were adults, meeting the International Classification of Headache Disorders (3rd edition, beta version, ICHD-3 beta) criteria (15) of either migraine without aura, migraine with aura, or chronic migraine for at least one year, with a minimum of four headache days per month, and a pattern of migraine symptoms stable over last six months. Exclusion criteria included a diagnosis of medication-overuse headache, a previously completed or current psychotherapy, a severe mental disorder or medical comorbidity, suicidal tendency, and pregnancy or lactating. Participants were excluded if they were currently taking a headache prophylactic medication or having therapy with botulinum toxin or neuromodulation. The face-to-face screening included a structured interview to validate the migraine diagnosis according to the ICHD-3 beta (15) as well as to assess comorbid mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition, DSM-5) (16).

Interventions

Both treatments (miCBT, RLX) comprised seven group sessions, each lasting 90 min. The sessions were carried out weekly. Both interventions are described in detail elsewhere (14), and the miCBT is published as a treatment manual (17). The miCBT comprised different behavioral approaches (e.g., patient education, lifestyle counseling, cognitive-behavioral techniques to improve coping with stress and fear, and trigger management, Figure 2). At the end of each session, the participants were taught a brief relaxation method. The RLX centered around progressive muscle relaxation (PMR) as an easy-to-learn and easy-to-apply relaxation technique with Grade A evidence in migraine prophylaxis (Figure 2) (18,19).

Assessments

After completion of the baseline measure, the treatment (miCBT or RLX) or the waiting period started. Immediately after the last treatment session (miCBT or RLX) or after seven weeks (WLC), the post-assessment was conducted (Figure 1). The WLC participants were

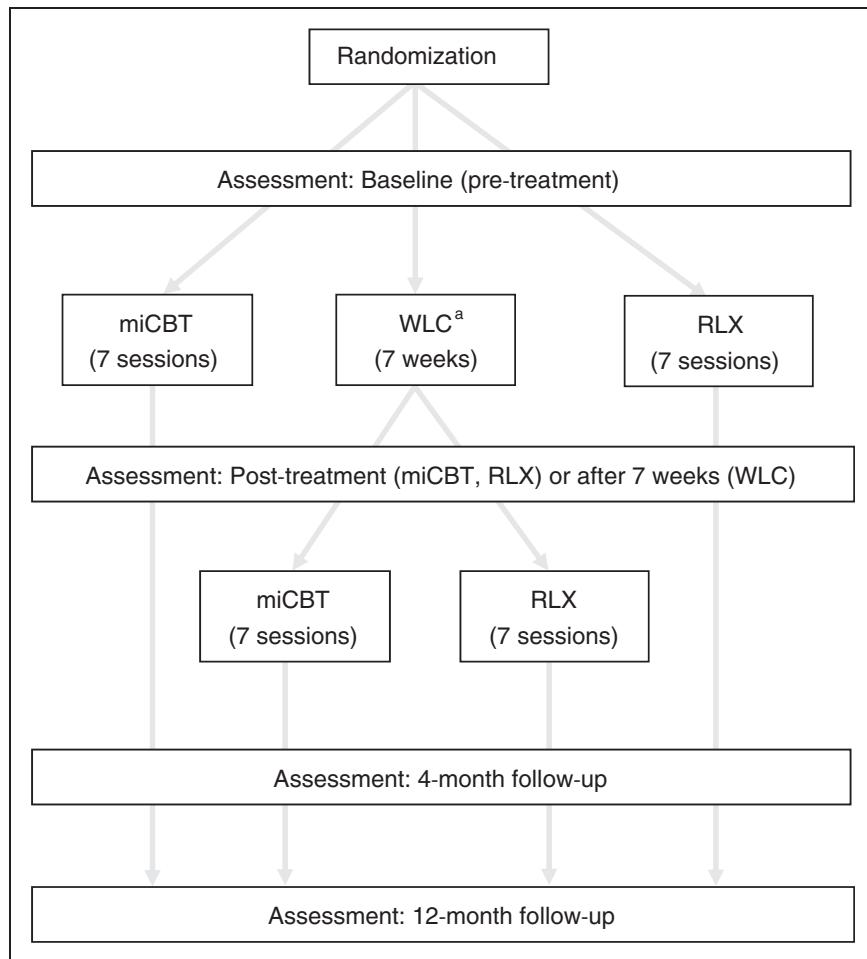


Figure 1. Study design and assessments. In total, four assessments were carried out (baseline, post-treatment, 4-month follow-up, and 12-month follow-up).

miCBT: migraine-specific cognitive-behavioral therapy; RLX: relaxation training; WLC: waiting-list control group.

^aIn the WLC condition, the second assessment (“post-treatment”) was carried out after the end of the waiting period (i.e., after seven weeks and not after completion of treatment). After completion of the second assessment, the participants of the WLC were randomized to one of the two interventions (miCBT or RLX).

randomized to one of the treatments after completion of the post-assessment. Follow-up assessments were carried out 4 and 12 months after completion of the treatment. Each assessment comprised a four-week online headache diary as well as an online survey, which included a set of questionnaires on headache-related factors.

In this study, we analyzed headache days at 12-month follow-up as measure of treatment effect (i.e., as outcome). The 12-month follow-up was selected to investigate the long-term effects of behavioral treatments (which are rarely studied in RCTs). The results of our RCT showed that treatment effects tended to improve even further from 4-month to 12-month follow-up. Thus, we assumed that moderation effects could be better determined for the 12-month follow-up. These long-term improvements were explained by the participants’ ability to select appropriate coping

strategies and successfully transfer them into everyday life. The increasing improvements were observed in all four main outcomes (headache days, disability, emotional distress, and self-efficacy) and were similar in both treatments (14). Since a reduction in headache or migraine days is still recommended as a primary endpoint in the respective guidelines (20,21), this parameter was selected as the measure of effect in the current study.

Potential moderators

Demographic moderators included sex and age, clinical characteristics included disease duration, migraine type, as well as comorbid mental disorders or somatic conditions. Headache-related disability was assessed via the Headache Disability Inventory (HDI/German version: IBK, Cronbach’s alpha, $\alpha=0.90$, range 0 to 4) (22),

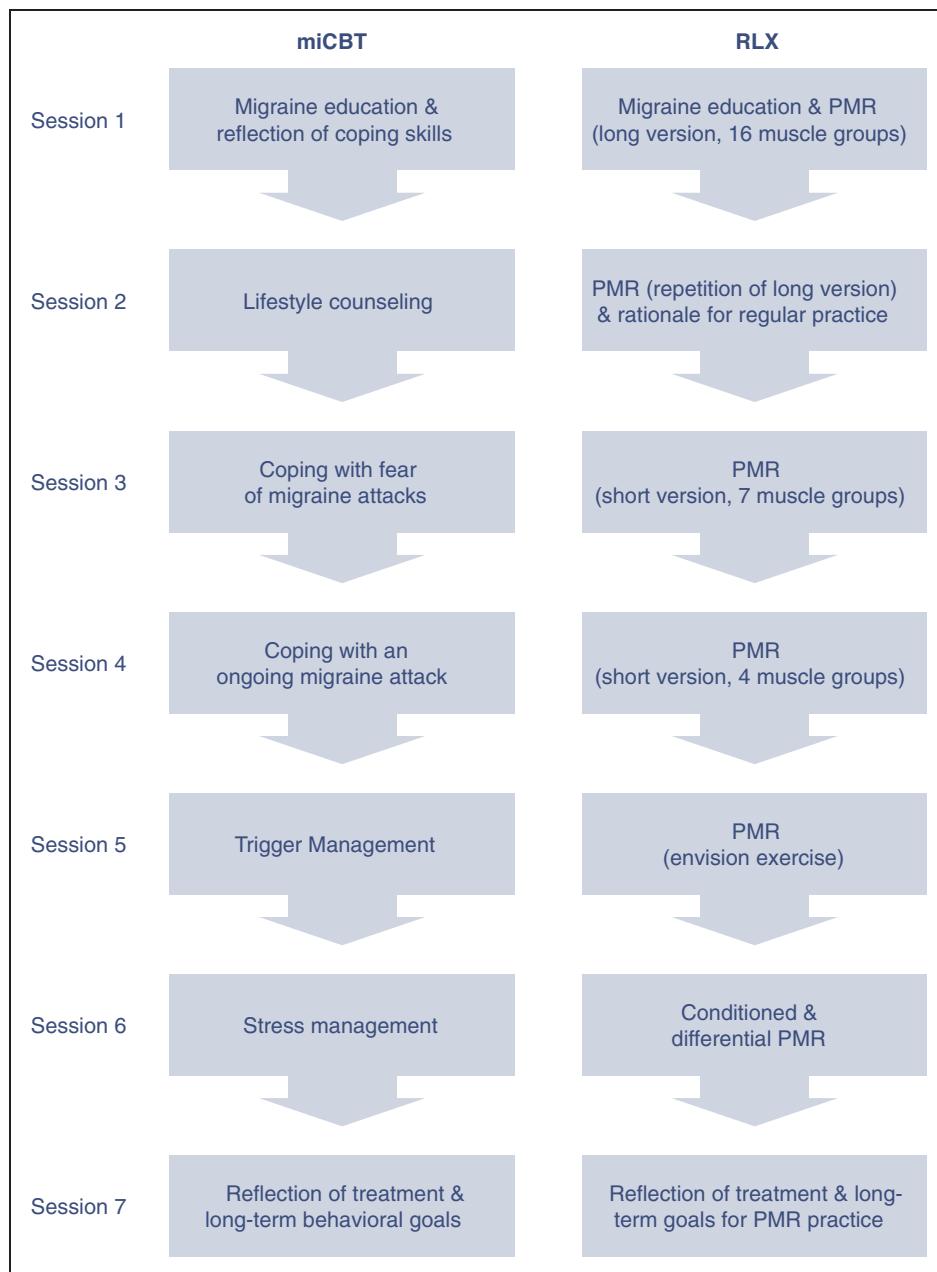


Figure 2. Description of treatment programs (miCBT, RLX).

miCBT: migraine-specific cognitive-behavioral therapy; PMR: progressive muscle relaxation; RLX: relaxation training.

the Headache Impact Test (HIT-6, $\alpha = 0.83$, range 6 to 13) (23), and the Pain Disability Index (PDI, $\alpha = 0.88$, range 0 to 10) (24). Headache-specific self-efficacy was assessed with the short form of the Headache Management Self-Efficacy Scale (HMSE-G-SF, $\alpha = 0.72$, range 1 to 7) (25). Emotional distress was assessed with the Depression Anxiety Stress Scales (DASS, range 0 to 3) (26), with the subscales Depression (DASS-D, $\alpha = 0.92$), Anxiety (DASS-A, $\alpha = 0.78$), and Stress

(DASS-S, $\alpha = 0.81$). Sensitivity to and avoidance of headache triggers was measured with the Headache Triggers Sensitivity and Avoidance Questionnaire (HTSAQ, $\alpha = 0.83$ to 0.86, range 1 to 5) (27). Acceptance of chronic pain was measured with the 20-item Chronic Pain Acceptance Questionnaire (CPAQ, $\alpha = 0.84$, range 0 to 6) (28). All questionnaires were provided in a German version (Cronbach's alphas are each from the credited source).

Statistical analyses

Descriptive statistics (mean, standard deviation, frequency, and percentage) were calculated to describe sample characteristics. To assess differences of subsamples (completer vs drop-out, miCBT vs RLX) regarding baseline characteristics (including candidate moderators), chi-square tests for categorical variables or *t*-tests for continuous variables (for independent samples) were conducted.

Moderation analysis was performed using the PROCESS macro (v. 3.5.3) in SPSS (v. 23) using ordinary least squares regression to estimate unstandardized coefficients (29). It was analyzed if the effect of treatment (predictor X with two levels: 0 = RLX, 1 = miCBT) on headache days at 12-month follow-up (criterion Y) was moderated by further variables when controlled for pre-treatment headache days. For each moderator, a separate moderation model was run (model 1 with 95% confidence intervals [95% CI] based on 10,000 bootstrapped samples, and heteroscedasticity consistent standard errors [HC3]). In the case of borderline *p*-values (around .05), the bootstrapped 95% CIs were taken into account, since a CI outside zero can be regarded as an alternative indicator of significance (30). In doing so, a significant moderation effect was qualified either by *p* < .05 and/or the bootstrapped 95% CI outside the value zero. Analyses were based on the complete-case sample (*n* = 77), including participants who (a) provided data at all measurement points, (b) completed the treatment, and (c) still met all defined inclusion and exclusion criteria (i.e., participants who became pregnant or started medication prophylaxis, e.g., with a monoclonal antibody, were excluded from further analyses).

In addition to the complete-case analyses, all participants who were randomly assigned to one of the two conditions (intention-to-treat sample, ITT) were analyzed. Since two participants of the WLC could not be randomized to a treatment (due to severe illness or a missing post-measurement), the ITT sample included *n* = 104 (instead of *n* = 106 for the pre-post analyses of the RCT) (14). Missing data at follow-up (18.9%) was replaced using last-observation-carried forward (LOCF), as a reproducible and conservative approach to missingness in RCTs, also reducing the risk of false positive values (31). Another reason for preferring the LOCF method was that multiple imputed data cannot be entered in the PROCESS macro, which can be considered one of the most appropriate tools for moderation analyses.

Results

Participant characteristics

Between January 2017, and April 2019, *N* = 121 participants were randomly assigned to miCBT (40), RLX (41), or WLC (40). The flowchart is displayed in the original study (14). The completer sample (*N* = 77) included mostly female participants (88%), having migraine with or without aura (97%) as headache diagnosis (Table 1). The mean age was 47.4 years (*SD* = 12.2, range 21 to 71). Both treatment groups (miCBT vs. RLX) did not differ statistically in candidate moderators or baseline characteristics. As well, the completer and the drop-out sample did not differ statistically in candidate moderators or baseline characteristics, except for headache days (Online Supplementary Table 1). The frequency of headache days was significantly higher (*M* = 11.1, *SD* = 5.2 vs. *M* = 7.5, *SD* = 3.7) in the drop-out sample.

Moderation analyses

Headache-related disability (assessed by the HIT-6) significantly moderated the effect of miCBT vs. RLX on headache days at 12-month follow-up (*B* = -0.41, *SE* = 0.20, *p* = .047, 95% CI: -0.85 to -0.10). With regard to the coding of the predictor (here: treatment group, with 0 = RLX and 1 = miCBT), the direction of the moderation effect means, miCBT was associated with better outcomes with increasing HIT-6 scores, whereas RLX was associated with better outcomes at lower HIT-6 scores (Figure 3a). For the DASS-A score, the confidence interval of the interaction effect was outside zero (*B* = -0.66, *SE* = 0.34, *p* = .056, 95% CI: -1.27 to -0.02), which indicates a moderation of the treatment effect in a similar direction. That means, miCBT was associated with better outcomes with increasing DASS-A scores, whereas RLX was associated with better outcomes at lower DASS-A scores (Figure 3b). As well, for the diagnosis of a comorbid mental disorder, the confidence interval of the interaction effect was outside zero (*B* = -4.98, *SE* = 2.53, *p* = .053, 95% CI: -9.42 to -0.29), indicating that miCBT was associated with better outcomes in persons with at least one comorbid mental disorder, whereas RLX was associated with better outcomes in persons without any comorbid mental disorder (Figure 3c).

Figure 3 is a model visualization of the moderation effects since the two lines of the outcome (headache days at 12-month follow-up, controlled for headache days at baseline) are constituted by only three (Figures 3a, 3b) or two (Figure 3c) reference markings.

Table 1. Baseline characteristics (completer sample, N = 77).^a

	miCBT n = 36	RLX n = 41	p ^b
Age (years)	47.8 (10.4)	47.0 (13.8)	.783
Female	34 (94%)	34 (83%)	.117
Disease duration (years)	22.5 (13.8)	21.5 (12.9)	.735
Headache diagnosis			.691
Migraine without aura	32 (89%)	34 (83%)	
Migraine with aura	3 (8%)	6 (15%)	
Chronic migraine	1 (3%)	1 (2%)	
Mental disorder as comorbidity			.191
No comorbid mental disorder	30 (83%)	29 (71%)	
Tentative diagnosis	4 (11%)	11 (27%)	
Comorbid mental disorder	2 (6%)	1 (2%)	
Comorbid somatic condition (yes)	14 (39%)	15 (37%)	.835
Headache days per month (28 days)	7.4 (3.6)	7.6 (3.8)	.795
Headache related variables			
HDI/IBK	47.4 (16.5)	52.0 (17.3)	.241
PDI	25.3 (10.1)	30.0 (15.0)	.132
HIT-6	59.4 (3.8)	61.3 (4.7)	.052
DASS			
Scale DASS-D	3.9 (4.6)	3.9 (4.0)	.986
Scale DASS-A	2.8 (2.5)	2.9 (2.9)	.842
Scale DASS-S	7.1 (5.3)	7.0 (5.0)	.962
HTSAQ ^c			
Scale Triggers	50.4 (10.2)	52.3 (12.4)	.468
Scale S (O)	47.7 (12.2)	50.7 (13.7)	.323
Scale S (T)	42.1 (13.0)	45.5 (16.2)	.317
Scale Avoidance	49.1 (9.4)	51.7 (11.2)	.274
CPAQ	63.9 (16.0)	61.6 (16.5)	.528
HMSE-G-SF	23.0 (9.8)	22.0 (9.8)	.672

CPAQ: Chronic Pain Acceptance Questionnaire; DASS: Depression, Anxiety and Stress Scales; DASS-A: Subscale Anxiety; DASS-D: Subscale Depression; DASS-S: Subscale Stress; HDI: Headache Disability Inventory; HIT-6: Headache Impact Test; HMSE-G-SF: Headache Management Self-Efficacy Scale, German version, Short-Form; HTSAQ: Headache Triggers Sensitivity and Avoidance Questionnaire; IBK: German version of the HDI; miCBT: migraine-specific cognitive-behavioral therapy; PDI: Pain Disability Index; RLX: relaxation training; S (O): Sensitivity compared with Others; S (T): Sensitivity compared with Time of least sensitivity.

^aData are n (%) or mean (standard deviation) unless otherwise stated.

^bp-values refer to chi-square tests for categorical variables or t-tests for continuous variables (for independent samples, miCBT vs. RLX).

^cThe HTSAQ comprises 26 triggers. Since two triggers are not listed before, and two triggers (i.e., smoking, menstrual cycle) do not apply to everyone, only the data of 22 triggers was taken into account.

The three reference markings in Figure 3a and 3b are -1 standard deviation, the mean, and $+1$ standard deviation since the moderator is continuous. The two reference markings in Figure 3c are the presence (“yes”) or absence (“no”) of any mental disorder (as a dichotomous variable). The figures show that with an increasingly higher disability (HIT-6) or an increasingly higher anxiety (DASS-A), the miCBT tends to be more effective than the RLX (in terms of reduced headache activity), and vice versa. For the dichotomous moderator “mental disorder” (yes/no), it becomes apparent that in the presence of at least one comorbid mental disorder, the miCBT tends to lead to a higher reduction of headache activity compared to the RLX (and vice versa).

The p-values of all candidate moderators are shown in Table 2 (see Table 3 for complete moderation models). No further significant moderation effects were observed in the completer sample. In the ITT sample, no significant p-values were observed, however, the confidence intervals of the interaction effects of comorbid mental disorder as well as of sex were outside zero (Online Supplementary Table 2).

Discussion

In an effort to facilitate patient-tailored treatment decisions, this secondary analysis evaluated candidate moderators of the efficacy of a newly developed, cognitive-behavioral migraine prophylaxis (miCBT)

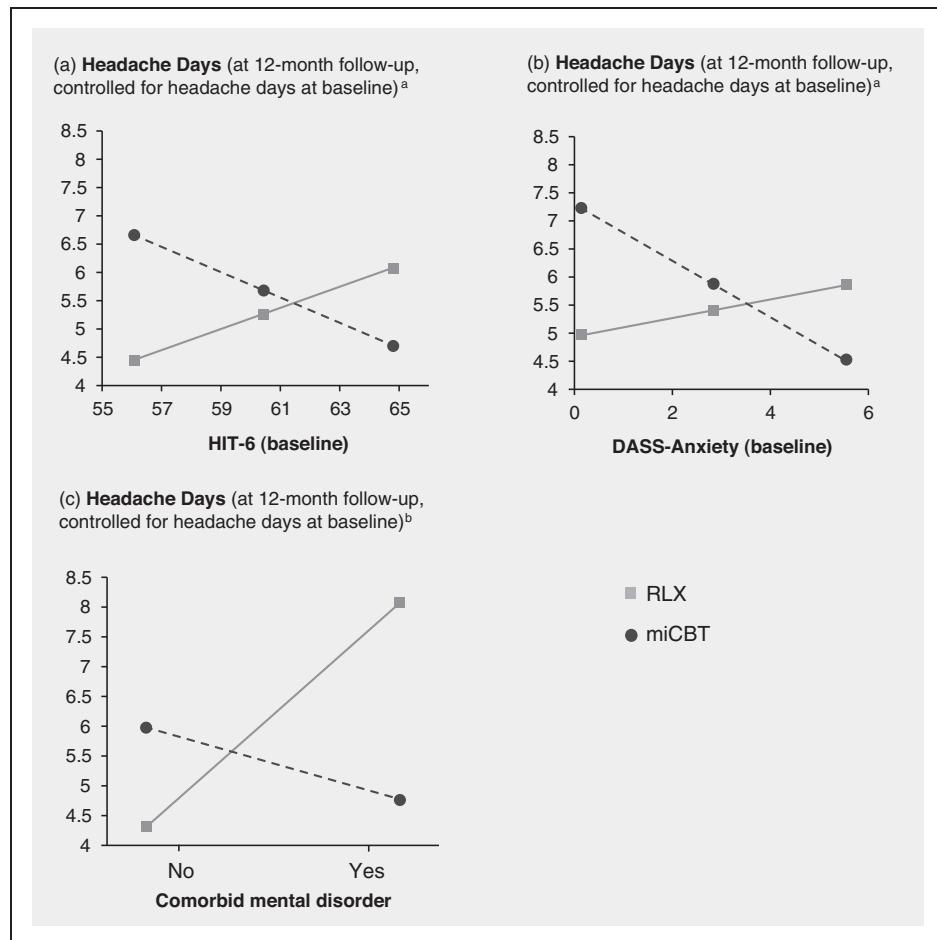


Figure 3. Visualization of the moderating effect of (a) headache-related disability (assessed by the HIT-6), (b) anxiety (assessed by the DASS-A), and (c) comorbidity of any mental disorder (yes/no), depicted each on the x-axis, on the treatment efficacy (miCBT vs. RLX) regarding headache days at 12-month follow-up as outcome (y-axis). The outcome is controlled for its baseline scores. DASS-A: Depression Anxiety Stress Scales, subscale “Anxiety”; HIT-6: Headache Impact Test; miCBT: migraine-specific cognitive-behavioral therapy; RLX: relaxation training.

^aThe values of the outcome are per default (PROCESS macro in SPSS) probed for the sample mean and ± 1 standard deviation of the moderator (x-axis). The sample mean and the standard deviation are referring to the completer sample ($n = 77$). The sample mean is displayed by the two markings in the middle of the two lines. The standard deviation is displayed each by two markings on the right and left edges of the two lines.

^bSince comorbidity is a dichotomous variable, no sample mean or standard deviation is displayed. The markings refer to the two manifestations of the moderator (yes or no).

compared to relaxation training (RLX). The previous primary analysis of this RCT showed comparable efficacy for the two treatment programs miCBT and RLX (14). Both treatment programs led to an average reduction of about two headache days per month (from pre to 12-month follow-up, responder rate each about 44%). Our current findings demonstrate that patients with high disability, increased anxiety, or comorbid mental disorder(s) benefited more from the miCBT compared to RLX, while patients with relatively lower disability or anxiety, as well as those without comorbid mental disorder(s) benefited more from RLX.

Our results indicate that the challenges of patients with higher psychosocial burden are probably not sufficiently addressed with relaxation training alone. Since high disability, anxiety, or a comorbid mental disorder are usually associated with dysfunctional behavioral patterns, a cognitive-behavioral treatment, which covers a wider range of coping strategies, is probably better suited than relaxation, which targets “only” the level of arousal. In contrast, RLX may be superior in patients who are less burdened. PMR is an effective, easy-to-learn technique for migraine prophylaxis. A strength of the RLX was its focus on this one technique. The repeated exercise of PMR contributed to the

Table 2. Univariate moderation analysis for the outcome headache days at 12-month follow-up (controlled for headache days at baseline) and treatment group as independent variable (miCBT vs RLX) for the completer sample ($n=77$).

Moderators ^a	Headache days ^b at 12-month follow-up (controlled for headache days at baseline)			
	B	SE	Bootstrapped 95% CI	p
Demographic variables				
Sex	1.30	1.39	[−1.13, 3.83]	.355
Age (years)	0.08	0.08	[−0.08, 0.23]	.367
Clinical characteristics				
Disease duration (years)	−0.03	0.06	[−0.14, 0.09]	.621
Migraine type ^c	−1.68	2.87	[−6.58, 3.08]	.560
Comorbid mental disorder ^d	−4.98	2.53	[−9.42, −0.29]	.053
Comorbid somatic condition	1.14	1.72	[−2.04, 4.45]	.508
Headache related variables				
HDI/IBK	−0.05	0.05	[−0.14, 0.05]	.357
PDI	−0.07	0.07	[−0.21, 0.06]	.355
HIT-6	−0.41	0.20	[−0.85, −0.10]	.047
DASS				
Scale DASS-D	−0.10	0.19	[−0.56, 0.25]	.602
Scale DASS-A	−0.66	0.34	[−1.27, −0.02]	.056
Scale DASS-S	−0.19	0.15	[−0.49, 0.08]	.216
HTSAQ ^e				
Scale Triggers	−0.06	0.07	[−0.20, 0.07]	.394
Scale S (O)	−0.06	0.06	[−0.18, 0.04]	.261
Scale S (T)	0.001	0.05	[−0.10, 0.09]	.989
Scale Avoidance	0.02	0.07	[−0.13, 0.14]	.819
CPAQ	0.04	0.05	[−0.06, 0.14]	.449
HMSE-G-SF	−0.01	0.10	[−0.19, 0.19]	.951

CI: Confidence interval; CPAQ: Chronic Pain Acceptance Questionnaire; DASS: Depression, Anxiety and Stress Scales; DASS-A: Subscale Anxiety; DASS-D: Subscale Depression; DASS-S: Subscale Stress; HDI: Headache Disability Inventory; HIT-6: Headache Impact Test; HMSE-G-SF: Headache Management Self-Efficacy Scale, German version, Short-Form; HTSAQ: Headache Triggers Sensitivity and Avoidance Questionnaire; IBK: German version of the HDI; miCBT: migraine-specific cognitive-behavioral therapy; PDI: Pain Disability Index; RLX: relaxation training; S (O): Sensitivity compared with Others; S (T): Sensitivity compared with Time of least sensitivity.

^aModerator x treatment condition (0 = RLX, 1 = miCBT) interaction. Each line refers to a separate model.

^bHeadache days refers to a 28-day period.

^cn = 75 (2 participants with chronic migraine excluded).

^dn = 75 (2 participants with tentative diagnosis excluded).

^eThe HTSAQ comprises 26 triggers. Since two triggers are not listed before, and two triggers (i.e., smoking, menstrual cycle) do not apply to everyone, only the data of 22 triggers was taken into account.

transfer to everyday life. Interventions for other issues (e.g., session 3 of the miCBT, coping with fear of attacks) could have a distracting effect on patients, who are not affected by the respective issue (here: fear of attacks). For less burdened patients it is probably better to focus on learning and implementing PMR (according to the principle “more from less”).

Our results provide a preliminary indication that different behavioral interventions have different effects depending on the subgroup of migraine. This finding supports the current German medical guideline on migraine prophylaxis, in which different escalation levels of behavioral treatments are recommended (12). Future headache diagnosis should take into account at least these psychosocial parameters, which are relevant for the selection of behavioral interventions. Martin (13) suggests a multiaxial system beyond categorical

headache diagnosis by recommending an assessment of (a) disability, (b) trigger sensitivity and avoidance, and (c) other psychosocial parameters such as lifestyle or dysfunctional coping. Contrary to expectations, trigger sensitivity and avoidance (assessed by the HTSAQ) could not be identified as moderators between treatments in our study. In the miCBT, the dose of trigger management with just one session may have been too low to lead to relevant effects, thus a higher number of sessions addressing this issue should be used for future studies.

In addition to the evaluation of complex, multicomponent treatments such as miCBT, more research (e.g., dismantling studies) is needed to identify moderators for specific treatment components such as trigger management or specific CBT strategies (e.g., coping with fear of attacks). When analyzing the treatment effects

Table 3. Full moderation models, i.e., (a) disability by HIT-6, (b) anxiety by DASS-A, and (c) comorbidity of any mental disorder (yes/no), each between treatment conditions (RLX vs. miCBT)^a for the outcome (headache days at 12-months follow-up, controlled for headache days at baseline) in the completer sample ($n = 77$).

	B	SE (HC3)	t	p
(a) disability (by HIT-6)				
$R^2 = 0.18$				
Constant	-9.11	8.69	-1.05	.298
Treatment	25.24	12.19	2.07	.042
HIT-6	0.19	0.14	1.31	.195
Treatment × HIT-6	-0.41	0.20	-2.02	.047
Headache days (baseline)	0.41	0.14	2.90	.005
(b) anxiety by DASS-A				
$R^2 = 0.19$				
Constant	1.75	1.18	1.48	.142
Treatment	2.36	1.31	1.79	.077
DASS-A	0.16	0.17	0.96	.339
Treatment × DASS-A	-0.66	0.34	-1.94	.056
Headache days (baseline)	0.43	0.14	3.12	.003
(c) comorbid mental disorder (yes/no)				
$R^2 = 0.26$				
Constant	1.77	1.04	1.71	.091
Treatment	1.66	0.86	1.94	.056
Comorbid mental disorder	3.76	1.11	3.39	.001
Treatment × comorbid mental disorder	-4.98	2.53	-1.97	.053
Headache days (baseline)	0.34	0.13	2.55	.013

DASS-A: Depression, Anxiety and Stress Scales, subscale Anxiety; HIT-6: Headache Impact Test; miCBT: migraine-specific cognitive-behavioral therapy; RLX: relaxation training.

^aTreatment: 0 = RLX, 1 = miCBT.

of specific behavioral treatments in migraine, the aspect of deterioration and negative effects should also be taken into account (32).

For migraine patients, who do not show any increased scores in a psychological assessment, headache education, in combination with lifestyle recommendations and the regular practice of relaxation may be the better choice. For migraine patients who show increased scores in certain problem areas (e.g., high attack-related fear), the corresponding behavioral intervention (e.g., CBT techniques to cope with attack-related fear) should be recommended.

Limitations

While interpreting our findings, certain limitations have to be considered. First, our explorative study was not powered adequately to detect small-sized interaction effects. Second, since our analyses focused on the completer sample and moderation effects could not be replicated in the ITT sample, the generalizability to a larger patient population with different treatment (non) response is limited. The drop-out sample differed from the completer sample only with regard to a higher frequency of headache days at the beginning of treatment.

The two main reasons for a drop-out were declining a measurement ($n = 7$) and the start of a prophylactic medication ($n = 7$). Presumably, at least in the latter case, there was a high headache activity (otherwise medication prophylaxis would not have been initiated), which may explain the overall higher headache frequency in the drop-out sample. As a third limitation, additional unmeasured variables such as attack-related fear could have also moderated the effect of miCBT. Since there are now more specific questionnaires with good psychometric properties (e.g., the Fear of Attacks in Migraine Inventory, FAMI, [33]), these parameters should be investigated further.

Conclusion

This secondary analysis of an RCT identified headache-related disability, anxiety, and mental disorder comorbidity as moderators of the effect of behavioral treatment (miCBT vs. RLX) on headache days in the long-term. While a more complex, migraine-specific treatment with several approaches (miCBT) may be indicated for patients with higher disability, anxiety, or a comorbid mental disorder, a simpler treatment approach (RLX) may be better for patients, who are

less burdened. Further, adequately powered studies are needed to confirm these preliminary results and

advance tailored multimodal treatment selection for migraine.

Clinical implications

- In migraine prophylaxis, it is still unclear which behavioral approach is best suited for which type of patient.
- Disability, anxiety, and comorbid mental disorder were identified as moderators of headache days at the 12-month follow-up between miCBT or RLX.
- Higher-burdened patients benefited more from miCBT whereas lower-burdened patients benefited more from RLX.
- Prospective studies are needed to confirm these preliminary results.

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Data sharing

De-identified data of the current study is available online at the Open Science Framework (OSF): Klan, T. (2022, December 29). Behavioral Treatment for Migraine Prophylaxis. Retrieved from osf.io/m9r7d

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CG has received honoraria for consulting and lectures within the past three years from Abbvie, Lilly, Novartis Pharma, Hormosan Pharma, Grünenthal, Sanofi-Aventis, Weber & Weber, Lundbeck, Perfood, and TEVA. CG is honorary secretary of the German Migraine and Headache Society. ELL has received honoraria for lectures within the past three years from Allergan Pharma, Lilly, and TEVA. ELL and TK published a treatment manual about CBT for migraine. All other authors declare no competing interests.

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STUDY PROTOCOL

Open Access



Comparison of a pediatric practice-based therapy and an interdisciplinary ambulatory treatment in social pediatric centers for migraine in children: a nation-wide randomized-controlled trial in Germany: “moma – modules on migraine activity”

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Abstract

Background: Migraine is common in childhood, peaks in adolescents and persists into adulthood in at least 40% of patients. There is need for early interventions to improve the burden of disease and, if possible, reduce chronicification. The aim of the project is to compare two types of ambulatory treatment strategies regarding their effect on headache days and quality of life in 6 to 11 year old children with migraine: 1) the routine care in pediatricians' practices (intervention group A) and 2) a structured interdisciplinary multimodal intervention administered at social pediatric centers (intervention group B).

Methods: The study is a nation-wide cluster-randomized study. Based on the postal codes the regions are randomly assigned to the two intervention-strategies. Children with migraine are recruited in the pediatric practices, as common outpatient-care in the German health-care system. Parents rate headache frequency, intensity and acute medication intake at a daily basis via a digital smartphone application specifically designed for the study. Migraine-related disability and quality of life are assessed every 3 months. Study duration is 9 months for every participant: 3 months of baseline at the pediatric practice (both groups); 3 months of intervention at the pediatric practice (intervention group A) or at the social pediatric center (intervention group B), respectively; 3 months of follow-up at the pediatric practice (both groups).

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Discussion: Results of the planned comparison of routine care in pediatric practices and interdisciplinary social pediatric centers will be relevant for treatment of children with migraine, both for the individual and for the health care system.

Trial registration: The study was approved by the ethics committee at the Ludwig-Maximilians-University Munich (number 18–804) and was retrospectively registered on 27 April 2021 in the WHO approved German Clinical Trials Register (number DRKS00016698).

Keywords: Migraine, Children, Intervention, Interdisciplinary, Pediatric practice

Background

Migraine is a chronic disease often starting in childhood. The Barmer health insurance company dataset, which is covering 11% of all German policyholders, showed that in 2015 approximately 1% of all children received a diagnosis of migraine already at the age of primary school (6 to 11 years of age) [1]. In patients with migraine diagnosed at the age of 7 years, migraine persists into adulthood in 65% of the affected females and 21% of the affected males [2].

The Barmer insurance data also reveal that only half of the primary school children diagnosed with migraine got appropriate medication e.g. NSAID, but 2.1% were at least once in inpatient treatment for migraine. Only 6% of the affected children received an interdisciplinary therapy at a social pediatric center (unpublished data). Social pediatric centers are regional neuropediatric centers offering interdisciplinary treatment for children with chronic diseases. They belong to the customary care institutions in Germany.

It has repeatedly been shown that interdisciplinary treatment is effective in adult patients with migraine: e.g., in one study 42.5% of patients achieved a reduction of headache days of more than 50% even in the long term [3] and in another study, the number of headache days was significantly reduced from 13.8 ± 7.6 to 8.2 ± 6.2 [4]. Comparisons with standard basic care have shown superiority of multimodal treatment [5, 6].

Studies about the efficacy of multimodal treatment in young children with migraine do not exist so far. Children with migraine have a shorter migraine history and less comorbidities, such as other pain syndromes or psychiatric disorders, than adult migraine patients. Therefore, an early interdisciplinary multimodal treatment in young children may lead to an even better outcome in comparison to adults and may prevent the establishing of co-morbidities in the long term. Effective elements of treatment seem to include counselling on life style factors [7, 8] and psychotherapeutic [9] and physiotherapeutic measures [9, 10]. These interdisciplinary multimodal approaches are a distinguishing feature of German social pediatric centers.

Therefore, we designed an interdisciplinary multimodal intervention for treatment of pediatric migraine in social pediatric centers and a randomized controlled study to evaluate its effectiveness compared with standard basic pediatric care over a 9 months interval (elements of the interdisciplinary intervention: see 2.3. Study Design).

The aim of the presented study is to evaluate if an early intervention in young children at the time migraine has just started leads to a reduction of headache days and headache intensity as well as to a lower intake of analgesics and to an amelioration of quality of life.

Methods/design

Patient involvement

Children with migraine are treated in pediatric practices and social pediatric centers in Germany. As interdisciplinary multimodal treatment showed superior effects in the care of adults with migraine, we included pediatric, psychological and physiotherapeutic modules in the treatment of children with migraine in our clinical work at the social pediatric center in Munich. The satisfaction with this treatment of both children with migraine and their parents thereby ameliorated in a significant way. Based on this experience, we developed the patient-centered, structured, interdisciplinary multimodal intervention “moma – modules on migraine activity”, presented in this protocol. Nevertheless, pediatricians in practice are the standard basic pediatric care for children with migraine in Germany and are often very effective. Thus, we chose treatment in pediatric practices as comparative intervention strategy in our study design. Another aspect of patient involvement in the study design was that, to our clinical experience, the acceptance of treatment support via digital applications is high among parents in the neuropediatric field. Therefore, we developed the “moma app” for smartphones to facilitate the documentation of headache symptoms for the parents of participating children with migraine. The results of the study will be disseminated not only in scientific journals but also in public media to attain transparency for patients and their parents about the effectiveness of different treatment strategies for children with migraine.

Selection of sample

Children between 6 and 11 years of age with migraine with a statutory health insurance (approx. 90% of the population) and whose parents consent to participation are eligible for the study. Children are recruited by their pediatricians in practice. The pediatrician diagnoses migraine according to the International Classification of Headache Disorders 3rd edition (ICHD-3) [11], with the help of a standardized, electronic migraine checklist that was developed for the study.

Inclusion criteria are as follows:

- Age 6 to 11 years
- Diagnosis of migraine (according to the International Classification of Diseases ICD-10, classification numbers G43.x), based on the International Classification of Headache Disorders (ICHD-3) [11] adapted to children (allowing shorter headache duration of 2 to 72 h, and bilateral instead of unilateral headache)
- History of migraine for at least 3 months
- At least 3 headache days in the last 3 months
- Migraine prophylactic medication (beta-blocker, amitriptyline, topiramate) allowed if kept constant for the duration of the study

Exclusion criteria are:

- Mental retardation (IQ < 70)
- Severe somatic or psychological, acute or chronic disease except headache
- Familiar hemiplegic migraine (genetically confirmed)
- Children will be excluded after the baseline phase if less than 3 headache days were present during the 3 months baseline phase

Sample size calculation

The primary outcome was defined as a difference in reduction of headache days between the baseline and the follow-up period of ≥ 2 headache days in 12 weeks. The significance level α was set at 0.05 and the power at 0.9. Power size calculation with these parameters shows that a sample of $n = 279$ in the intervention group A (pediatric practice) and $n = 507$ children in the intervention group B (interdisciplinary treatment in social pediatric centers) is needed. For the sample size calculation an intra-class correlation coefficient (ICC) of 0.1 was assumed.

The estimated number for recruitment is based on an analysis of the Barmer insurance database of 2017 [1]. Approximately $n = 270,000$ statutorily insured children at the age of 6 to 11 years are likely to obtain a diagnosis of a primary headache disorder. About 70% of these see a pediatrician for primary care. As approximately 20% of

pediatricians in practice use the website "PädiExpert", which provides the electronic migraine checklist, inclusion and exclusion criteria and access to the study platform, we calculated that $n = 28,350$ children per year are available for screening of migraine at the pediatric practices. We estimate that of these, 17.5% in fact receive a migraine diagnosis, resulting in $n = 4961$ children.

Germany was divided in 77 regions according to the postal codes, in a way that every postal code region contained at least one social pediatric center. The postal code regions were then randomized at a 2:1 ratio to intervention B and to intervention A regions. We estimated that in 75% of the intervention B regions at least one social pediatric center would be willing to participate in the study. We assumed that up to 20% of children will be excluded after the baseline phase or drop out later in the study: 1) because of more than 33% of missing data in the electronic headache diary during the baseline phase or 2) because of less than three documented headache days during the 3 months baseline or 3) because of more than 66% of missing data in the electronic headache diary during the follow-up period or 4) because they are lost to follow-up.

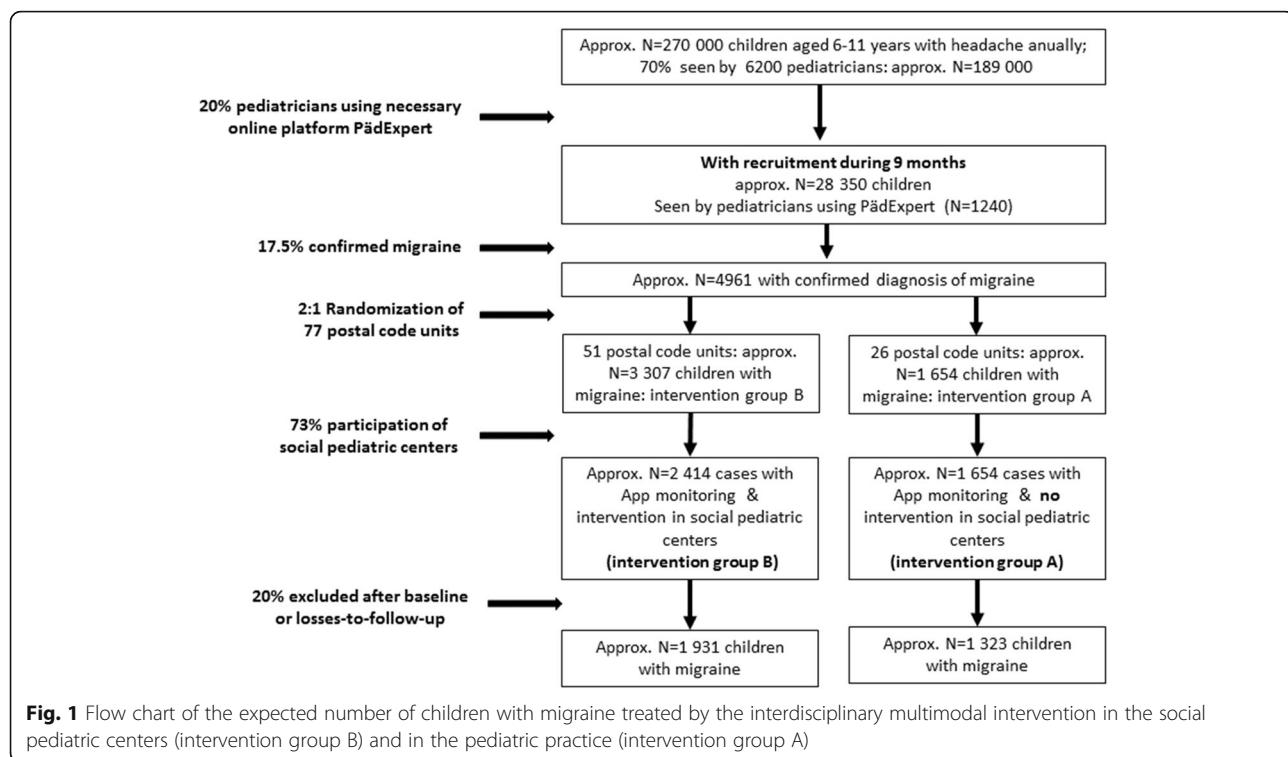
As shown in the flow chart (Fig. 1) the actual percentage of regions where at least one social pediatric center participated (intervention group B) was 73% (only slightly lower than estimated). Because of an assumed further drop out of 20% after recruitment, the numbers expected were $n = 1931$ and $n = 1323$ for the intervention B (social pediatric centers) and intervention A (pediatric practice) group respectively. These numbers exceed the required numbers as estimated in the power calculation. We chose a broad safety margin because of uncertainties related to the COVID-19 pandemic.

Study design

Overview (Fig. 2)

As described above, the study compares the pediatric practice treatment (intervention group A) and the interdisciplinary multimodal treatment (intervention group B). The timeline is illustrated in Fig. 2.

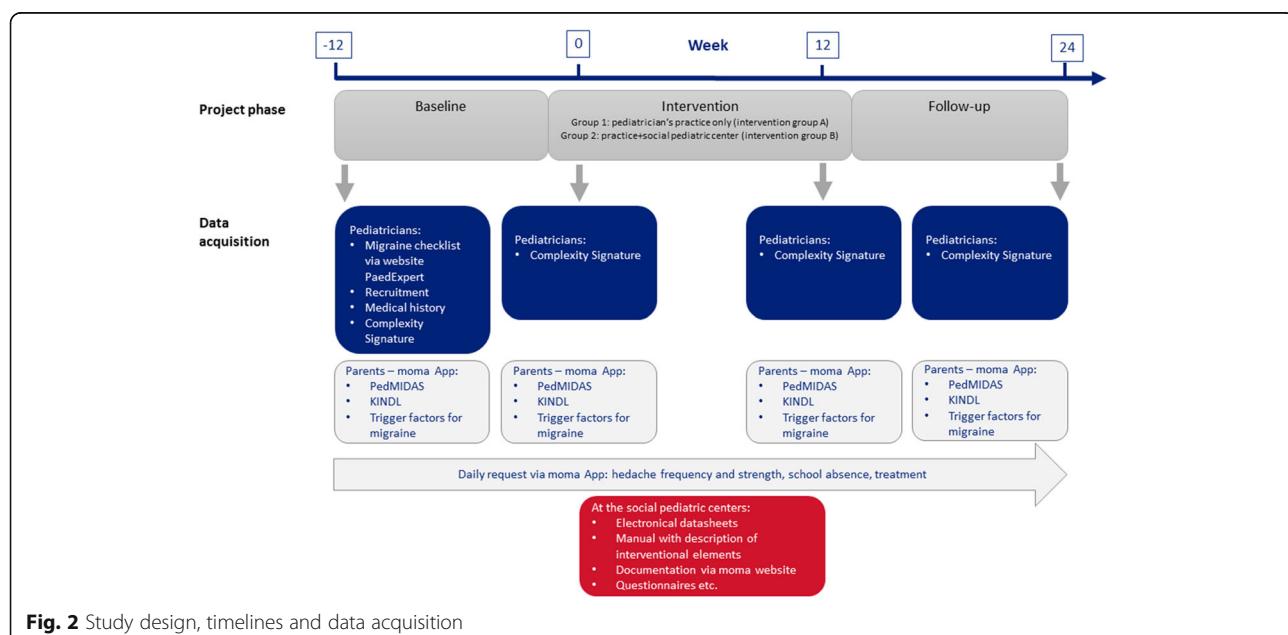
In both groups, children are diagnosed with migraine by their pediatrician in practice, included in the study and, if they have at least 3 days of headache in the baseline phase (week -12 to 0), go on to the intervention phase (week 0–12). The intervention phase includes treatment at the pediatric practice for both groups, and treatment at the social pediatric center only for the interdisciplinary multimodal group (intervention group B). There, children are treated with the structured multimodal interdisciplinary intervention "moma" as described below. After the intervention the follow-up



(week 12 to 24) is performed by the treating pediatrician in practice again.

Every participant has four study visits at the pediatric practice at time points -12, 0, 12 and 24 weeks. The interdisciplinary multimodal intervention group has three additional study (intervention) visits at the social pediatric centers.

At the first visit, the moma web application generates a hashcode for pseudonymization of the patient, which is given to the parents by the pediatrician. The parents use the hashcode to log into the "moma App", in which they document headache frequency, intensity and acute headache medication of their child on a daily basis.



Interdisciplinary multimodal intervention

The elements of the presented structured multidisciplinary intervention for children at the age of 6 to 11 years “moma” include:

- 1) pediatric elements such as exclusion of secondary causes and comorbidities by neurological examination and blood tests, and counselling regarding the bio-psycho-social model of pain,
- 2) physiotherapeutic elements such as examination of myofascial trigger points in the neck and shoulder muscles, education about the association of muscle tenderness and migraine and about individual exercise and self-administered stretching measures,
- 3) psychological elements such as evaluation of psychosocial circumstances, relevant psychological and behavioral factors for migraine, introduction of relaxation techniques and individual counselling to address the identified factors and improve self-efficacy.

The pathophysiological rationale for choosing these therapeutic elements is as follows:

According to epidemiological data, 45 to 85% of German adolescents with migraine (depending on migraine frequency) also suffer from muscle pain of neck or shoulders [9]. The pathophysiological explanation for this association is the concept of the trigemino-cervical complex (TCC) with its convergence of nociceptive afferents from cervical muscles to the caudal trigeminal nuclei [12]. As invasive or drug treatment is often not successful in young children, one focus of the presented intervention is on the cervical muscles as the easily accessible peripheral input of TCC [10]. With physiotherapeutic treatment of the muscle, including self-massage and stretching, the tenderness of the muscles is reduced which in our clinical experience leads to a decrease of headache frequency and/or intensity.

In addition, progressive muscle relaxation, which was shown to be effective in adults with migraine [13] was adapted for young children and is integrated in the psychological module of the presented intervention. Psychologists also screen for psychological stress and psychiatric comorbidities which are more frequent in patients with migraine compared to healthy persons [14]. The treated children are asked to draw their headache to visualize individual symptoms of migraine (Fig. 3) [15].

Measures

All outcome parameters are assessed via the dedicated smartphone application ‘moma app’, which is filled in by the parents over the 9 months study duration (Fig. 2).



Fig. 3 Drawing of his headache by a 9-year-old child

The app contains the following features:

1. Headache diary (based on established diaries [16, 17]) including a daily reminder function (missed entries days can be caught up within 2 weeks), with daily assessment of the following items
 - Presence of headache (yes/no)
 - Headache intensity (numeric rating scale 0–10 presented as a slider)
 - Headache duration (slider from 0 to 24 h)
 - Missed school (yes/no)
 - Inability to perform leisure activities (yes/no)
 - Use of headache medication (yes/no, tool for recording medication and dose)
2. Questionnaires are presented within the app at the start and end of the baseline (weeks – 12 and 0), at the end of the intervention (week 12) and at the end of the follow-up (week 24). The following questionnaires are used:

- PedMIDAS (Pediatric Migraine Disability assessment score) [18]
- KINDL [19] (German tool for assessing pediatric quality of life).

3. At the time points used for the questionnaires, the smartphone app also asks for

- typical triggers of headache in the last 3 months (within the categories: school stress, family problems, conflicts with friends, noise, sport, inactivity, weather, lack of sleep, drinks containing caffeine, reduced fluid intake, high use of electronic media, infection, others)
- headache prophylactic measures taken in the last 3 months (within the categories: physiotherapy, trigger point therapy, osteopathy, acupuncture, homeopathy, alternative practitioner, naturopathy, peppermint oil, magnesium, vitamin D, medication, others)

Additionally to the ‘moma App’, pediatricians in practice and social pediatric centers use the ‘moma website’ (www.moma-migraine.de) [1] to document the individual clinical presentation and characteristics of the child, for example individual migraine symptoms, important aspects of the medical history, results of the neurological examination, psychosocial factors and the therapeutic recommendations given to the family. Furthermore, they estimate the complexity of the disease for each child using the ‘moma complexity signature’, which has been developed by our group specifically for this study based on the bio-psycho-social model (see Fig. 3 for time points of data acquisition).

Outcome parameters

All outcome parameters are assessed via the parents’ entries in the ‘moma App’. For all outcome parameters, the difference from baseline to follow-up is measured and compared between the two groups.

The primary outcome parameter is the number of headache days per 12 weeks (84 days). Our hypothesis is that the reduction of headache days from baseline to follow-up will be at least 2 days larger for the group with interdisciplinary multimodal intervention in social pediatric centers (intervention group B) compared to the group with basic treatment in pediatric practices (intervention group A).

Secondary outcomes are:

- 1) Number of responders, defined as patients with a reduction of more than 50% of headache days per 12 weeks from baseline to follow-up;
- 2) Headache intensity (averaged over headache days per 12 weeks);
- 3) Number of days missed at school due to headache per 12 weeks;
- 4) Number of days with cancelling of leisure activities due to headache per 12 weeks;
- 5) Headache-related disability (PedMIDAS questionnaire) [18], assessed every 3 months;
- 6) Quality of life (KINDL questionnaire, every 3 months) [19, 20];
- 7) Number of days with intake of acute medication because of headache per 12 weeks.

Data analysis plan

The statistical analysis is performed according to the CONSORT Statement recommendations for cluster-randomized trials [20]. In the intention-to-treat analysis all patients having started to use the ‘moma App’ are included. Primary endpoint is the number of headache days per 12 weeks (84 days).

Two forms of analysis are performed:

1. Intention-to-treat analysis (“Full Analysis Set”)

All patients who started to use the electronic headache diary (moma app) and fulfill the baseline criteria (see below) are included in the intention-to-treat analysis. Patients who have less than three headache days during the 12 weeks of baseline or from whom less than 33% of the days of the headache diary are filled in during baseline are excluded and are not part of the intention-to-treat analysis.

2. On-treatment analysis (“per protocol set”)

Patients who additionally completed all 4 study visits at the pediatric practices and (only in the intervention group) the three visits at the social pediatric centers and provided electronic headache diary data with less than 33% of the days missing during the intervention and follow-up phase are included in the per protocol analysis.

For headache diary data, missing data are treated as follows. If less than 33% of the days are missing, the missing data is replaced by the mean values of the existing data. If 33 to 66% of the headache diary data is missing, a modified last observation carried forward (LOCF) approach will be performed for the intention to treat analysis. To this end, missing days are replaced by the

mean values of the last 3-month period that has less than 33% missing data. If more than 66% of the data of the headache diary data is missing, a simple LOCF principle will be applied. For this, the data of the entire 3-month period will be replaced by the mean value of the last 3-month period with less than 33% missing data.

If one or more items of the PedMIDAS (6 items) is missing, the scale will be excluded from statistical analysis of this patient at this time point because it does not retain sufficient clinical informative value.

The KINDL questionnaire (4 subscales with 4 items each) allows one missing item per subscale which is replaced by the mean value of the other items of the subscale [19, 20].

For the primary end point (number of headache days per 12 weeks) a mixed linear regression model is performed with the difference of headache days per 12 weeks from baseline to follow-up as dependent variable, the intervention in a social pediatric center (yes/no) as independent variable and random effects for the different social pediatric centers. Age, sex and headache frequency per 12 weeks at baseline are included as possible confounders. Quality of life (KINDL) and migraine related disability (PedMIDAS) at baseline are possible effect modifying elements and therefore integrated in the model as interaction effects. The significance level α is set at < 0.05 . The same model is used for analysis of the secondary outcome parameters.

Discussion

Ethics, trial registration and data management

The study was approved by the local ethics committee at the Ludwig-Maximilians-University Munich (number 18–804, leading ethics committee) and approval was confirmed by all the other German ethics committees relevant for the study ($n = 15$). The study was retrospectively registered on 27 April 2021 in the WHO approved German Clinical Trials Register (number DRKS00016698). Data protection is established according to the European data protection regulation 2016/679. Only the data necessary for study conduction and analysis is obtained via the smartphone app (from the parents) and via the moma website (from the pediatricians in practice and from the social pediatric centers). The study data is saved on a dedicated server located at the University of Hof, Germany. Data is pseudonymized at the time point of collection using a hash-code based on the patient's name and birth date. This hash-code is only used to link data from the same patients on the server. It does not allow back-tracing of the patient's name or birth date. The data will be stored for ten years.

Importance and dissemination

Migraine is a prevalent and disabling disease in childhood. Therapeutic options are scarce or not well tolerated by the children or their parents. Studies about the efficacy of non-invasive, non-pharmaceutical interdisciplinary treatment in young children with focus on the association of muscle tenderness and migraine do not exist so far. Hence, the presented intervention study is of high interest not only for the young patients but also for the pediatric and scientific communities as well as for the health systems worldwide. Therefore, we plan to publish the results of the multimodal intervention study in international scientific medical journals with a high distribution rate among pediatricians and neurologists. As the topic is also relevant for health politics, the results will also be published at the homepages or newsletters of relevant medical professional societies. The study outcomes will also be discussed at national and international congresses for (Neuro-) Pediatrics.

Strengths and limitations

The first strength of the study is the possible positive impact of the results for the participating child with migraine and its family. The second strength is the randomized controlled design with planned nationwide participation of pediatricians in practice and of interdisciplinary social pediatric centers. The third strength is the clinical and political importance of the study subject: interdisciplinary intervention programs for children with migraine are mandated but efficacy studies in this age group are lacking.

A limitation pertains to health system differences between countries, reducing generalizability of study results. The realization of study might be cumbersome because of challenges for pediatric practices related to the current COVID-19 pandemic.

Abbreviations

a: Significance level; App: Smartphone application; approx: Approximately; COVID-19: Coronavirus disease 2019; G-BA: Gemeinsamer Bundesausschuss = Federal Joint Committee; ICC: Intra-class correlation coefficient; ICD-10: International Classification of Diseases 10th revision; ICHD-3: International Classification of Headache Disorders 3rd edition; IQ: Intelligence quotient; KINDL: Name of a German tool for assessing pediatric quality of life; LOCF: Last observation carried forward; moma: Modules on migraine activity = name of the study; n: Number; NSAID: Nonsteroidal antiinflammatory drugs; PedMIDAS: Pediatric Migraine Disability Assessment Score; TCC: Trigemino-cervical complex; WHO: World Health Organization

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Authors' contributions

All authors have read and approved the manuscript. MNL contributed to the idea and to the concept of the study as well as to the definition of relevant outcome parameter and gave input to the study design based on her clinical expertise in pediatrics and in the care of children with migraine. She also participated in the development of the interdisciplinary structured intervention in the social pediatric centers and took part in the

communication with them and with the pediatricians in practice. Furthermore, she essentially contributed to the creation of the project website and App.FH contributed to the idea and to the concept of the study as well as to the definition of relevant outcome parameter and gave input to the study design according to his clinical expertise in pediatrics and in the care of children with migraine. He gave essential input in the development of the project tools and of the intervention at the social pediatric centers. LG contributed by discussing statistical, clinical and political relevance of the planned study and needed design changes. CK contributed in the development of the interdisciplinary structured intervention in the social pediatric centers based on her psychological expertise regarding children with migraine. Furthermore, she contributed to the creation of the project website and App RR contributed to the study design and definition of outcome parameters and in the conception and development of the moma App and website. AS contributed to the idea and to the concept of the study as well as to the definition of relevant outcome parameter and gave input to the study design according to his clinical expertise in neurology and in the care of adults with migraine. JS contributed to the development of the moma App and moma Website allowing the collection and analysis of data for interpreting study results. SvM contributed to the statistical calculations and to the achievement of all ethical approvals throughout Germany. VO contributed to the definition of outcome parameters, to the power and sample size calculation. RvK contributed to the idea and to the concept of the study as well as to the reflection, how to reach a study participation all over Germany based on his epidemiological expertise. He also contributed to the definition of relevant outcome parameter and to the power and sample size calculations. He developed the data analysis model and did the randomization according to the postal code zips.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee at the Ludwig-Maximilians-University Munich (number 18–804, leading ethics committee) and approval was confirmed by all the other German ethics committees relevant for the study ($n = 15$). A written informed consent is required from each child and parent for this study. The informed consent forms are stored at the treating pediatricians' practice. The study was retrospectively registered on 27 April 2021 in the WHO approved German Clinical Trials Register (number DRKS00016698), https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00016698. The first version of the protocol, which is published here, was developed in 2017 and was not changed until now.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Hybrid Cognitive Behavioral Therapy Intervention for Adolescents with Co-Occurring Migraine and Insomnia: A Single-Arm Pilot Trial

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Abstract

Objective—This study aimed to evaluate feasibility and acceptability of a hybrid cognitive behavioral therapy intervention for adolescents with co-occurring migraine and insomnia.

Background—Many youth with chronic migraine have co-occurring insomnia. Little research has been conducted to evaluate behavioral treatments for insomnia in youth with migraine.

Design and Methods—We conducted a single arm pilot trial to evaluate the feasibility and acceptability of delivering cognitive-behavioral therapy for insomnia to 21 youth (mean age 15.5, standard deviation 1.6) with co-occurring chronic migraine and insomnia. Adolescents completed up to six individual treatment sessions over six to twelve weeks, and one booster session one month later. Assessments included a prospective 7-day headache and sleep diary, and self-report measures of insomnia, sleep quality, sleep habits, and activity limitations at pretreatment, immediate posttreatment, and three-month follow-up.

Results—Adolescents demonstrated good treatment adherence and families rated the intervention as highly acceptable. Preliminary analyses indicated improvements from pre-treatment to post-treatment in primary outcomes of headache days ($M = 4.7$, $SD = 2.1$ vs. $M = 2.8$, $SD = 2.7$) and insomnia symptoms ($M = 16.9$, $SD = 5.2$ vs. $M = 9.5$, $SD = 6.2$) which were maintained at three-month follow-up ($M = 2.7$, $SD = 2.8$; $M = 9.3$, $SD = 5.0$, respectively). We also found improvements in secondary outcomes of pain-related activity limitations as well as sleep quality, sleep hygiene, and sleep patterns.

Conclusions—These preliminary data indicate that hybrid cognitive-behavioral therapy is feasible and acceptable for youth with co-occurring chronic migraine and insomnia. Future

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randomized controlled trials are needed to test treatment efficacy on migraine, sleep, and functional outcomes.

Keywords

Cognitive-behavioral therapy; insomnia; headache; migraine; child; adolescent

Introduction

Migraine and insomnia are among the most common reasons adolescents present to pediatric health-care providers^{1,2}. These disorders frequently co-occur; up to 50% of adolescents with migraine report insomnia symptoms^{3–5}. When considered separately, chronic migraine (defined as migraine 15 days per month for 3 months) and insomnia (characterized by difficulties falling or staying asleep with associated daytime impairment) in youth are linked to poor quality of life, anxiety and depression, and functional disability^{1,6}.

A growing body of research suggests that insomnia may contribute to the onset, maintenance and progression of migraine and other primary headache disorders. In cross-sectional studies, insomnia has been associated with more frequent and disabling headache^{3,4}.

Longitudinal studies of adolescents and adults suggest that insomnia increases risk for the persistence of headache over time as well as progression from episodic to chronic headache status^{7,8}. Temporal daily associations between sleep and headache have revealed that poor sleep is a strong predictor of the onset and severity of next-day headache in adolescent and adult samples^{9,10}. Taken together, these data suggest that insomnia may be a promising treatment target for interventions that aim to reduce headache frequency and related disability^{11,12}.

Cognitive-behavioral therapy for insomnia (CBT-I) is the frontline treatment for insomnia in adults¹³ and numerous randomized controlled trials (RCTs) have demonstrated efficacy for improving sleep outcomes¹⁴. There have been a few RCTs which have demonstrated benefit of CBT-I for improving sleep in adolescents with insomnia^{15–18}, however, most have excluded youth with co-morbid conditions. As an exception, our research team recently demonstrated feasibility and preliminary efficacy of CBT-I for improving sleep in youth with insomnia and co-occurring psychiatric and physical health conditions¹⁹. Research is needed to understand the feasibility and efficacy of insomnia treatment for youth with chronic migraine.

CBT-I has demonstrated efficacy for improving sleep in adults with chronic migraine²⁰ and other chronic pain conditions^{21,22}. However, effects on pain have been inconsistent. It is possible that more favorable results could be achieved with a hybrid CBT intervention that simultaneously targets headache and insomnia. Hybrid CBT has demonstrated feasibility and acceptability in two small pilot studies of adults with chronic pain and insomnia^{23,24}. There has also been one randomized controlled trial comparing hybrid CBT to CBT for pain management in adults with osteoarthritis and insomnia, which found superior efficacy for hybrid CBT on both sleep and pain outcomes²⁵. Research is needed to determine whether hybrid CBT would be feasible and beneficial for youth. Indeed, CBT for pain management is a well-established intervention for youth with headache and has demonstrated benefit for

reducing headache frequency and disability in large clinical trials²⁶ and meta-analyses^{27,28}. However, most CBT for pain management protocols either do not include sleep as a treatment target, or provide very brief (1 session) sleep hygiene education²⁹.

To address this gap, we developed a hybrid cognitive-behavioral therapy intervention (hybrid CBT) for adolescents with chronic headache and co-occurring insomnia and evaluated whether the intervention was feasible to implement and acceptable to patients in a single arm pilot clinical trial. We hypothesized that treatment feasibility would be demonstrated through favorable study recruitment/enrollment statistics, session attendance, therapist ratings of participants' treatment engagement, and completion of study assessments. We also expected that adolescents and parents would rate the intervention as highly acceptable on self-report measures. To inform sample-size estimates for future trials, we also conducted preliminary analyses examining changes in headache frequency and insomnia symptoms (primary outcomes), as well as pain intensity, pain-related activity limitations, sleep quality, sleep hygiene, and sleep patterns (secondary outcomes) from pre- to posttreatment and three-month follow-up.

Methods

Study Design

Adolescents were recruited over a 12-month period (9/2016 – 9/2017) from a pediatric neurology clinic and a pediatric pain clinic at an academic medical center in the Pacific Northwest. Given the predominant focus on feasibility and acceptability, we chose to use a pre-post single arm trial design with three measurement points (baseline, immediate posttreatment, and 3-month follow-up). All participants received up to six sessions of hybrid CBT over a period of six to 12 weeks as well as a booster session one month after completing treatment. For our primary aim to evaluate feasibility and acceptability of the treatment protocol, our target enrollment was 20 participants for this pilot trial. The trial was terminated as planned after all three-month follow-up assessments were completed. Our Institutional Review board approved this study. Parents provided informed consent and adolescents provided assent prior to the initiation of study procedures. This trial was registered at clinicaltrials.gov: NCT03137147.

Participants

Eligible participants met the following criteria: 1) 11 to 17 years old (representing peak prevalence of chronic headache in childhood^{30,31}); 2) evaluated by a medical provider in the pediatric neurology or pain clinics; 3) diagnosed with chronic migraine or tension-type headache by a pediatric neurologist or pediatric pain physician using the *International Classification of Headache Disorders*, 3rd Edition Beta (ICHD-III β)³² criteria, 4) headache frequency of 15 or more days in the past month based on a telephone administered screening, and 5) met research diagnostic criteria for insomnia based on a telephone administered screening (self-reported difficulty initiating or maintaining sleep 3 or more nights during the past month and at least one daytime sleep-related problem). Potential participants were excluded for any of the following reasons: 1) serious co-morbid chronic medical condition (e.g., cancer, diabetes), 2) did not read or speak English, 3) active

psychosis or suicidal ideation, or 4) previous psychological treatment for insomnia or headache in the six months prior to screening.

Procedures

Potential participants were identified by providers during clinic visits and were given a study flyer. Providers requested permission to share contact information with the study staff.

Potentially eligible families underwent a telephone administered screening twice over a six-week period to determine whether they met study eligibility criteria. Headache frequency was determined based on responses to the following question: "On how many days in the past month did you have a headache or migraine?" The presence of insomnia was determined using a pediatric version of the Research Diagnostic Criteria for Insomnia^{19,33}. Adolescents and parents completed informed consent and assent prior to initiating any study procedures.

At pretreatment, parents completed online questionnaire measures assessing demographics, adolescent emotional and behavioral functioning (the Child Behavior Checklist; CBCL), and sleep disordered breathing (the Pediatric Sleep Questionnaire). At all three assessment time points, adolescents completed online questionnaire measures about pain-related activity limitations and sleep, as well as a prospective online 7-day headache and sleep diary. All questionnaire measures and diaries were completed privately in patients' homes via the secure web-based application REDCap³⁴. All assessment procedures were administered by a research assistant who was not involved in treatment delivery.

Following completion of the pretreatment assessment, adolescents and their parents scheduled up to 6 treatment sessions over a 6–12 week period, as well as 1 booster session scheduled 1 month after the final treatment visit. Each session was 60–90 minutes in duration. All sessions were completed in person at our research institute. Families were provided with gift cards for completion of assessments (\$80/family) and transportation/parking was reimbursed (\$20/visit) for participation in intervention visits.

Hybrid Cognitive-Behavioral Therapy for Chronic Headache and Insomnia (Hybrid CBT)

Hybrid CBT interventions have been developed to simultaneously target two or more conditions and have been studied in a variety of areas. Specifically in the context of pain conditions, hybrid CBT simultaneously targets co-morbid conditions known to impact the onset and maintenance of chronic pain³⁵. Per the guidelines outlined by Tang (2017), we developed our hybrid CBT protocol by identifying treatment components from existing evidence-based treatment manuals for CBT for insomnia and CBT for pain management^{19,29,36}, reviews on treatment effectiveness for both interventions^{27,37}, and research on shared mechanisms between headache and sleep disturbance^{3,4,7–10}. For this study, treatment materials were adapted from an existing CBT-I protocol for adolescents with insomnia¹⁹ and an existing CBT protocol for adolescents with chronic pain³⁸. A research team composed of pediatric psychologists and a pain physician with expertise in pain management, headache, sleep, insomnia, cognitive-behavioral therapy, and parent and family interventions adapted the treatment materials.

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Our hybrid CBT protocol includes three core treatment components from the published CBT-I protocol¹⁹: 1) sleep hygiene education, which promotes healthy sleep habits (e.g., avoiding caffeine, using an alarm clock); 2) stimulus control, which re-associates the bed with sleep; and 3) sleep restriction, which increases sleep efficiency by limit time spent awake in bed. Based on our prior research evaluating effective treatment components of CBT for pediatric headache²⁹, we included four core components from the published CBT pain management protocol³⁸: 1) headache education, 2) relaxation training, 3) pleasant activity scheduling and positive thought tracking, and 4) parent operant training to reinforce adolescent skills practice and reduce inadvertent reinforcement of pain behaviors (i.e., praise vs. ignoring, reward systems).

We retained two optional treatment modules from the original CBT-I protocol (anxiety management and fatigue management), and adapted the optional treatment content to include a module on activity pacing³⁸. As in the original protocol, optional treatment modules could be delivered at any point based on the therapist's clinical judgement. Treatment materials included a therapist manual, a parent manual, an adolescent manual, and skills worksheets. Treatment materials were reviewed and revised by the research team (available from the first author on request). A brief summary of the treatment content is provided in Table 1.

Based on study therapist feedback from a prior trial of CBT-I for youth¹⁹, we extended the number of treatment sessions from four to six and added a booster session. Adolescents reported on sleep patterns in an electronic daily diary during the intervention period, which study therapists used to calculate average sleep and wake times and sleep efficiency at each session. These data were used to titrate sleep restriction schedules each week. Parents met individually with the study therapist in session 1 and session 4 to receive operant training. Parents were included in all or part of the remaining sessions depending on the developmental needs of the adolescent and the therapist's clinical judgement. Session structure was flexible so that content not covered in one session could be addressed in the next session. Homework was assigned each week to titrate sleep restriction and facilitate skills practice.

Therapist Qualifications, Training, and Treatment Fidelity

Treatment was delivered by two trained postdoctoral psychology fellows who had experience in CBT for youth with chronic pain. Study therapists were trained via a 2-hour in-person workshop that included didactic instruction in pediatric headache and sleep problems, training in the intervention protocol, and discussion of case examples. To support treatment fidelity, the therapist manual was scripted and included structured worksheets to deliver skills training. Fidelity was monitored in weekly supervision using a case conference format led by the first author (a licensed pediatric psychologist with prior experience in hybrid CBT). Corrective feedback was provided as needed to ensure treatment delivery was consistent with the manual.

Measures

Pretreatment sample characteristics—Parents reported on their relationship to the adolescent, marital status, education, household income, age, and race. Parent's also reported on their child's age, race, and current prescription and over-the-counter (OTC) medication use.

To screen for sleep-related breathing disorders, parents completed the 22-item Sleep-Related Breathing Disorders Scale of the Pediatric Sleep Questionnaire³⁹. Higher scores indicate a greater risk of sleep-related breathing problems. Scores greater than 0.33 are considered to be clinically elevated. The Pediatric Sleep Questionnaire has demonstrated reliability and validity³⁹ and has been used in prior studies of youth with co-morbid insomnia and medical symptoms¹⁹.

Parents also completed the 120-item Child Behavior Checklist (CBCL) to screen for adolescent emotional and behavioral concerns⁴⁰. We examined T-scores for the internalizing symptoms, externalizing symptoms, and total problems scales. Higher scores are indicative of greater symptoms, and T-scores greater than 63 are considered clinically elevated. The CBCL has well-established reliability and validity, and has been used in prior studies of youth with chronic medical conditions including headache⁴¹.

Treatment feasibility—Treatment feasibility was assessed using three metrics: 1) study recruitment/enrollment statistics, 2) treatment adherence as demonstrated by session completion, missed/rescheduled treatment sessions, and therapist ratings of participants' homework completion, motivation to learn, understanding of the treatment principles, and rapport on a 0–10 Likert scale (completed at the end of each session and averaged across sessions for analysis), and 3) completion of study assessments.

Treatment acceptability—Parents and adolescents completed an adapted version of the Treatment Evaluation Inventory, Short Form⁴² (TEI-SF) at immediate posttreatment. The TEI-SF includes 9 items and was adapted to be specific to pediatric headache and sleep problems (e.g., "I find this treatment to be an acceptable way of dealing with children's headache and sleep problems"). Items are scored on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree") and are summed for a total score (range 9 to 45). Scores greater than 27 indicate "moderate" treatment acceptability⁴². The TEI-SF has been used in prior studies of CBT for youth with insomnia¹⁹ and youth with headache⁴³.

Headache outcome measures—Our primary headache outcome was headache frequency (number of days with headache). Adolescents completed an electronic 7-day daily diary at each assessment time point, and reported on whether or not they had a headache each day. The total number of days with headache across the 7-day diary period was used in analyses. Adolescents also reported on daily headache pain intensity using an 11-point numerical rating scale (NRS) ranging from 0 ("no pain") to 10 ("worst pain")⁴⁴. Mean pain intensity ratings across the 7-day period were used in analyses. This electronic 7-day daily diary has been used successfully to assess headache frequency and pain intensity in prior studies of adolescents with headache⁴³.

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Adolescents reported on pain-related activity limitations using the Child Activity Limitations Interview-21 (CALI-21)⁴⁵. The CALI-21 includes 21 items rated on a 5-point Likert scale ranging from 0 (“not very difficult”) to 4 (“extremely difficult”). Items are summed to create a total score, with higher scores representing greater difficulty with activity participation due to pain. The CALI-21 has been widely used to assess activity limitations in youth with chronic pain conditions including headache and has excellent psychometric properties^{43,45}.

Sleep outcome measures—Our primary sleep outcome was insomnia symptoms, which we measured using the 7-item adolescent self-report Insomnia Severity Index⁴⁶ (ISI). Items are summed to create a total score ranging from 0 to 28. Higher scores indicate more severe insomnia symptoms. The ISI has demonstrated good reliability and validity⁴⁶ and has been previously used to assess insomnia symptoms in adolescents with chronic pain conditions¹⁹.

We assessed sleep quality using the 33-item adolescent self-report Adolescent Sleep Wake Scale (ASWS)⁴⁷. Items are scored on a 6-point Likert scale ranging from 1 (“always”) to 6 (“never”). The total sleep quality score was used in analyses (range 1–6), with higher scores indicating better sleep quality. This measure has acceptable reliability and validity⁴⁷, and has been widely used to assess sleep quality in pediatric populations⁴⁸.

Adolescents also completed the Adolescent Sleep Hygiene Scale⁴⁷ (ASHS) to assess sleep hygiene behaviors over the past month. The ASHS includes 24-items rated on a 6-point Likert scale ranging from 1 (“always”) to 6 (“never”). The total sleep hygiene score was used in analyses (range 24–144), with higher scores indicating better sleep hygiene. The ASHS has demonstrated acceptable psychometric properties⁴⁷.

Sleep patterns were assessed using the electronic 7-day daily diary, where adolescents reported on sleep patterns from the previous night. Daily sleep diaries are a low-cost and accurate method of recording sleep patterns in adolescents⁴⁹, and have been used to assess sleep patterns in prior studies of youth with insomnia and medical comorbidities¹⁹. Across each 7-day assessment, average sleep efficiency, WASO (number of minutes awake after sleep onset), sleep onset latency, and total sleep time were extracted for analyses. Sleep efficiency was calculated as the ratio of estimated total sleep time divided by the sleep period, and is reported as a percentage, with values closer to 100 indicating more time asleep and less time awake in bed.

Adverse events—Participants were asked about adverse events due to study procedures at each assessment period in an open-ended manner.

Data Analysis Plan

Analyses were conducted using SPSS v. 25 (IBM Corp, 2015. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). We conducted descriptive statistics to summarize demographic and pretreatment clinical characteristics of the sample as well as quantitative ratings of treatment feasibility. To inform sample-size estimates for future trials, we conducted preliminary analyses to evaluate change over time in treatment outcomes using multilevel modeling (MLM). Outcome measures were scored and missing data

addressed per published scoring manuals, and all available data were included in analyses. MLM accounts for repeated measures within subjects, accommodates missing data, and includes all available data in analyses. Linear growth model specification procedures were based on Shek & Ma⁵⁰. Using a random intercepts model, time was treated as a categorical variable and pretreatment values were specified as the reference point so that results were interpreted as change from pretreatment to immediate posttreatment and pretreatment to follow-up. Separate linear growth models were conducted for each outcome measure. The beta, p value, and effect size (Cohen's d) are reported for each outcome. A significance level of $p = .05$ was used in this pilot trial. Effect size estimates can be interpreted as follows: $d = 0.20$ indicates a small effect, $d = .50$ indicates a medium effect, and $d = .80$ indicates a large effect⁵¹. As an exploratory analysis, we conducted a Pearson correlation to examine the association between headache frequency change scores from pretreatment to follow-up with insomnia symptoms change scores from pretreatment to follow-up.

Results

Participants

Pretreatment descriptive statistics for the sample are provided in Table 2. Participants were 21 adolescents between the ages of 11–17 years ($M = 15.5$, $SD = 1.6$) and their parents. Adolescents were predominantly female (81%) and white (81%), as were their parents (90.5% female, 95.2% white). All of the adolescents had a diagnosis of chronic migraine (100%) per their referring physician. On the Pediatric Sleep Questionnaire, none of the adolescents had clinically elevated symptoms of sleep-disordered breathing. Parent-reported CBCL scores indicated that two-thirds of the sample had clinically elevated Internalizing Problems and over one-third of the sample had clinically elevated Total Problems scores. Per parent report, most youth (90.5%) were using prescription and over the counter medications; most commonly melatonin (42.8%), topiramate (23.8%), gabapentin (19.0%), and amitriptyline (14.2%). Means and standard deviations of headache and sleep outcomes at each assessment time point are presented in Tables 3 and 4, respectively.

Treatment Feasibility

Study recruitment and enrollment—Potential participants were recruited sequentially in the order they were referred. Recruitment occurred over 12 months and resulted in 80 referrals. Twenty of the referred patients were unable to be reached during the recruitment period. Of the 60 participants who could be reached, 23 participants did not meet research criteria for insomnia on screening and an additional 16 participants declined due to distance from our research institute. The remaining 21 participants enrolled in the study and were included in analyses (overall recruitment/enrollment rate = 35%).

Treatment adherence—Four of the 21 enrolled families chose to discontinue study participation during the trial due a major health event (i.e., injury or illness) that was unrelated to the study procedures. One family discontinued study participation after completing the pretreatment assessment but prior to starting the intervention, and the remaining three families discontinued study participation after completing the pretreatment assessment and one to three treatment sessions. Of the remaining 17 participants, 100%

completed all six treatment sessions and most ($n = 13$, 75%) completed the booster session. Families who did not complete treatment did not differ from completers on demographics or pretreatment characteristics.

Participants were adherent to scheduled treatment sessions with few missed sessions (range 0 – 2; $M = 0.14$, $SD = .48$) and few rescheduled sessions (range 0–4; $M = 1.14$, $SD = 1.32$). Therapists rated participants as highly compliant with homework completion ($M = 9.50/10$, $SD = .74$), motivated ($M = 9.52/10$, $SD = .62$) and understanding of the treatment principles ($M = 9.59/10$, $SD = .76$). Therapists also reported having strong rapport with participants ($M = 9.42/10$, $SD = 1.02$).

Assessment completion—Assessment completion was high. All 21 enrolled dyads completed the pretreatment assessment (100%). As described above, 4 families subsequently withdrew from the trial, and all of the remaining 17 dyads (81%) completed the posttreatment and follow-up assessments including self-report questionnaires and prospective 7-day diaries. On average, participants completed 5 of 7 diary days at each assessment time point.

Treatment Acceptability

Parents and adolescents found the intervention to be highly acceptable (TEI-SF M parents = 40.67, $SD = 4.48$; TEI-SF M adolescents = 39.13, $SD = 5.10$). Parent and adolescent mean TEI scores exceeded the threshold mean of 27 indicating “moderate” treatment acceptability⁴²

Changes in Headache and Sleep Outcomes

Primary headache outcome: Headache frequency—Adolescents reported a significant reduction in headache frequency on the prospective 7-day diary from pretreatment to posttreatment ($b = -1.91$, $p = .004$, $d = .84$) which was maintained at follow-up ($b = -2.16$, $p = .002$, $d = .87$). These were large effects. Twelve of the 17 participants (70.5%) achieved at least a 50% reduction in headache frequency at follow-up.

Secondary headache outcomes: Headache pain intensity and activity

limitations—Headache pain intensity did not change from pretreatment to posttreatment ($b = .40$, $p = .25$, $d = -.28$) or follow-up ($b = -.15$, $p = .68$, $d = -.28$). Activity limitations were stable from pretreatment to posttreatment, and significantly improved at follow-up, with a medium effect size ($b = -11.57$, $p = .029$, $d = .69$). Means and standard deviations of headache outcomes at each assessment time point are presented in Table 3.

Primary sleep outcome: Insomnia symptoms—Adolescents reported a significant and large reduction in insomnia symptoms from pre- to posttreatment ($b = -7.32$, $p = .001$, $d = 1.31$), which was maintained at follow-up ($b = -7.60$, $p = .001$, $d = .50$).

Secondary sleep outcomes: Sleep quality, sleep hygiene, and sleep patterns—Sleep quality and sleep hygiene significantly improved from pretreatment to posttreatment ($b = .74$, $p = .001$, $d = -1.32$; $b = .51$, $p = .001$, $d = -1.09$, respectively), with medium to

large effect sizes that were maintained at follow-up ($b = .67, p = .002, d = -1.06; b = .42, p = .008, d = -.73$, respectively).

Adolescents generally reported improvements in their sleep patterns as assessed by the prospective 7-day diary. Adolescents reported a significant improvement in sleep efficiency from pretreatment to posttreatment ($b = 9.31, p = .008, d = -.60$) which was maintained at follow-up ($b = 13.51, p = .001, d = -.95$). These were medium to large effect sizes.

Adolescents reported significantly lower WASO and shorter SOL from pretreatment to posttreatment ($b = -22.98, p = .012, d = .73; b = -38.28, p = .015, d = .71$ respectively) which were medium effects, and these improvements were sustained at follow-up ($b = -23.37, p = .01, d = .74; b = -41.87, 15.21, d = .67$). Total sleep time was stable from pretreatment to posttreatment ($b = 7.53, p = .776, d = -.02$) and increased significantly from pretreatment to follow-up ($b = 89.85, p = .003, d = -.56$) which was a medium effect. Means and standard deviations of sleep outcomes at each assessment time point are presented in Table 4.

Exploratory analysis—Improvements in headache frequency from pretreatment to follow-up were highly correlated with improvements in insomnia symptoms from pretreatment to follow-up ($r = 0.50$).

Adverse Events

Four families reported serious health-related events during the trial (i.e., concussion, surgery); these were unrelated to study procedures.

Discussion

Our preliminary findings demonstrate feasibility and acceptability of a six-session hybrid CBT intervention for adolescents with chronic migraine and co-occurring insomnia. The majority of participants completed assessments, adhered to scheduled treatment visits, and completed homework assigned in therapy. Therapists rated participants as motivated to learn, demonstrating good understanding of the treatment principles, and having strong rapport. Adolescents and parents rated the treatment as highly acceptable. To our knowledge, this study is the first to deliver a hybrid CBT intervention targeting chronic headache and co-occurring insomnia in adolescents.

Although our trial was open to adolescents with chronic migraine and chronic tension-type headache, all of the participants who enrolled in our study had a diagnosis of chronic migraine. This may reflect the higher prevalence of co-morbid insomnia symptoms in youth with migraine compared to youth with other primary headache disorders⁵. Our findings demonstrate that we were able to recruit, screen, and deliver treatment to these youth, including those who had significant impairments in their daily activity participation and psychiatric functioning.

To inform future trials, we conducted preliminary analyses examining change in headache and sleep outcomes from pre- to posttreatment and 3-month follow-up. Given the small size of this single-arm pilot study, these results should be interpreted cautiously. In our small

sample, we found significant and sustained improvements in our primary outcomes of headache frequency and insomnia symptoms. Most youth who received the intervention (70.5%) achieved at least a 50% reduction in headache frequency during the study period. Adolescents also reported significant improvements in sleep quality and sleep hygiene from pretreatment to posttreatment which were maintained at follow-up. We found that activity limitations significantly improved at 3-month follow-up, following sustained improvements in headache frequency and sleep. Effect sizes for most outcomes were medium to large.

We also examined sleep patterns using a prospective 7-day diary. Consistent with the goals of CBT-I, we found that sleep efficiency significantly increased while sleep onset latency and WASO significantly decreased during the study period. We also found that diary-reported total sleep time increased by about 60 minutes from pretreatment to three-month follow-up. Other trials of CBT-I in adolescents with comorbid conditions have demonstrated similar improvements in diary-reported sleep patterns and questionnaire measures of sleep¹⁹. In our exploratory analysis, we found that improvements in headache frequency were highly correlated with improvements in insomnia symptoms.

Strengths and Limitations

A strength of this study was the use of a brief six-session treatment format, which may support feasibility and efficiency of implementation in busy primary and secondary care clinics. In standard practice, for example, CBT for headache and insomnia are typically delivered in separate courses of 4–8 sessions^{38,52}. Hybrid CBT, in contrast, provides treatment for two problems simultaneously and requires fewer points of contact for care, which has the potential to address known barriers to care related to cost and distance from trained professionals⁵³. Hybrid CBT also enables clinicians to match treatment components to patient's specific treatment needs³⁵ (i.e., co-occurring conditions), and represents a potential step towards individualized medicine for youth with migraine.

That being said, findings from our study should be considered in light of several limitations. Our sample size was small and our trial did not include a control group. We cannot determine whether improvements in headache and sleep outcomes occurred because of hybrid CBT, other treatments received during the trial (e.g., medications), and/or the passage of time. Many youth were taking medications during the trial including melatonin, topiramate, gabapentin, and amitriptyline which may have impacted results and should be considered in future studies with larger sample sizes that may be able to tease apart differences by medication status in response to treatment. In addition, we used a 7-day prospective diary to measure headache frequency in this pilot trial. It is possible that a different pattern of results could emerge with a longer assessment period (e.g., 28-day headache diary⁵⁴).

Future Directions

Our recruitment/enrollment rate was 35%, and distance from our research institute was cited as a primary reason potential participants declined to enroll in our trial. To improve accessibility, we encourage the consideration of technology (e.g., mobile app, website) to implement intervention, which could address barriers related to distance. Technology-

delivered CBT interventions have previously demonstrated efficacy for children and adolescents with chronic pain⁵⁵ and insomnia¹⁸. We believe that hybrid CBT could be successfully delivered via technology, and this is an important direction for future research.

There is a clear need for large RCTs to definitively evaluate efficacy of hybrid CBT. In addition to primary co-end points of headache frequency and insomnia symptoms, we encourage assessment of additional secondary outcome domains such as psychiatric symptoms and parenting behaviors. Future trials will need to carefully tease apart the impact of medications for headache and sleep on response to intervention. This could be accomplished by directly comparing CBT vs medication treatment arms and their combination. For example, prior large RCTs have demonstrated superior efficacy of CBT for pain management plus amitriptyline compared to amitriptyline only for adolescents with chronic migraine²⁶. Large scale RCTs may also provide opportunities to further elucidate shared cognitive or behavioral mechanisms between headaches and sleep disturbance, such as examining treatment processes that change during treatment (e.g., self-efficacy, coping) and their influence on treatment outcomes.

We are also aware of several small trials in adults and children with headache which have demonstrated efficacy of brief sleep hygiene education alone for reducing migraine frequency^{56,57}. It is possible that some youth may benefit from brief sleep hygiene education, whereas others may require more intensive treatment such as hybrid CBT or a combination of hybrid CBT with medication management. To develop adaptive interventions that can be adjusted based on patient's individual treatment needs, we encourage consideration of novel approaches to clinical trial designs such as Sequential Multiple Assignment Randomized Trial (SMART)^{58,59} approaches which can be used to determine optimal sequencing of treatment components (e.g., what is the ideal sequence for delivering sleep hygiene education, hybrid CBT, and medication management and for which patients?).

Conclusions

Our findings have several clinical implications. First, neurologists and pediatric pain physicians should be prepared to screen for sleep disturbances in adolescents with chronic headache and consult with sleep medicine specialists when needed. Second, our findings indicate that it is feasible to deliver hybrid CBT to youth with chronic migraine and co-occurring insomnia and that families found hybrid CBT to be highly acceptable and satisfactory.

Insomnia is among the most common comorbid conditions experienced by youth with chronic migraine. Hybrid CBT interventions targeting both headache and insomnia have the potential to improve outcomes for these youth while also improving efficiency of treatment delivery. Hybrid CBT is deserving of further attention by clinicians and researchers.

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Abbreviations

CBT	cognitive-behavioral therapy
CBT-I	cognitive-behavioral therapy for insomnia
RCT	randomized controlled trial
WASO	minutes awake after sleep onset

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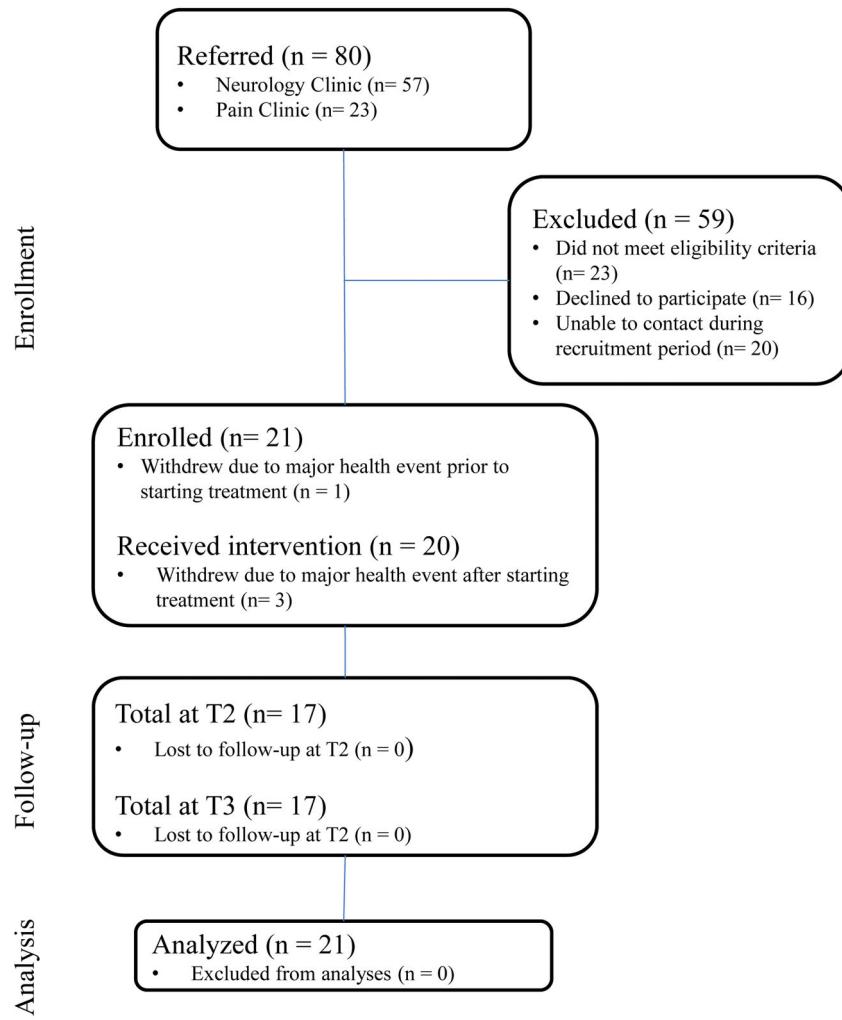


Figure 1.

Treatment Description: Hybrid CBT for Adolescents with Co-Ocurring Headache and Insomnia

Table 1

Session	Goals and content
1	<ul style="list-style-type: none"> • Establish rapport by obtaining sleep and headache history. • Provide headache and sleep education, and orient to treatment. • Begin training in sleep hygiene; select 2 healthy sleep habits for homework. • Introduce parental operant strategies (praise vs. ignoring).
2	<ul style="list-style-type: none"> • Review sleep diary and orient to use of diary data for sleep schedule. • Review success/barriers with sleep hygiene homework. • Introduce sleep restriction. Develop new sleep schedule using sleep diary data. • Introduce stimulus control. Develop nesting place and wind down routine. • Introduce relaxation methods for pain management. Training in deep breathing, plan for daily practice.
3	<ul style="list-style-type: none"> • Review sleep diary and success/barriers with homework. • Set new sleep schedule based on sleep diary. Revise stimulus control plans as needed. • Develop wake up routine. • Training in mindful breathing, plan for daily practice.
4	<ul style="list-style-type: none"> • Review sleep diary and success/barriers with homework. • Set new sleep schedule based on sleep diary. Revise stimulus control plans as needed. • Continue parent operant training (reward systems).
5	<ul style="list-style-type: none"> • Review sleep diary and success/barriers with homework. • Set new sleep schedule based on sleep diary. Revise stimulus control plans as needed. • Training in pleasant activity scheduling and positive piggy bank, plan for daily practice. • Training in progressive muscle relaxation, plan for daily practice.
6	<ul style="list-style-type: none"> • Review treatment skills, plan for maintenance and relapse prevention.
Booster	<ul style="list-style-type: none"> • Review treatment skills, plan for maintenance and relapse prevention.
Optional Interventions	<ul style="list-style-type: none"> • Anxiety management: Positive self-talk, scheduled worry time, cognitive restructuring • Activity Pacing

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Session	Goals and content	Fatigue management
	.	

Table 2

Adolescent and parent demographic characteristics at pre-treatment (n=21).

Adolescent characteristics	
Age, M (SD)	15.5 (1.6)
Sex (female), n (%)	17 (81%)
Race, n (%)	
Anglo-American	17 (81%)
Black or African-American	1 (4.8%)
Asian	1 (4.8%)
American Indian or Alaskan Native	1 (4.8%)
Other	1 (4.8%)
Headache diagnosis, n (%)	
Chronic migraine	21 (100%)
Chronic tension-type	0 (0%)
Medications, n (%)	
Antidepressants	5 (23.8%)
Anticonvulsants	2 (9.5%)
Prescription pain medications	10 (47.6%)
OTC pain medications	15 (71.4%)
Prescription sleep medications	4 (19%)
OTC sleep medications	7 (33.3%)
Other prescription medications	14 (66.7%)
Other OTC medications	9 (42.9%)
CBCL Total problems, M (SD)	59.10 (10.03)
Above clinical cutoff, n (%)	8 (38.1%)
CBCL Internalizing problems, M (SD)	64.52 (11.72)
Above clinical cutoff, n (%)	12 (66.7%)
CBCL Externalizing problems, M (SD)	48.52 (10.73)
Above clinical cutoff, n (%)	2 (9.5%)
PSQ Sleep disordered breathing M, (SD)	.13 (.06)
Above clinical cutoff, n (%)	0 (0%)
Parent characteristics	
M (SD) or n (%)	
Age, M (SD)	49.9 (6.8)
Sex (female), n (%)	19 (90.5%)
Race, n (%)	
Anglo-American	20 (95.2%)
Black or African-American	1 (4.8%)
Marital status (married), n (%)	15 (71%)
Education, n (%)	
High school or less	1 (4.8%)
Vocational school/College	13 (61.9%)

Adolescent characteristics	
Graduate/Professional school	7 (33.3%)
Annual household income, n (%)	
< \$69,999	8 (38.0%)
\$70,000 – \$100,999	3 (14.3%)
> \$100,999	10 (47.6%)

Table 3

Descriptive statistics for headache outcomes by assessment time point.

Treatment outcome	Pretreatment <i>M</i> (<i>SD</i>)	Posttreatment <i>M</i> (<i>SD</i>)	Follow-up <i>M</i> (<i>SD</i>)
Headache frequency (days per week) ^{a, b}	4.7 (2.1)	2.8 (2.7)	2.7 (2.8)
Headache pain intensity	5.2 (1.6)	5.6 (1.6)	4.6 (2.1)
Activity limitations ^b	32.7 (17.2)	24.8 (14.6)	21.19 (15.8)

Notes.

^a $p < .05$ from pre-treatment to post-treatment;

^b $p < .05$ from pre-treatment to follow-up.

Table 4

Descriptive statistics for sleep outcomes by assessment time point.

Treatment outcome	Pretreatment <i>M</i> (<i>SD</i>)	Posttreatment <i>M</i> (<i>SD</i>)	Follow-up <i>M</i> (<i>SD</i>)
Insomnia symptoms ^{a, b}	16.9 (5.2)	9.5 (6.2)	9.3 (5.0)
Sleep quality ^{a, b}	3.3 (0.4)	4.1 (0.8)	4.0 (0.9)
Sleep hygiene ^{a, b}	4.5 (0.5)	5.0 (0.4)	4.9 (0.6)
Sleep patterns			
Sleep efficiency (%) ^{a, b}	80.8 (12.3)	88.1 (12.0)	90.8 (6.5)
Wake after sleep onset ^{a, b}	32.0 (35.1)	11.5 (11.4)	10.6 (12.6)
Sleep onset latency ^{a, b}	1:15 (0:52)	0:39 (0:48)	0:43 (0:39)
Total sleep time ^b	7:36 (1.29)	7:38 (1:30)	8:25 (1.23)

Notes. Times are reported as hours:minutes;

^a $p < .05$ from pre-treatment to post-treatment;

^b $p < .05$ from pre-treatment to follow-up.



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Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine

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Abstract

BACKGROUND—Which, medication, if any, to use to prevent the headache of pediatric migraine has not been established.

METHODS—We conducted a randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg per kilogram of body weight per day), topiramate (2 mg per kilogram per day), and placebo in children and adolescents 8 to 17 years of age with migraine. Patients were randomly assigned in a 2:2:1 ratio to receive one of the medications or placebo. The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of a 24-week trial. Secondary outcomes were headache-related disability, headache days, number of trial completers, and serious adverse events that emerged during treatment.

RESULTS—A total of 361 patients underwent randomization, and 328 were included in the primary efficacy analysis (132 in the amitriptyline group, 130 in the topiramate group, and 66 in the placebo group). The trial was concluded early for futility after a planned interim analysis. There were no significant between-group differences in the primary outcome, which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group (amitriptyline vs. placebo, $P = 0.26$; topiramate vs. placebo, $P = 0.48$; amitriptyline vs. topiramate, $P = 0.49$). There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Patients who received amitriptyline or topiramate had higher rates of

*A complete list of investigators in the Childhood and Adolescent Migraine Prevention (CHAMP) trial is provided in the Supplementary Appendix, available at NEJM.org.
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several adverse events than those receiving placebo, including fatigue (30% vs. 14%) and dry mouth (25% vs. 12%) in the amitriptyline group and paresthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group. Three patients in the amitriptyline group had serious adverse events of altered mood, and one patient in the topiramate group had a suicide attempt.

CONCLUSIONS—There were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks. The active drugs were associated with higher rates of adverse events. (Funded by the National Institutes of Health; CHAMP ClinicalTrials.gov number, NCT01581281).

More than 6 million children and adolescents in the United States have migraines.^{1–3} The majority continue to have headaches into adulthood, taking a toll on the U.S. economy of approximately \$36 billion and resulting in substantial effects on quality of life.^{4–7} Pediatric clinical practice guidelines for migraine treatment are consensus based rather than evidence based,^{8,9} with no Food and Drug Administration (FDA)–approved migraine prevention medication for children younger than 12 years of age.

The Childhood and Adolescent Migraine Prevention (CHAMP) trial tested the effects of amitriptyline and topiramate in comparison with each other and with placebo in pediatric migraine. Previous studies of this disorder have shown high placebo response rates (up to 50 to 60%).^{10–14} The two medications were chosen on the basis of a survey of pediatric headache specialists, who indicated that these drugs were the most commonly used preventive medications.^{8,9} Both the International Headache Society Clinical Trial Guidelines¹⁵ and respondents to the same survey indicated that a clinically meaningful end point is a reduction of 50% or more in days on which a patient had headache. The CHAMP trial involved three hypotheses related to the primary end point of a relative reduction of 50% or more in the number of headache days from the 28-day baseline period to the final 28 days of the 24-week trial: that amitriptyline would provide greater relief than placebo, that topiramate would provide greater relief than placebo, and that one of the active treatments would provide greater relief than the other active treatment.

METHODS

TRIAL DESIGN AND OVERSIGHT

The CHAMP trial was a phase 3, multicenter, double-blind, placebo-controlled trial funded by the National Institutes of Health.¹⁶ An independent data and safety monitoring board that was appointed by the National Institute of Neurological Disorders and Stroke (NINDS) participated in the protocol review and provided trial oversight in collaboration with the NINDS. The trial was conducted under an investigational new drug application with the FDA. Patients were enrolled from 31 sites in the United States. Written permission from a parent or guardian and, when appropriate, child assent were obtained.¹⁷ Randomization was stratified according to age (8 to 12 years vs. 13 to 17 years) and the number of headache days on the basis of the diary kept during the 28-day baseline period (4 to 14 [episodic] vs. 15 [chronic]).

The authors were responsible for all elements of the trial, including design, data collection, analysis, and interpretation. Data were collected by the site investigators and site trial staff and were transmitted electronically to a data coordinating center for analysis: all data remained confidential and blinded during the trial. All the authors were involved in each stage of the manuscript development and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org. The data and safety monitoring board and the NINDS reviewed and provided feedback on the manuscript to the authors, who had full editorial control of the manuscript.

The investigational pharmacy at Cincinnati Children's Hospital Medical Center purchased generic drugs for this trial with the use of grant funds. Trial drugs and placebo were enclosed in capsules to maintain blinding.

TRIAL POPULATION

Children and adolescents 8 to 17 years of age were eligible for participation. Inclusion criteria^{16,17} included a diagnosis of migraine with or without aura or chronic migraine without continuous headache, as defined by the International Classification of Headache Disorders, 2nd Edition¹⁸; a score on the Pediatric Migraine Disability Assessment Scale (PedMIDAS) of 11 to 139 (range, 0 to 240, with a score of 0 to 10 indicating no disability, 11 to 30 mild disability, 31 to 50 moderate disability, and >50 severe disability)¹⁹; and a headache frequency of 4 or more days from a prospective headache diary over a baseline period of 28 days.

TRIAL INTERVENTION

After the baseline period, eligible patients were randomly assigned in a 2:2:1 ratio to receive oral amitriptyline, topiramate, or placebo, administered in a divided dose of 1 capsule twice daily. The target dose was 1 mg per kilogram of body weight per day for amitriptyline and 2 mg per kilogram per day for topiramate. Dose escalation occurred every 2 weeks over a period of 8 weeks, with dose modification based on side effects. A 16-week constant-dose (maintenance) phase followed at the highest dosage achieved. Site investigators ended drug treatment for patients with severe side effects occurring during the maintenance period of the trial, but these patients were followed for safety monitoring. Decisions regarding cessation of medication and withdrawal from the trial were made with input from the family, site-investigator judgment, and medical-monitor recommendations. After the 24-week treatment period, a 2-week weaning period and a 4-week follow-up occurred. Details of the trial protocol were published previously.^{16,17}

TRIAL ASSESSMENTS

Patients completed a daily headache diary, in accordance with the NINDS Common Data Elements.²⁰ A headache day was defined as any day during which a headache occurred within a 24-hour period starting at midnight. The PedMIDAS, which assesses the effect of migraines on school, home, play, and social activities, was used to determine the change in headache-related disability between baseline and the end of the trial. Safety was assessed with the use of adverse-event reports that were collected from parents and patients by means

of a structured interview. Weight, height, vital signs, clinical laboratory tests, and physical and neurologic examinations were serially monitored, according to the protocol. Serious adverse events were reported by site investigators, then reviewed on an urgent basis by the medical safety monitor, who determined the potential relationship to treatment. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 11.0. The Child Depression Inventory (with raw scores ranging from 0 to 54 and higher scores indicating more severe depression),²¹ Behavior Rating Inventory of Executive Function (BRIEF),²² and electrocardiographic (ECG) measures were used in conjunction with the review of adverse events by the medical monitor on a quarterly basis to further assess safety. Adherence was assessed by means of central analysis of blood levels of amitriptyline or topiramate, depending on the treatment assignment.

TRIAL OUTCOMES

The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of the 24-week trial. Four secondary outcomes were headache disability, as measured by absolute change in the PedMIDAS score; the absolute reduction in the number of headache days, from the 28-day baseline period to the final 28-day period of treatment; number of trial completers, as assessed by the percentage of patients who completed the 24-week treatment period; and serious adverse events that emerged during treatment.

STATISTICAL ANALYSIS

We chose the sample size to ensure adequate power, assuming that 50% of the patients receiving placebo versus 70% of those receiving amitriptyline or topiramate would have a reduction in the number of headache days of 50% or more, with a 15% dropout rate. We planned to enroll 675 patients (270 in the amitriptyline group, 270 in the topiramate group, and 135 in the placebo group) to provide at least 85% power to detect all differences between active treatment and placebo and 90% power to detect a difference of 15 percentage points between the two active treatments. Interim assessments for futility as well as efficacy were planned when 225 and 450 patients had completed their 24-week visit. Stopping for futility was to occur if the conditional power based on the prespecified effect for both treatments compared with placebo fell below 20 percentage points.

In November 2014, the first of two planned interim analyses occurred on the basis of data from 225 randomly assigned patients who had completed the trial; another 103 randomly assigned patients subsequently completed the trial, for a total of 328 patients analyzed for the primary outcome, as described below. The conditional power at the time of the interim analysis was 16 percentage points for the comparison between amitriptyline and placebo and 14 percentage points for the comparison between topiramate and placebo, and both met the threshold for futility. After considering all the evidence, including the conditional power calculated in a number of sensitivity analyses (e.g., multiple imputation and observed data only) to assess the effect of missing data, the data and safety monitoring board recommended early closure of the trial for futility. The NINDS accepted the recommendation and closed the trial.

Owing to the early stopping of the trial, the primary efficacy analyses and secondary analyses of disability, headache frequency, and drug discontinuation included all patients who either had complete headache-diary data at the end-point visit or had a date for an expected end-point visit on or before the target date for completion of the last weaning visit in the original closeout plan (February 4, 2015). All randomly assigned patients were included in the safety analyses.

The primary analysis used a logistic-regression model. The models and corresponding odds ratios were adjusted for age and for the number of headache days during the 28-day baseline period. Each was tested with the use of a Bonferroni corrected significance level of 0.017 (i.e., $0.05 \div 3$). These analyses followed the intention-to-treat principle.

For the primary analyses, we imputed an outcome of treatment failure for any patient who either withdrew early for any reason or did not provide headache-diary data at week 24. We used a series of sensitivity analyses to assess the effect of missing data on the primary analysis results. In alternative imputation approaches, we assumed that all patients who withdrew owing to side effects had treatment failures. For all other patients, end points were imputed with the use of a series of sensitivity analyses.

Secondary end points were analyzed with the use of linear regression for continuous variables and binary data methods for categorical variables. These models were adjusted for age and the number of headache days during the baseline period. In the analysis of headache-related disability, we also adjusted for the baseline PedMIDAS score. A multiple-comparisons adjustment similar to that used for the primary analysis was implemented for the secondary comparison of the difference in the change in mean headache days over the 24-week treatment period but not for any of the other secondary comparisons.

Continuous variables were summarized by means, standard deviations, and minimum and maximum variables. Categorical variables were summarized by percentages. Comparisons of baseline variables between trial groups were performed with the use of t-tests for continuous variables and Fisher's exact test for categorical variables. No adjustments were made for baseline comparisons.

The mean T score from the Child Depression Inventory and the mean BRIEF global composite score (with the raw score converted to a T score of 0 to 100 and higher scores indicating more [or more severe] symptoms for both inventories) were calculated and compared among trial groups at baseline, visit 5, and visit 8. Binary indicators of a Child Depression Inventory T score greater than 80 and an answer of "yes" to the item on suicidal intent or ideation were also compared with the use of Fisher's exact test among the groups.

RESULTS

PATIENTS

From July 16, 2012, through November 24, 2014, a total of 488 children and adolescents agreed to participate in the trial and were assessed for eligibility. Of those patients, 361 underwent randomization (Fig. 1) to receive amitriptyline (144 patients), topiramate (145

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patients), or placebo (72 patients) in a 2:2:1 ratio. The baseline characteristics of the patients were similar across the three groups (Table 1). The mean (\pm SD) age was 14.2 ± 2.4 years, and the trial population was predominantly female (68%) and white (70%). The mean number of headache days in the first 28 days of diary recordings for all patients was 11.4 ± 6.1 .

Additional baseline data have been published previously.¹⁷ The final average dose was 0.99 ± 0.18 mg per kilogram for amitriptyline and 1.93 ± 0.40 mg per kilogram for topiramate.

PRIMARY OUTCOME

In the intention-to-treat analysis of 328 patients included before trial closure, the percentage of patients who had a relative reduction of 50% or more in the number of headache days was 52% in the amitriptyline group, 55% in the topiramate group, and 61% in the placebo group, in the comparison of the 28-day baseline period with the last 28 days of the 24-week trial (Table 2 and Fig. 2). The adjusted odds ratio for the primary outcome was 0.71 (98.3% confidence interval [CI], 0.34 to 1.48; $P = 0.26$) for amitriptyline versus placebo and 0.81 (98.3% CI, 0.39 to 1.68; $P = 0.48$) for topiramate versus placebo. There was no significant difference in effect when the two active drugs were compared with each other (odds ratio for amitriptyline vs. topiramate, 0.88; 98.3% CI, 0.49 to 1.59; $P = 0.49$).

In sensitivity analyses using headache data obtained at baseline and week 24, there were 264 patients available for analysis. The percentage of patients with a relative reduction of 50% or more in the number of headache days was 66% with amitriptyline, 71% with topiramate, and 68% with placebo. Adjusted odds ratios were 0.94 for amitriptyline versus placebo ($P = 0.86$), 1.18 for topiramate versus placebo ($P = 0.64$), and 0.80 for amitriptyline versus topiramate ($P = 0.45$). The results of an additional sensitivity analysis involving multiple imputation are shown in Figure 2. By combining these approaches, we estimated that 52 to 66% of the patients in the amitriptyline group, 55 to 71% of the patients in the topiramate group, and 61 to 68% of the patients in the placebo group had a relative reduction of 50% or more in the number of headache days. Owing to the consistency of results across all the sensitivity analyses examining the effect of missing data, the results described below are from the subgroup of patients with data at both baseline and the end-point visit (visit 8).

SECONDARY OUTCOMES

Headache-Related Disability—The baseline PedMIDAS score did not differ significantly among the three trial groups ($P = 0.77$). The absolute change in the score was -22.5 (95% CI, -27.6 to -17.4) with amitriptyline, -26.8 (95% CI, -32.2 to -21.5) with topiramate, and -22.6 (95% CI, -30.2 to -15.0) with placebo (Table 2). There were no significant model-adjusted differences between groups: amitriptyline versus placebo, -0.4 (95% CI, -6.6 to 6.0 ; $P = 0.91$); topiramate versus placebo, -4.8 (95% CI, -11.2 to 1.5 ; $P = 0.13$); and amitriptyline versus topiramate, 4.5 (95% CI, -0.9 to 9.9 ; $P = 0.10$).

Headache Days—In the comparison of the number of days on which patients had a headache in the 28-day baseline period and the 28 days preceding week 24, patients with both measurements showed an absolute change of -6.7 days (95% CI, -7.9 to -5.5) with amitriptyline, -6.7 days (95% CI, -7.6 to -5.7) with topiramate, and -5.9 days (95% CI, -7.7 to -4.1) with placebo (Table 2). There were no significant model-adjusted differences

between groups: amitriptyline versus placebo, -0.7 days (98.3% CI, -2.6 to 1.2; $P = 0.36$); topiramate versus placebo, -0.6 days (98.3% CI, -2.5 to 1.2; $P = 0.41$); and amitriptyline versus topiramate, -0.1 days (98.3% CI, -1.7 to 1.5; $P = 0.90$).

Trial Discontinuation—The percentage of randomly assigned patients who completed the 24-week treatment phase was 80% with amitriptyline, 78% with topiramate, and 89% with placebo (Table 2). There were no significant differences in dropout rates between trial groups (amitriptyline vs. placebo, $P = 0.16$; topiramate vs. placebo, $P = 0.08$; and amitriptyline vs. topiramate, $P = 0.76$).

Serious Adverse Events—A total of 12 serious adverse events that emerged during treatment were reported (6 in the amitriptyline group, 4 in the topiramate group, and 2 in the placebo group), occurring in 11 patients. Investigators who were unaware of treatment assignments determined that 5 serious adverse events were treatment-related: 3 instances of altered mood (in the amitriptyline group) and 1 incidence each of a suicide attempt (in the topiramate group) and syncope (in the amitriptyline group). No significant trends were observed in serious adverse events that emerged during treatment across the three groups.

SAFETY

A total of 852 adverse events were reported (301 with amitriptyline, 419 with topiramate, and 132 with placebo), in 272 patients (Table 3). There were no deaths in the trial.

Adverse events that occurred significantly more often in the amitriptyline group than in the placebo group were fatigue (30% vs. 14%, $P = 0.01$) and dry mouth (25% vs. 12%, $P = 0.03$). Adverse events that occurred significantly more often in the topiramate group than in the placebo group were paresthesia (31% vs. 8%, $P < 0.001$) and decreased weight (8% vs. 0%, $P = 0.02$). Other commonly occurring adverse events with topiramate were fatigue (25%), dry mouth (18%), memory impairment (17%), aphasia (16%), cognitive disorder (16%), and upper respiratory tract infection (12%).

There were no observed differences in any of the Child Depression Inventory characteristics (mean score, percentage of patients with a T score >80 , or percentage of patients with an answer of “yes” to the item on suicidal intent or ideation), the mean BRIEF T score, or results of the ECG readings at baseline, visit 5, or visit 8.

ADHERENCE AND CROSSOVER

A total of 205 patients in the active-treatment groups had end-point data, and treatment adherence was assessed for 202 patients (103 in the amitriptyline group and 99 in the topiramate group). Of these patients, 81% of those who received amitriptyline and 74% of those who received topiramate had detectable drug levels in their blood samples. Crossover between trial groups occurred in only 1 patient, who was assigned to amitriptyline but who took topiramate 3 weeks before the end of the trial; this patient was imputed to have had a treatment failure owing to a lack of end-point headache data. Because all the patients who did not provide trial data at the final visit were imputed to have had treatment failures in the

primary analysis, it is unlikely that crossover or adherence had any meaningful effect on the overall trial results.

DISCUSSION

This trial, which was stopped early owing to futility, showed that neither of two preventive medications for pediatric migraine was more effective than placebo in reducing the number of headache days over a period of 24 weeks. Patients who received amitriptyline or topiramate had higher rates of adverse events than those who received placebo. During the trial, the FDA approved topiramate for the treatment of episodic migraine in adolescents 12 to 17 years of age. Although our trial included patients outside this age range and included those with either episodic or chronic migraine, the trial results suggest that prevention medication for pediatric migraine might be reexamined.

In this trial, we found a high placebo response rate that was similar to the rate reported in previous headache and pain trials.^{10–14,23,24} It is possible that this effect can be advantageous for children and adolescents with migraine.¹² In planning for the CHAMP trial, statistical simulations¹⁶ included the possibility of a placebo effect of 40 to 55% and medication response rates of 50 to 95%. Results indicated a probability of more than 95% that we would find no significant differences when a high placebo response rate and a low drug response rate occurred. In this trial, we did not find age-related contributions to the placebo or drug response. It is possible that the percentage of patients who completed the 24-week treatment period might have differed significantly between the medication groups and the placebo group if the trial had continued to enroll the full anticipated sample.

Given the null outcome in this trial and the adverse events and serious adverse events reported in the amitriptyline and topiramate groups, the data do not show a favorable risk–benefit profile for the use of these therapies in pediatric migraine prevention, at least over the 24-week duration of the trial. Our findings also suggest that the adult model of headache treatment, in which amitriptyline and topiramate have been effective, may not apply to pediatric patients.²⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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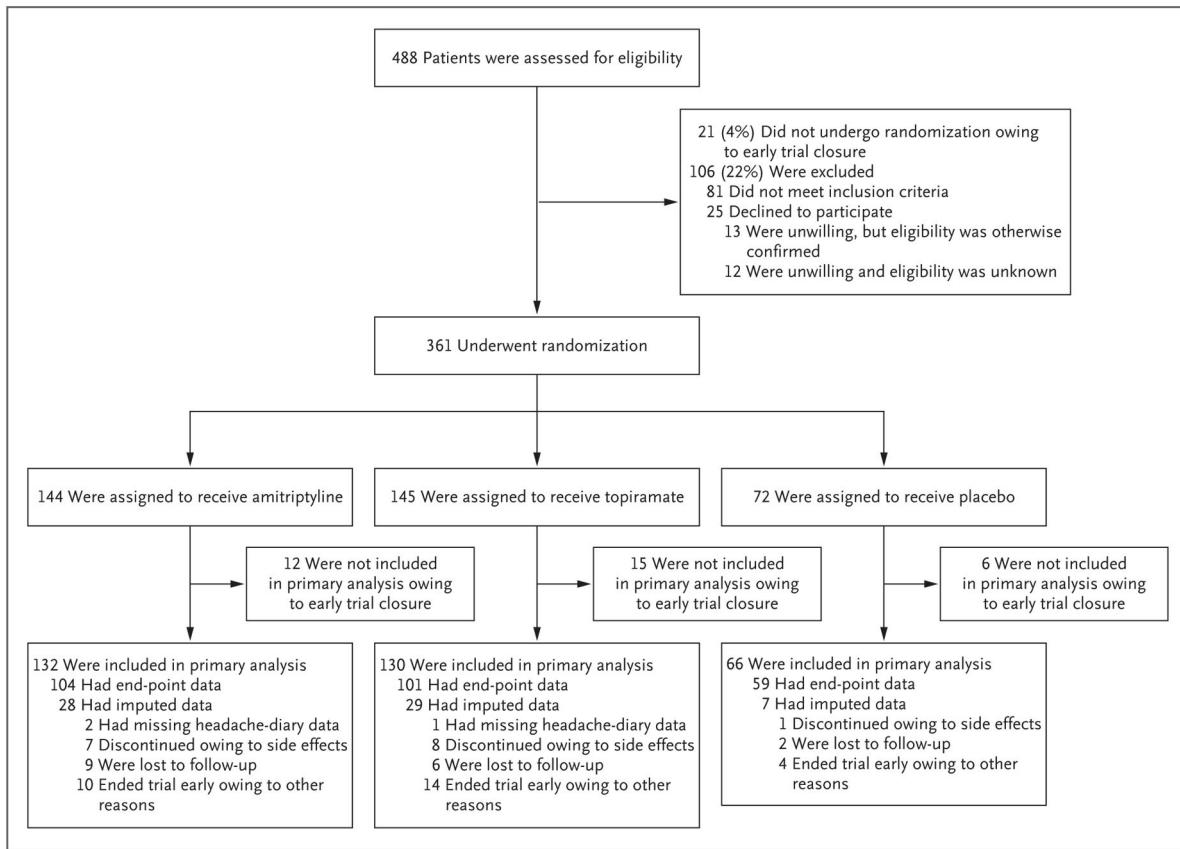


Figure 1. Randomization and Follow-up

Among the patients who did not meet the inclusion criteria, the primary reasons for ineligibility included headache frequency (38 patients), score on the Pediatric Migraine Disability Assessment Scale (23 patients), and other medical conditions (15 patients). Among the patients who declined to participate, the primary reasons included concerns about side effects (4 patients), lack of time (3), and other reasons (12 patients). The trial was stopped early for futility on the recommendation of the data and safety monitoring board.

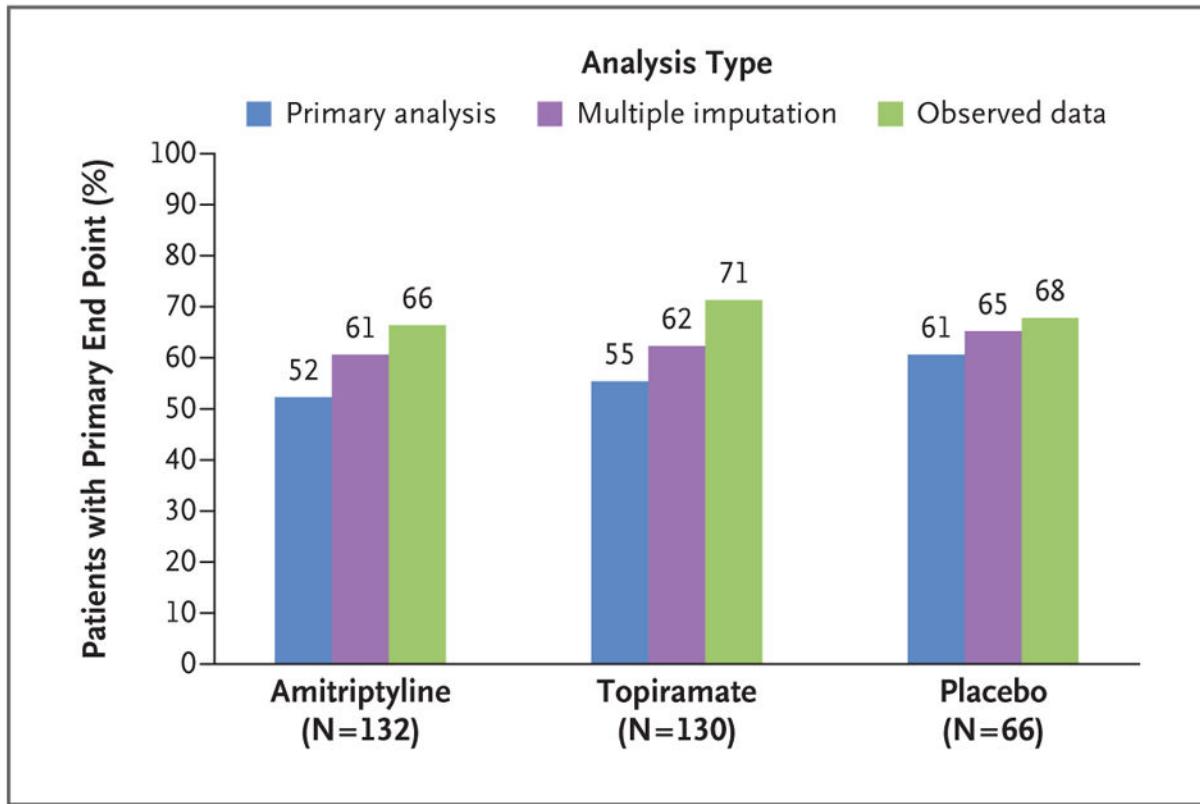


Figure 2. Patients with a Relative Reduction of 50% or More in the Number of Headache Days

Shown is the percentage of patients with a relative reduction of 50% or more in the number of headache days in the comparison of the 4-week baseline period with the last 4 weeks of a 24-week trial (primary end point). Results are shown for the primary analysis and two a priori sensitivity analyses to assess the effect of missing data. Sample sizes for the trial groups represent the primary analysis population. For observed data, the population is the subgroup with observed data at week 24.

Table 1

Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N = 361)	Amitriptyline (N = 144)	Topiramate (N = 145)	Placebo (N = 72)
Age — yr	14.2±2.4	14.2±2.4	14.2±2.5	14.2±2.2
Female sex — no. (%)	247 (68)	97 (67)	101 (70)	49 (68)
Race or ethnic group — no. (%)†				
White	253 (70)	107 (74)	98 (68)	48 (67)
Black	67 (19)	26 (18)	24 (17)	17 (24)
Asian	6 (2)	0	6 (4)	0
American Indian or Alaska Native	27 (7)	8 (6)	14 (10)	5 (7)
Native Hawaiian or Pacific Islander	1 (<0.05)	0	1 (1)	0
Not reported or unknown	7 (2)	3 (2)	2 (1)	2 (3)
Non-Hispanic ethnic group	316 (88)	128 (89)	123 (85)	65 (90)
PedMIDAS score‡	41.9±26.8	40.6±26.4	42.6±27.4	42.9±26.7
Headache days during 28-day baseline period	11.4±6.1	11.5±6.2	11.5±6.1	11.0±6.3

* Plus-minus values are means ±SD. There were no significant differences among the three groups.

† Race and ethnic group were reported by the patient or surrogate.

‡ Scores on the Pediatric Migraine Disability Assessment Scale (PedMIDAS) range from 0 to 240, with a score of 0 to 10 indicating no disability, 11 to 30 mild disability, 31 to 50 moderate disability, and more than 50 severe disability.

Table 2

Primary and Secondary Outcomes.*

Outcome	Amitriptyline (N = 132)	Topiramate (N = 130)	Placebo (N = 66)
Primary outcome[†]			
50% Relative reduction in headache frequency — no. (%)	69 (52)	72 (55)	40 (61)
98.3% CI	42 to 63	45 to 66	45 to 75
P value for pairwise comparison with placebo	0.26	0.48	—
Secondary outcomes			
PedMIDAS score [‡]			
At baseline	41.3±27.9	41.2±25.0	42.0±27.0
At wk 24	18.8±25.3	14.4±17.3	19.4±20.8
Observed absolute difference (95% CI)	-22.5 (-27.6 to -17.4)	-26.8 (-32.2 to -21.5)	-22.6 (-30.2 to -15.0)
P value for pairwise comparison with placebo	0.91	0.13	—
Headache days per 28-day period [§]			
At baseline	11.3±6.0	11.3±5.7	11.1±6.5
At wk 24	4.6±4.6	4.6±5.3	5.2±6.5
Observed absolute difference (95% CI)	-6.7 (-7.9 to -5.5)	-6.7 (-7.6 to -5.7)	-5.9 (-7.7 to -4.1)
P value for pairwise comparison with placebo	0.36	0.41	—
Completion outcomes[¶]			
Patients who completed the trial — no. (%)	106 (80)	102 (78)	59 (89)
95% CI	73 to 86	71 to 85	80 to 95
Patients who withdrew owing to side effects — no. (%)	7 (5)	8 (6)	1 (2)
95% CI	3 to 11	3 to 12	<0.5 to 8

* Plus-minus values are means ±SD. No pairwise comparisons met the criteria for statistical significance. CI denotes confidence interval.

[†]The primary efficacy analysis population included all the patients who either had an observed end-point visit with complete headache-diary data or had a target date for an expected end-point visit on or before the target date for completion of the last weaning visit in the original closeout plan (February 4, 2015).

[‡]The analysis population included all the patients who had observed end-point data: 107 in the amitriptyline group, 104 in the topiramate group, and 60 in the placebo group.

[§]The analysis population included all the patients who had observed end-point data: 104 in the amitriptyline group, 101 in the topiramate group, and 59 in the placebo group.

[¶]According to the statistical analysis plan, a concern about side effects was defined as a percentage of patients who complete the 24-week treatment period for the two active-treatment groups that was significantly lower than the percentage among patients receiving placebo or a percentage that was significantly less than 65%.

Adverse Events and Serious Adverse Events.*

Table 3

Adverse Event	All Patients (N = 361)		Amitriptyline (N = 144)		Topiramate (N = 145)		Placebo (N = 72)	
	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events
<i>Nervous system</i>								
Aphasia	43 (12)	13 (9)	0	0	23 (16)	0	7 (10)	0
Cognitive disorder	45 (12)	14 (10)	0	0	23 (16)	0	8 (11)	0
Dizziness	13 (4)	3 (2)	0	0	9 (6)	0	1 (1)	0
Memory impairment	42 (12)	11 (8)	0	0	24 (17)	0	7 (10)	0
Paresthesia	61 (17)	10 (7)	0	0	45 (31)†	0	6 (8)	0
Syncope	3 (1)	3 (2)	1 (1)	0	0	0	0	0
General: fatigue	89 (25)	43 (30)†	0	0	36 (25)	0	10 (14)	0
<i>Gastrointestinal</i>								
Dry mouth	71 (20)	36 (25)†	0	0	26 (18)	0	9 (12)	0
Intussusception	1 (<0.5)	0	0	0	1 (1)	1 (1)	0	0
<i>Infection</i>								
Appendicitis	1 (<0.5)	0	0	0	0	0	1 (1)	1 (1)
Streptococcal pharyngitis	12 (3)	7 (5)	0	0	1 (1)†	0	4 (6)	1 (1)
Upper respiratory tract infection	42 (12)	14 (10)	0	0	18 (12)	0	10 (14)	0
<i>Psychiatric</i>								
Altered mood	29 (8)	11 (8)	3 (2)	14 (10)	0	4 (6)	0	0

Adverse Event	All Patients (N = 361)		Amitriptyline (N = 144)		Topiramate (N = 145)		Placebo (N = 72)	
	Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events
<i>Injury, poisoning, or procedural complication</i>								
Contusion	7 (2)	3 (2)	0	1 (1)	1 (1)	1 (1)	3 (4)	0
Hand fracture	3 (1)	0 [#]	0	0 [#]	0	0	3 (4)	0
Traumatic liver injury	1 (<0.5)	0	0	1 (1)	1 (1)	0	0	0
Respiratory: bronchospasm	5 (1)	3 (2)	1 (1)	1 (1)	1 (1)	0	1 (1)	0
Immune system: anaphylactic reaction	1 (<0.5)	1 (1)	1 (1)	0	0	0	0	0

* Shown are serious adverse events, adverse events occurring in more than 5% of the patients in a trial group, and adverse events that differed significantly between an active-treatment group and the placebo group. A total of four serious adverse events in the amitriptyline group (one event of syncope and three events of altered mood) and one serious adverse event in the topiramate group (one suicide attempt) were considered to be treatment-related by the medical safety monitor. No patients had more than one treatment-related serious adverse event.

[#] The difference in the comparison with placebo was significant in this category.

RESEARCH ARTICLE

Analysis of Trigger Factors in Episodic Migraineurs Using a Smartphone Headache Diary Applications

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Abstract

Background

Various stimuli can trigger migraines in susceptible individuals. We examined migraine trigger factors by using a smartphone headache diary application.

Method

Episodic migraineurs who agreed to participate in our study downloaded smartphone headache diary application, which was designed to capture the details regarding headache trigger factors and characteristics for 3 months. The participants were asked to access the smartphone headache diary application daily and to confirm the presence of a headache and input the types of trigger factors.

Results

Sixty-two participants kept diary entries until the end of the study. The diary data for 4,579 days were analyzed. In this data set, 1,099 headache days (336 migraines, 763 non-migraine headaches) were recorded; of these, 772 headache events had trigger factors, and 327 events did not have trigger factors. The common trigger factors that were present on headache days included stress, fatigue, sleep deprivation, hormonal changes, and weather changes. The likelihood of a headache trigger was 57.7% for stress, 55.1% for sleep deprivation, 48.5% for fatigue, and 46.5% for any trigger. The headaches with trigger factors were associated with greater pain intensity ($p < 0.001$), headache-related disability ($p < 0.001$), abortive medication use ($p = 0.02$), and the proportion of migraine ($p < 0.001$), relative to those without trigger factors. Traveling (odd ratios [OR]: 6.4), hormonal changes (OR: 3.5), noise (OR: 2.8), alcohol (OR: 2.5), overeating (OR: 2.4), and stress (OR: 1.8) were significantly associated with migraines compared to non-migraine headaches. The headaches that were associated with hormonal changes or noise were more often

migraines, regardless of the preventive medication. The headaches due to stress, overeating, alcohol, and traveling were more often migraines without preventive medication, but it was not evident with preventive medication.

Conclusion

Smartphone headache diary application is an effective tool to assess migraine trigger factors. The headaches with trigger factors had greater severity or migraine features. The type of triggers and the presence of preventive medication influenced the headache characteristics; hence, an investigation of trigger factors would be helpful in understanding migraine occurrences.

Introduction

Migraines are characterized by recurrent headaches and a hypersensitivity to sensory stimuli [1]. Various external and internal stimuli can lead to migraine events in susceptible individuals, which can be considered as migraine triggers or precipitants [2, 3]. The reported migraine triggers include stress, sleep, fatigue, fasting, physical exercise, hormonal changes, weather, sunlight, alcohol, and various sensory stimuli [4–9]. Most studies that examined migraine trigger factors were based on participant reports. These trigger factors are found in 73–80% of migraineurs [10, 11].

Most migraineurs encounter their migraine triggers daily without suffering a migraine attack, and only some migraineurs experience a migraine attack provoked by a trigger factor [4]. To avoid general exposure to migraine triggers, a process to identify personal headache triggers in real life may be useful for migraine sufferers. Moreover, the estimation of the degree of each trigger factor's contribution to a headache occurrence is meaningful. Schurks et al. recently proposed that triggering or precipitating factors were important for the characterization of migraine phenotypes, despite being excluded from the current diagnostic criteria for a headache disorder [12]. Diary studies using advanced statistical modeling techniques may be required for the reliable identification of one's migraine trigger factors [13, 14]. In a paper diary study using a Cox regression analysis, hormonal changes exerted the most prominent influence, increasing the likelihood of a headache occurrence [15].

While most patients have reported one or more triggers, the major limitation to accepting these triggers as precipitating factors resides in the reliability of the patient's migraine trigger recall and selection [3, 10]. In addition, the causal relationships between triggers and migraines are currently uncertain.

Traditionally, the paper diary has been used to investigate the association between a trigger exposure and a migraine attack. Electronic diaries may be superior to paper diaries in that they offer advantages, such as a reduction of recall bias, easy accessibility for physicians and patients, and improved compliance [16–19]. Recently, advances in information technology have resulted in the development of electronic headache diaries using hand-held devices, such as smartphones. However, only a few headache diary studies using smartphones or handheld devices have evaluated the association between trigger exposures and migraine attacks [17, 20]. Computer-based electronic diaries require special equipment, such that real-time data collection can be difficult [16, 20]. In order to overcome the limitations associated with an internet-based online diary, we created the Smartphone Headache Diary Application (SHD), which is easy to use and accessible, in order to enable patients to record data on a near real-time basis [21–23].

Therefore, in this study, we investigated the frequencies and impacts of triggers in episodic migraine patients using our SHD.

Methods

Participants and baseline survey

The participants who met the inclusion criteria were recruited between September 2014 and January 2015. This study was conducted at the neurology outpatient clinics of university hospitals.

The following inclusion criteria were applied: 1) age between 19 and 55 years and migraines with or without auras, as defined by the International Headache Society Criteria for Migraine (ICHD-3 beta) [24]; 2) an of 2–14 headache days per month; 3) stable headache characteristics for at least 1 year prior to study entry; and 4) the possession of a personal platform smartphone that was capable of operating the SHD.

The following exclusion criteria were applied: 1) headaches attributed to secondary causes; and 2) inability to complete questionnaires, to use our specially designed SHD, or to comply with the SHD usage requirements.

For the baseline survey, the participants were asked to choose their potential triggers on the basis of their previous experiences from a list of 18 trigger factors. Those factors were selected on the basis of the results of previous studies about migraine trigger factors, and included stress, excessive sleep, sleep deprivation, exercise, fatigue, hormonal changes, emotional changes, weather changes, sunlight, noise, odors, fasting, overeating, caffeine, smoking, alcohol, cheese/chocolate, and traveling [2, 5, 6, 8, 9]. The participants were also asked to complete the Hospital Anxiety and Depression Scale to determine their anxiety and depression levels [25]. They also completed the Korean versions of the Migraine Disability Assessment Scale (MIDAS) and the Headache Impact Test-6 to determine the impact of their migraines on their daily functioning [26, 27].

The ethical approval for the study was granted by the Dongtan Sacred Heart Hospital Institutional Review Board/Ethic Committee (IRB approval number: 2014–132) and Uijeongbu St. Mary's Hospital, the Catholic University of Korea College of Medicine Institutional Review Board/Ethic Committee (IRB approval number: UC14OIM10085). The participants received an explanation of the study's aims and procedures and provided written informed consent.

SHD development and contents

Two registered nurses, a project coordinator, a web-support project manager, and three headache specialists developed the SHD together.

The SHD included systematic instructions for its use during the study. The patients' recorded SHD data were available to them after their enrollment in the study.

A series of reports, which included each participant's missing diary days, was automatically uploaded. These reports allowed researchers to track each participant's status and alert the participants if increased compliance was needed. The SHD was programmed to check the participants' incidence of headache and the potential triggers on a daily basis. In addition to the potential trigger factors identified at the initial assessment, the participants were able to input details concerning other headache triggers.

Data collection using the SHD

Subsequent to SHD installation, a registration number and password were provided to each participant to maintain security. The participants could upload information into the diary simply

by touching the screen. They were asked to complete the SHD on a daily basis for 3 months. A short message was sent every two weeks to remind the participants to enter information.

Every day, regardless of the presence of a headache, the participants were asked to touch the SHD icon shown in their smartphone. After doing so, they could log into the SHD. The first screen asked the patient whether he/she had a headache. If the patients noted that there was no headache, then it was automatically recorded as a ‘no headache day’. However, if there was any form of a headache present, he/she was asked to record the headache characteristics their headache (e.g., headache intensity, duration, and the presence of photophobia or phonophobia), any headache self-treatment, and headache-related functional disability (e.g., MIDAS, if any). Finally, the patients were asked to select the triggers from the list of 18 trigger factors presented during the same day. The triggers present during the 1–3 days preceding the headache were not considered or selected. In addition, the patients were asked to record those trigger factors daily, regardless of the presence of a headache.

The participants were interviewed by the researchers and received a personal summary of their daily records for the preceding 3 months at the study’s completion.

Data analysis

We analyzed the effect of trigger factor exposure on the headache occurrence using the daily records from the participants’ diary entries. The frequency for each trigger factor was acquired by calculating the number of headache days with certain trigger factors divided by the total number of headache days. There were many terms for the occurrence of a headache, such as intensity or probability; we chose the likelihood of a headache [3, 19]. Likelihood of a headache during the presence of each trigger factor was obtained with the following equation:

$$\text{Frequency} = \frac{\text{the number of headache days with certain trigger factors}}{\text{total number of headache days}} \times 100$$

$$\text{Likelihood} = \frac{\text{the number of headache days with certain trigger factor}}{\text{the number of days with presence of the same trigger factor}} \times 100$$

Each headache was classified as a migraine or non-migraine headache, according to the diagnostic criteria B–D of item 1.1 of migraine without aura in the ICHD-3 beta.

The categorical variables were presented as percentages, and the continuous variables were summarized using descriptive statistics, such as the means and standard deviations. The clinical variables for the headache were compared according to the presence or absence of trigger factors, using t-tests for continuous variables, and a chi-square test or Fisher’s exact test for the frequency variables.

The trigger factor frequency was compared between the migraine and non-migraine headaches by using a chi-square test or Fisher’s exact test. The associations of the 18 trigger factors and migraine were examined using a stepwise multiple logistic regression analysis with 153 possible combinations of trigger factors. A variable must have had a p value of less than 0.15 to be entered into the regression model. SAS statistical software (SAS version 9.3, SAS Institute, Inc., Cary, NC) was used for all analyses. The statistical significance was set at $p < 0.05$.

Results

Demographic characteristics

Initially, 113 patients were recruited from two centers. However, 30 patients withdrew before the end of the study; therefore, 83 patients finished the study. Of these, 62 patients kept a diary

for at least 50% of the study period. We analyzed the headache diary data from 62 patients ([S1 File](#)). Sixty patients had a migraine without aura, and two had a migraine with aura. The participants' mean age was 37.7 ± 8.6 years of age, with 83% of participants being women. The mean illness duration was 9.7 ± 8.2 years ([Table 1](#)).

The required recording time per day was 2.1 ± 1.2 (1–5) minutes. All patients preferred to use the smartphone diary rather than the paper diary, as assessed by a survey after the end of the study.

Personal triggers estimated at the baseline survey and on the SHD

At the initial study session, the participants were asked to provide a retrospective estimate of the number of migraine triggers of which they were aware. Of the participants analyzed, 39 (62.9%) reported any trigger(s) and the median number of triggers was 3 (range: 0–11). The participants estimated that 64.5% of their headaches were related to triggers.

In total, 4,579 diary days were recorded from 62 patients, with an 86.3% recording rate during 85 ± 13.4 days. The median number of headaches per patient was 15 during the period (range: 4–60). The proportion of patients who reported any trigger(s) on the SHD was higher than that found in the baseline survey (80.6% vs. 62.9%, $p = 0.002$). The number of possible trigger(s) for each patient was higher on the SHD [median: 7 (range 0–17)] than that in the baseline survey [median: 3 (range 0–11)].

Trigger frequencies and likelihood of headache in presence of the triggers on the whole SHD

During the study period, 1,099 headache days were recorded ([Fig 1](#)). The median number of triggers on each recording headache day was 2 (range: 1–9); 80% of the headache diary listed 0–2 triggers ([Table 2](#)). The proportion of days with the presence of a trigger was 65.7% on the headache day and 25.6% on a day without a headache. There was no influence of the trigger number on the likelihood of a headache in the Chi-square analysis ([S1 Table](#)).

When headaches were reported in the SHD, the common triggers were stress (27.6%), followed by fatigue (20.7%), sleep deprivation (20.4%), hormonal changes (11.5%), and weather changes (9.9%) ([Fig 2](#)).

Table 1. Demographic and headache characteristics of the participants.

Age, years	37.7 ± 8.6
Female	82.3%
Duration of illness, years	9.7 ± 8.2
Pain intensity, VAS	7.5 ± 1.3
Monthly Headache days	6.4 ± 5.1
Headache duration, hours	31.1 ± 26.3
Frequency of abortive treatment per month	4.6 ± 3.6
Current prophylactic medication	40.3%
HIT-6	62.4 ± 9.7
MIDAS	22.0 ± 24.5
HADS-D/ HADS-A	$9.5 \pm 13.9 / 6.5 \pm 3.1$

Mean \pm standard deviation; VAS, visual analogue scale; HIT-6, Headache impact test-6; MIDAS, Migraine Disability Assessment Scale; HADS-D, Score of Hospital anxiety depression scale-depression part; HADS-A, Score of Hospital anxiety depression scale-anxiety part

doi:10.1371/journal.pone.0149577.t001

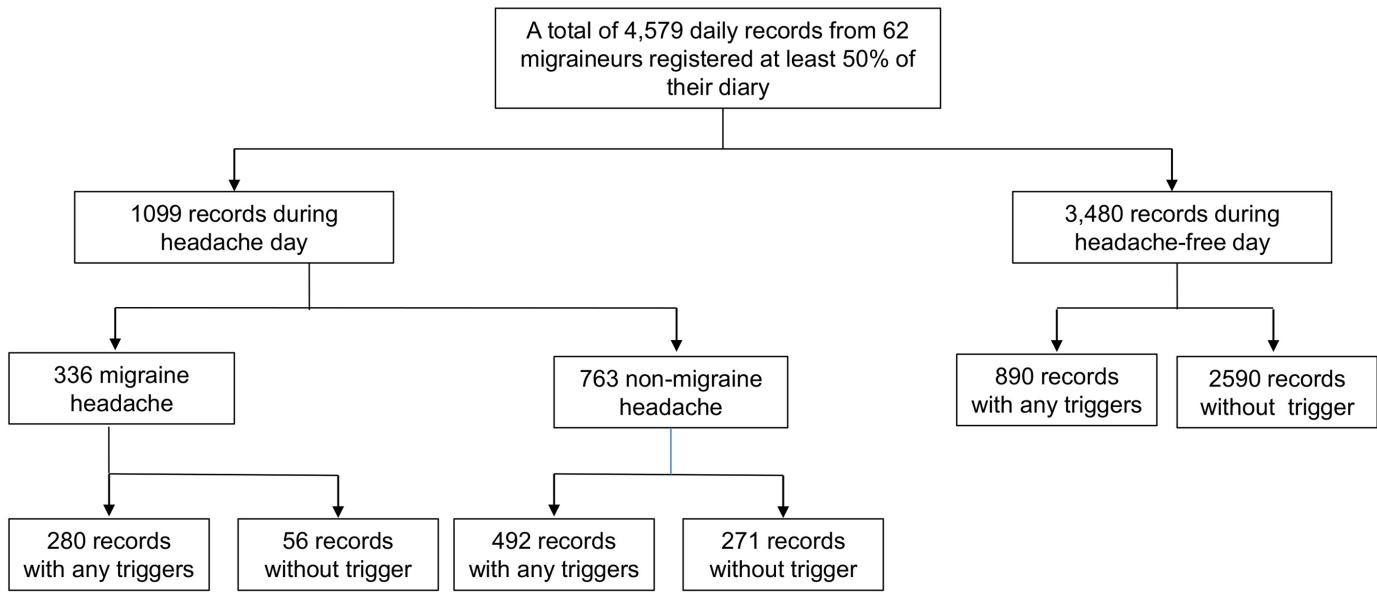


Fig 1. Flow Chart Depicting Subject Participation and the Number of Records. There were 722 headache days with certain triggers and 357 headache days without triggers. In total, 1662 days with a trigger and 2917 days without a trigger were recorded.

doi:10.1371/journal.pone.0149577.g001

Of the 1662 days that included a trigger, 772 day records (46.5%) were recorded as headache days. The following triggers were likely to trigger a headache: 78.6% for alcohol, 71.8% for odor, 68.8% for emotional change, 64.2% for hormonal changes, and 57.7% for stress, 55.1% for sleep deprivation, and 48.5% for fatigue.

Analysis of headache characteristics among the 1099 headache day records on the SHD

Of the total number of headache days, 70.2% (772/1,099) were recorded as days that included triggers (Fig 1).

The headaches with triggers were related to a greater pain intensity ($p < 0.001$), the use of abortive treatment ($p = 0.015$), headache-related disability ($p < 0.001$), and the proportion of migraine ($p < 0.001$) than were those without triggers (Table 3). The headache duration did not differ between the two groups ($p = 0.57$).

Of the total number of headache days, 30.6% (336/1,099) of the headaches met the criteria for a migraine (Fig 1).

The presence of stress, sleep deprivation, hormonal changes, noise, odors, alcohol, fasting, overeating, cheese/chocolate consumption, and traveling were significantly more frequent in migraines relative to non-migraine headaches (Table 4). A stepwise multiple logistic regression analysis with the 18 trigger factors and the 153 possible combinations of the trigger factors revealed that traveling (odds ratio [OR]: 6.4, confidence interval [95% CI]: 1.2–10.2), hormonal

Table 2. The Number of Trigger of each Recording Day with and without Headache.

Number of triggers	0	1	2	3	4	5	6	7	8	9	Total
Headache days	327	305	247	139	56	18	3	2	1	1	1099
No headache	2587	351	267	182	76	14	1	0	1	1	3480
Total	2914	656	514	321	132	32	4	2	2	2	4579

doi:10.1371/journal.pone.0149577.t002

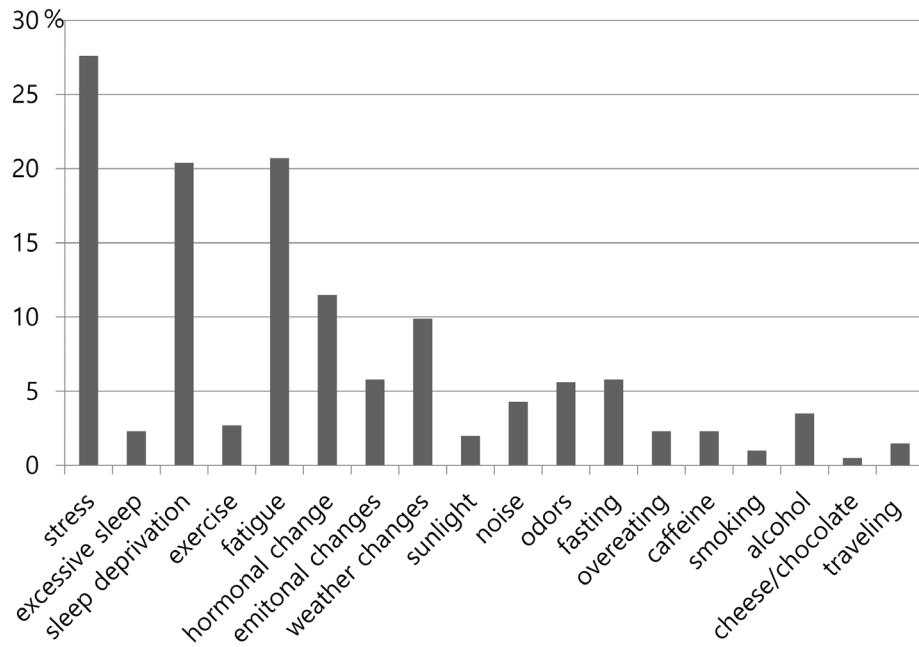


Fig 2. Distribution of each Trigger related to Headache according to Their Frequency.

doi:10.1371/journal.pone.0149577.g002

changes (OR: 3.5, 95% CI: 2.3–5.2), noise (OR: 2.8, 95% CI:1.4–4.9), alcohol (OR: 2.5, 95% CI:1.3–5.0), overeating (OR: 2.4, 95% CI:1.1–5.7), and stress (OR: 1.8, 95% CI:1.4–2.4) were significantly associated with migraines ([Table 4](#)). Two trigger combinations were selected during the stepwise logistic analysis. In situations with stress, but without hormonal changes, the OR did not change compared to the OR of stress alone. In situations with stress and hormonal changes, the migraine risk was not significant. The associations of noise and travel were similar ([Table 4](#)).

The headaches with the presence of hormonal changes or noise were more likely to be migraines, regardless of any preventive medications. The headaches with the presence of stress, overeating, alcohol, and traveling were more often migraines without the use of preventive medication, but migraines were not evident with the use of preventive medication. The headaches with the presence of odors were more likely to be migraines only with preventive medication. The influences of the other trigger factors on the headache type were not different with the use of preventive medication ([Table 5](#)).

Table 3. Comparison of the Headache Variables according to Trigger presence on a Smartphone Application-based Electronic Headache Diary.

Headache Variables	Headache not associated with Trigger (N = 327)	Headache associated with Trigger (N = 772)	P-value
Pain intensity, VAS	3.9±2.0	4.6±2.3	<0.001
Duration of headache, hours	7.7±5.7	8.0±5.8	0.57
Usage of abortive treatment	56.9%	64.8%	0.02
Disability associated with headache	33.6%	53.6%	<0.001
Proportion of migraines	17.1%	36.3%	<0.001

Mean ± standard deviation; VAS, visual analogue scale

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Table 4. Comparison of Triggers between Migraines and Non-migraine headaches on the Smartphone Application-based Electronic Headache Diary.

Triggers	NMH (N = 763)	Migraine (N = 336)	P-value*	Stepwise multiple logistic regression analysis	
				Odd ratio (95% confidence interval)	P-value
Stress	24.0%	36.0%	<0.001	1.8 (1.4–2.4)	<0.001
Excessive sleep	2.2%	2.4%	0.88	NA	
Sleep deprivation	18.6%	24.4%	0.03	NA	
Exercise	1.3%	1.5%	0.78	NA	
Fatigue	19.9%	22.3%	0.37	NA	
Hormonal changes	6.8%	18.5%	<0.001	3.5 (2.3–5.2)	<0.001
Emotional changes	5.1%	7.4%	0.13	NA	
Weather changes	10.8%	8.0%	0.17	NA	
Sunlight	2.1%	1.8%	0.73	NA	
Noise	2.6%	8.0%	<0.001	2.8 (1.4–4.9)	0.002
Odors	3.9%	9.2%	<0.001	NA	
Fasting	4.5%	8.9%	0.003	NA	
Overeating	1.3%	4.5%	0.001	2.4 (1.1–5.7)	0.009
Caffeine	2.2%	2.4%	0.88	NA	
Smoking	1.1%	0.6%	0.73	NA	
Alcohol	2.2%	6.3%	<0.001	2.5 (1.3–5.0)	0.009
Cheese/chocolate	0%	1.5%	0.003	NA	
Traveling	0.8%	3.3%	0.002	6.4 (1.2–10.2)	0.003
Stress*Hormonal changes = 0	24.0%	38.1%	<0.001	1.8 (1.3–2.5)	0.03
Stress*Hormonal changes = 1	31.9%	23.7%	0.31	0.7 (0.3–1.6)	
Noise*Travel = 0	2.4%	8.1%	<0.001	2.8 (1.4–5.4)	0.01
Noise*Travel = 1	42.9%	10.0%	0.12	0.1 (0.1–1.2)	

* Chi-square analysis

NMH, Non-migraine Headaches; NA, not available due lack of inclusion in the stepwise multiple regression analysis

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Discussion

The main findings of the current study were as follows: 1) the SHD was comprehensive in detecting the trigger factors of episodic migraineurs; 2) the frequent trigger factors on headache days were stress, fatigue, and sleep deprivation; the likelihood of a headache was 57.7% for stress, 55.1% for sleep deprivation, 48.5% for fatigue, and 46.5% for any trigger; 3) the headaches with trigger factors were more severe relative to those without trigger factors, 4) traveling, hormonal changes, noise, alcohol, overeating and stress increased the risk of migraines; and 5) hormonal changes and noise increased the risk of migraine regardless of preventive medication, whereas stress, overeating, alcohol, and traveling increased the risk of migraine in situations without preventive medication.

Our SHD was developed for clinical and research purposes. It has major advantages for researchers, including data entry by the participants, big data set collection, immediate and frequent data analysis, and no requirements for special diary equipment [22, 23]. For participants, SHD was easy to use. The summary report could be obtained from the clinician and the SHD after the end of the study. The SHD facilitated the research regarding migraine trigger factors, and has a great potential to enhance the communication between the physician and their patient [22, 28].

Table 5. Influence of Preventive Medication on the Headache Features with their Trigger Factors.

Triggers	without Preventive Medication (n = 579)			with Preventive Medication (n = 520)		
	NMH (n = 417)	Migraine (n = 162)	P-value	NMH (n = 346)	Migraine (n = 174)	P-value
Stress	25.7%	43.8%	<0.001	22.0%	28.7%	0.09
Excessive sleep	1.4%	1.9%	0.72	3.2%	2.9%	0.85
Sleep deprivation	16.6%	22.2%	0.12	21.1%	26.4%	0.85
Exercise	0.5%	1.2%	0.31	2.3%	1.7%	0.76
Fatigue	19.4%	22.8%	0.36	20.5%	21.8%	0.73
Hormonal changes	8.4%	20.4%	<0.001	4.9%	16.7%	<0.001
Emotional changes	6.0%	9.9%	0.10	4.1%	5.2%	0.56
Weather changes	10.8%	6.8%	0.14	10.7%	9.2%	0.59
Sunlight	0.7%	0.6%	1.00	3.8%	2.9%	0.60
Noise	2.2%	6.2%	0.02	3.2%	9.8%	0.002
Odors	1.9%	1.9%	1.00	6.4%	16.1%	<0.001
Fasting	4.6%	9.3%	0.03	4.3%	8.6%	0.05
Overeating	1.7%	7.4%	<0.001	0.9%	1.7%	0.41
Caffeine	2.2%	4.9%	0.10	2.3%	1.7%	0.41
Alcohol	3.1%	9.9%	<0.001	1.2%	2.9%	0.17
Traveling	0.2%	2.5%	0.02	1.5%	4.0%	0.12

Smoking and cheese/chocolate were not analyzed because more than one cell was zero. NMH, Non-migraine Headaches

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Among the 1099 headache days, 70.2% were related to trigger factors in this study. Compared to the baseline survey that was based on life experience, the actual frequency of each trigger factor was lower. The contributions of individual trigger factors were similar, and the proportion of patients who reported any trigger(s) was higher in the SHD for 3 months. The frequent trigger factors in this analysis were in line with previous studies [2, 3, 10, 29–30]. Several studies have suggested that stress is related to hormones, including cortisol and thyroid hormone, and may have a role in migraine pathogenesis [2, 29]. Fatigue was considered to be a migraine-specific trigger and may be related to sleep quality [31]. Sleep disturbances were 3–17 times more likely to be triggers for migraines, tension-type headaches, and chronic headaches in a population-based study. It has been suggested there is an overall pain-promoting effect of sleep deprivation [32]. Sleep deprivation was a predictor for severe headaches among chronic migraine patients, but was not associated with episodic migraines in this study [33]. Stress, fatigue, and sleep deprivation may be modifiable triggers for migraines, so proper attention to psychiatric disorders, sleep hygiene, and life habits is important in learning to cope with triggers [33–35].

The likelihood of a headache on a day with any trigger factor was 46.5%. Alcohol, odor, and emotional changes were not frequently associated with headaches, but the likelihood of a headache occurrence was more than 70% when the patients were exposed to those factors. Although the avoidance of all triggers is impractical in everyday life, the avoidance or pre-emptive approach for certain triggers may be reasonable [11].

The additional effects of triggers were not seen in the logistic analysis with 153 possible combinations of two triggers, although stress*menstruation and noise*travel were selected in the model. A previous study using natural triggers in migraine auras showed no additional effects of a flickering light and physical activity [4]. One study about odorant-triggered migraines showed the association of perfume odors within other factors, such as cleaning,

cooking, beauty products, and foul odors [6]. The addictive effect of triggers on headache occurrence or severity is still uncertain and worth investigating with advanced statistical modeling techniques [13, 14].

One of the important methodological issues in studying trigger factors of migraines is the individual models (within-person) and population-level models (using an individual diary) [19]. The impact of trigger factors on migraines was analyzed by using population-level models based on 1099 headache diaries; 30.6% (336/1,099) of the headaches fulfilled the criteria for migraines in this study. A substantial proportion of the reported by migraine sufferers may be a manifestation of mild migraine attacks. These attacks were probable migraines or were treated before the full development of migraine symptoms [36]. There is the possibility of a tension-type headache; the prevalence of tension-type headaches in migraine individuals was similar to the general population [37,38]

The headaches with triggers were more severe and related to migraines in this study. People with triggers frequently had more severe headache profiles. The menstrual migraine is a good example [3, 39–41]. In a study that used paper diaries, hormonal changes demonstrated a hazard ratio increase of up to 96%, while the values for all other factors were less than 35% [42]. Migraineurs with allodynia were reported to have a higher number of triggers relative to those without, indicating that triggers may play a role in the exacerbation of a migraine [43].

Hormonal changes and noise increased the risk of a migraine regardless of preventive medication in this study. Considering that short-term migraine prevention uses triptans for menstrual migraines, conventional preventive medication would not change the features of a headache triggered by menstruation [39]. The associations of stress, overeating, alcohol, and traveling with migraine were not evident with preventive medication. Preventive medication may change the feature of headaches [44].

The study had some limitations. First, the temporal sequence and relationships between the triggers were not evaluated. The changes from the previous levels and associations between the trigger factors may have influenced the headache onset and severity [20]. The differentiation from the premonitory symptoms with functional imaging may be promising [45], Second, we analyzed one-day diaries; the triggers that were present during the preceding 1–3 days were not considered [33, 46], which limits the predictability and direct causality associations between the triggers and headaches. Third, the compliance rate of this study was based on more than 50% of recording period (74.7%), which is not high. However, the recording rate of the SHD (86.3%) observed in this study was comparable to those of previous studies and reasonable for clinical settings [18, 20, 39]. Fourth, most triggers influenced a subgroup of migraineurs, but we did not analyze the risk of migraine by using an individual model [4, 19]. Fifth, we relied on the participants' judgment for recording the triggers and cannot rule out the possibility of selection bias from the clinical setting and recall or confirmation bias by participant [3].

The merits of this study were analyzing trigger factors in regards to frequency, headache occurrence, headache features, and the influence of preventive medication by using a statistical method and patient-friendly SHD in episodic migraineurs.

Conclusion

The SHD is an effective tool in the assessment of migraine trigger factors. Headaches with trigger factors had greater severity or migraine features. The type of triggers and the presence of preventive medication may influence headache features, so the investigation of trigger factors is helpful in understanding the pathophysiology of migraines and developing a preemptive strategy for trigger factors.

Supporting Information

S1 File. Dataset of 62 patients, 1099 Headache Diary Records, and 4579 Diary Records.
(XLS)

S1 Table. Chi-square analysis about the likelihood of Headache and the Number of Triggers.
(PDF)

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Author Contributions

Conceived and designed the experiments: JWP MKC SJC JMK SGP. Analyzed the data: JWP MKC SJC JMK SGP. Wrote the paper: JWP MKC SJC SGP. Designed the smartphone application used in analysis: JWP MKC SJC.

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Effects of Lifestyle Modification on Vestibular Migraine

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Objective: To evaluate effects of lifestyle modification on symptoms of dizziness and headache in patients diagnosed with definite vestibular migraine.

Study Design: Prospective within-participants repeated-measures study.

Setting: Otolaryngology tertiary care.

Participants: Twenty-eight adults with definite vestibular migraine who were willing to be treated without pharmacological intervention.

Intervention(s): Information and instructions were provided on lifestyle modification; participants were instructed to improve restful sleep, exercise, eat at regulated mealtimes, and avoid dietary triggers. Participants were asked to maintain the modifications for at least 60 days.

Main Outcome Measure(s): Two self-report inventories were used pre- and post-intervention to evaluate participants' perceived dizziness handicap and headache disability using the Dizziness Handicap Inventory and Headache Disability Inventory, respectively. Questions were also used to evaluate the extent to which participants reported compliance with lifestyle factors pre- and post-intervention.

Results: Significant improvement was observed after the lifestyle intervention with mean improvements in Dizziness Handicap Inventory and Headache Disability Inventory of

14.3 points. As a group, improvement in restful sleep was related to improvement in both dizziness and headache symptoms. At the individual participant level, 39% and 18% of participants reported significant reduction in dizziness handicap and headache disability, respectively.

Conclusions: Lifestyle modifications are an effective intervention for symptoms of dizziness and headache in participants with definite vestibular migraine. Participants who reported a larger increase in restful sleep were more likely to also report larger improvements in dizziness handicap and headache disability. Effect sizes using the current intervention were comparable or better than some reported pharmacological interventions but less than others. Our lifestyle modification intervention produced significant improvement in dizziness for a larger percentage of individual participants and in headache for a similar percentage of participants compared to data reported with other lifestyle modification interventions. Lifestyle modifications, especially restful sleep, have the potential to reduce the impact of vestibular migraine on patients' lives, with limited risk. Clinical Trials Registration: NCT03979677. **Key Words:** Dizziness—Headache—Intervention—Vestibular migraine.

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Vestibular migraine (VM) is the most frequently encountered cause of episodic vertigo (1), having prevalence rates from 7% to 16% in clinics serving patients with dizziness and imbalance (1,2). Importantly, not only is VM common but also nearly 70% of patients diagnosed with VM rated their symptoms as having a moderate to

severe impact on health-related quality of life (HRQOL) (3). The criteria for definite VM were formalized by the International Headache Society and the International Barany Society more recently (4), although alternative terms such as migraine-associated dizziness, migraine-related dizziness, and migraineurs with dizziness were used prior to consensus to diagnose patients with presumed VM. Within the current investigation, we will use VM as defined by the consensus groups (4).

The suggested interventions for VM have overlap with intervention for other types of migraine and include lifestyle modification and medications, either in isolation or in combination (5–7). Although many reports of VM management focused on treatment with medications (8–10), there is also evidence symptoms can be improved with interventions that involve lifestyle modifications (11,12) including dietary restrictions (13,14), exercise, and sleeping recommendations (15). Collectively, the

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extant literature demonstrates improvement in symptoms using lifestyle modifications alone in 11% to 16% of patients with VM (11,13). However, these studies are limited in number and are predominantly retrospective.

It is unsurprising that lifestyle modification would improve symptoms of VM. There is sufficient evidence in the literature that lifestyle modification is beneficial for non-VM forms of migraine that we will refer to collectively as migraine. Migraine symptoms have been shown to improve in 63% to 93% of patients through dietary interventions (16) and in 48.9% of patients through cognitive behavioral therapy to treat insomnia (17). Conversely, missing meals or fasting has been reported to trigger migraines in as many as 57% of migraineurs (18). Finally, low-level physical activity and exercise have been shown to reduce migraine symptoms (19,20). However, avoidance of dietary triggers, restful sleep, mealtime regularity, and exercise has not yet been systematically investigated as a comprehensive approach to management of symptoms of VM.

More work is needed to determine the outcomes of lifestyle modification on VM. As noted, VM accounts for a large percentage of individuals affected by symptoms of dizziness and imbalance. It is also important to understand the effects of lifestyle modification on VM to assist with evaluation of other interventions, including pharmacological ones. The purpose of the current investigation was to prospectively evaluate the effects of common lifestyle modifications on symptoms of dizziness and headache in patients diagnosed with definite VM.

MATERIALS AND METHODS

Design and Participants

Participants were recruited from patients seen for consultation for dizziness and/or imbalance in the John S. Odess Otolaryngology - Head and Neck Surgery Clinic. Consultations were provided by two nurse practitioners and one otolaryngologist. All clinicians were experienced in diagnosis and management of dizziness and imbalance including VM. All adult patients diagnosed with definite VM using the consensus criteria (4) were eligible for inclusion. Patients who were determined to need pharmacological management at initial consultation were excluded.

Forty-one patients were consented and enrolled as participants. Thirteen (31.7%) of the participants did not complete

this investigation for the following reasons: seven requested pharmacological intervention during the experimental period and were withdrawn, one was diagnosed with Rocky Mountain Spotted Fever and withdrawn, and five were lost to follow-up. Twenty-eight participants (68.3%) completed the investigation. Analysis was performed for the 28 participants with completed data sets. Mean age was 46.4 years (standard deviation = 16) and participants were 78.6% female.

Study Materials

Participants completed the Dizziness Handicap Inventory (DHI) (21), Headache Disability Inventory (HDI) (22), and lifestyle scale (Table 1) prior to and again after lifestyle modification intervention. The DHI and HDI are 25-item self-report tools that examine impact of dizziness symptoms and headache symptoms on HRQOL. Lower total scores indicate less impact of the symptoms on HRQOL. The lifestyle scale was developed for this study to gain an understanding of self-perceived restful sleep, mealtime regularity, exercise, and avoidance of dietary triggers. Participants indicated their level of agreement with each statement using a 5-point Likert scale. Higher scores indicated better self-perceived compliance with the lifestyle component.

Procedures

Data were collected either paper/pencil or using an online Redcap (23) survey, depending on participant preference and in-person COVID-related limitations. Participants completed the DHI, HDI, and lifestyle scale during a clinic appointment before and after the intervention. On average, participants completed post-intervention surveys after 105 days (standard deviation = 78.1).

Intervention

The intervention addressed four areas related to lifestyle modification that have been shown to be effective in at least some patients with VM or with migraine (1,11,13–17,19). These areas were restful sleep, mealtime regularity, exercise, and elimination of dietary triggers. The diagnosing clinicians provided a four-page handout (see Supplemental digital content, <http://links.lww.com/MAO/B318>) with information about each area after their diagnosis and after the patient completed the informed consent process.

For restful sleep, we provided helpful tips adapted from the National Institute on Aging (24). To bring focus to mealtime regularity, the handout provided informational statements that skipping or missing meals can lead to symptoms and the participant should prepare ahead to ensure they are eating on a schedule. We also encouraged participants to continue or

TABLE 1. Scale used to measure self-reported pre- and post-intervention agreement with statements related to four targeted lifestyle areas. These areas were recommended for modification as the nonpharmacologic intervention for definite vestibular migraine

Statement	Strongly Disagree			Strongly Agree
I sleep well and awake feeling rested.	1	2	3	4
I always eat every meal at the same time each day.	1	2	3	4
I exercise every day.	1	2	3	4
I avoid foods and drinks that make me have headaches and/or cause dizziness.	1	2	3	4

Consider each statement. Circle the number that best represents your agreement or disagreement with the statement. Circling a “5” would indicate you “Strongly Agree” while circling a “1” would indicate you “Strongly Disagree.”

resume a preferred exercise program or start some type of formal exercise. A sample-walking program from the National Heart, Lung, and Blood Institute (25) was adapted and provided along with the caveat to only begin such a program if medically cleared. Finally, we combined information from published research (16) and other publicly available resources (26) to develop a comprehensive elimination list of potential dietary triggers. Participants were asked to follow this four-part intervention until follow-up, with an initial goal of at least 60 days.

Statistical Methods

Scores on the lifestyle scale were analyzed using linear mixed-effects models with two within-participant factors, intervention (pre-intervention, post-intervention), and lifestyle factor (restful sleep, exercise, mealtime regularity, avoiding dietary triggers). Scores on the two handicap inventories, DHI and HDI, were also analyzed using linear mixed-effects models with two within-participant factors, intervention (pre-intervention, post-intervention) and inventory (DHI, HDI). For all models, participant was included as a random factor. Models were constructed using the *lmer* function of the *lme* package (27) in R (28) and were analyzed using the *anova* function in base R. Significant main effects and interactions were evaluated using the *emmeans* function of the *emmeans* package (29). Pairwise comparisons were adjusted to account for false-discovery rates (30).

Inter-individual variability in pre- to post-intervention scores were analyzed by calculating change scores (subtracting post-intervention from pre-intervention scores [DHI and HDI] or

subtracting pre-intervention from post-intervention scores [lifestyle scale]). Two linear mixed models were constructed, one for each inventory, with the change scores as the dependent variable. Independent variables were participant sex, age, and lifestyle change score for each lifestyle question. Models were constructed and analyzed with the *lmer* and *anova* functions, respectively.

Finally, to determine individual participant post-intervention change, we compared pre- and post-total scores for the DHI and HDI. On the DHI, a change of 18 points is considered significant (21). For the HDI, a change of 29 points is considered significant (22).

RESULTS

This project was approved by the Institutional Review Board (IRB Number 191276) of Vanderbilt University Medical Center and was entered with ClinicalTrials.gov Identifier: NCT03979677. No one ethnic group or sex was targeted for inclusion or excluded from participation in this study; participants reflect the ethnic composition of the patient base of the Middle Tennessee region.

Lifestyle Scores

Scores on the lifestyle scale are displayed in Figure 1. Analysis revealed significant main effects of intervention ($F[1, 189] = 57.78, p < 0.0001$) and lifestyle factor ($F[3,$

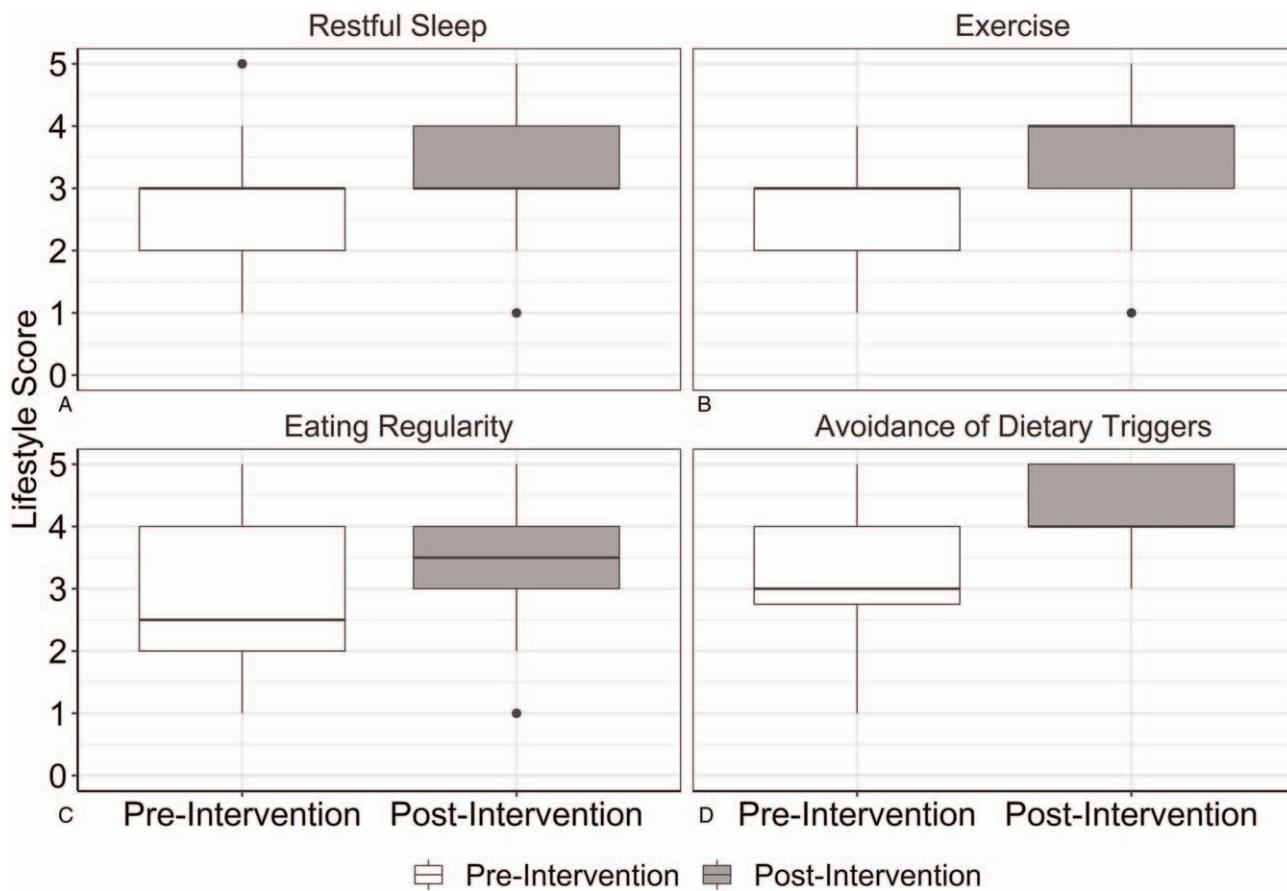


FIG. 1. Scores in response to the four lifestyle scale items. Higher scores indicate more compliance with a lifestyle area. Solid bars indicate median scores; boxes indicate first through third quartile; whiskers indicate minimum and maximum scores; dots indicate outliers.

TABLE 2. Pairwise comparisons of lifestyle scores

	<i>M</i> Difference	95% CI	<i>t</i> Ratio	<i>p</i>
Restful sleep – exercise	0.05	–0.41 to 0.52	0.31	0.919
Restful Sleep – eating regularly	0.02	–0.45 to 0.48	0.1	0.919
Restful sleep – avoidance of food/drink triggers	0.7	0.23–1.16	3.99	<0.0001
Exercise – eating regularly	–0.04	–0.5 to 0.43	–0.2	0.919
Exercise – avoidance of food/drink triggers	0.64	0.18–1.11	3.69	0.001
Eating regularly – avoidance food/drink triggers	0.68	0.21–1.14	3.89	<0.0001

Higher scores indicate more compliance with healthy lifestyle on each question. For all comparisons, standard error = 0.17 and degrees of freedom = 189. Significant comparisons are indicated by bold typeface.

189] = 7.47, $p < 0.0001$). The intervention \times lifestyle factor interaction was not statistically significant. Lifestyle factor scores increased from pre-intervention to post-intervention (*M* difference = 0.94, 95% CI: –0.69 to 1.18, $p < 0.0001$), indicating participants significantly altered their lifestyle during the intervention. In addition, the scores on the lifestyle scale were different from each other (see Table 2 for calculated differences between lifestyle scores). Briefly, participants were generally more likely to avoid dietary triggers than engage in the other lifestyle behaviors. However, the lack of significant interaction indicates the intervention similarly changed all four lifestyle behaviors.

Handicap Inventory Scores

Scores on the two inventories, DHI and HDI, are displayed in Figure 2. Analysis revealed a significant effect of intervention ($F[1, 81] = 28.14, p < 0.0001$). The effects of inventory and the intervention \times inventory

interaction were not statistically significant. Pairwise comparisons revealed inventory scores were lower post-intervention than pre-intervention (*M* difference = 14.30, 95% CI: 8.94–19.67, $p < 0.0001$), indicating the intervention significantly reduced handicap scores and the benefits were comparable on the DHI and the HDI.

Analysis of inter-individual variability revealed no association between DHI and HDI change and participant age, sex, or three of the lifestyle change scores (see Table 3). However, there was a significant relationship between improvement in restful sleep and improvement in dizziness handicap (Fig. 3, panel A) as well as improved headache disability (Fig. 3, panel B).

Considering clinically significant changes, 11/28 (39.2%) of individual participants had a post-intervention DHI score that was at least 18 points lower ($M = 33.1$ points; standard deviation = 16.9). Only one participant had a clinically significant increase in dizziness handicap (18-point increase in DHI). For the HDI, 5/28 (17.9%)

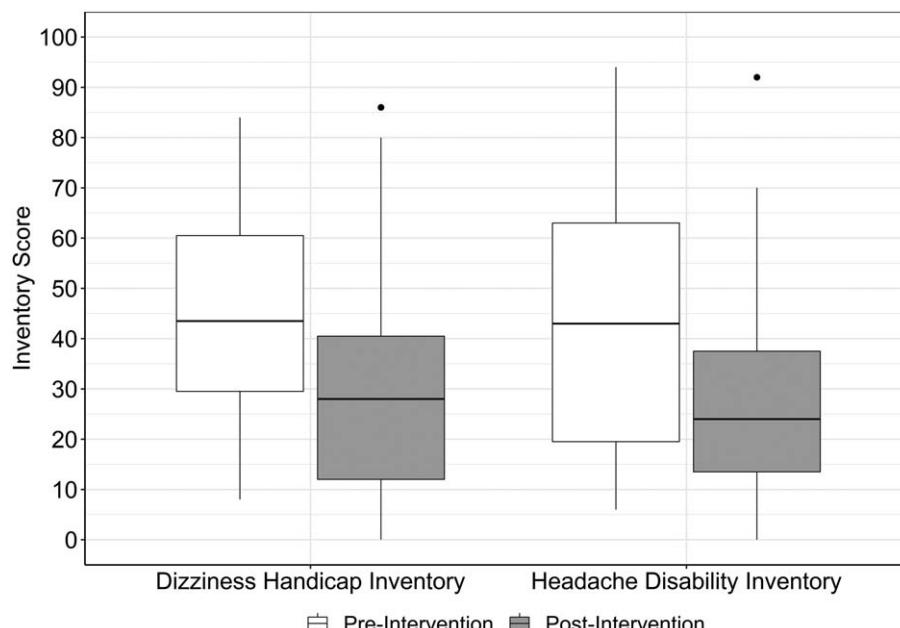


FIG. 2. Dizziness Handicap Inventory and Headache Disability Inventory scores before and after lifestyle modification intervention. Lower scores indicate improvement in perceived handicap or disability. Solid bars indicate median scores; boxes indicate first through third quartile; whiskers indicate minimum and maximum scores; dots indicate outliers.

TABLE 3. Results of linear mixed-effects model analysis of post-intervention Dizziness Handicap Inventory and Headache Disability Inventory scores

Predictors	DHI			HDI		
	Estimates	95% CI	p	Estimates	95% CI	p
(Intercept)	-14.01	-44.16 to 16.15	0.345	-7.39	-43.60 to 28.82	0.676
Age	0.14	-0.32 to 0.60	0.525	-0.02	-0.57 to 0.53	0.942
Sex [M]	18.66	-2.14 to 39.46	0.076	4.09	-20.88 to 29.07	0.737
Restful sleep	12.72	3.4521.99	0.01	14.49	3.36–25.62	0.013
Exercise	1.09	-5.40 to 7.59	0.73	0.84	-6.96 to 8.64	0.824
Eating regularly	0.82	-6.82 to 8.47	0.825	7.34	-1.84 to 16.52	0.111
Avoidance of dietary triggers	6.55	-0.62 to 13.73	0.071	3.65	-4.97 to 12.26	0.388
Observations		28			28	
R ² /R ² adjusted		0.322/0.128			0.352/0.166	

Significant predictors are indicated by bold typeface. DHI, Dizziness Handicap Inventory; HDI, Headache Disability Inventory.

participants had a post-intervention HDI score at least 29 points lower ($M = 48.8$ points; standard deviation = 17.8) than the pre-intervention HDI score. No participant had HDI scores suggesting a worsening of disability after intervention (29-point criterion).

DISCUSSION

The purpose of this investigation was to determine the effects of comprehensive lifestyle modification on VM by measuring change in self-reported lifestyle

factor compliance, dizziness HRQOL, and headache HRQOL. Our results indicated that all lifestyle responses were higher following the intervention compared to pre-intervention, indicating participants increased their compliance with four lifestyle factors during the intervention period. While not all studies include metrics for tracking lifestyle modification compliance, our findings are consistent with Johnson (12) who noted 10 patients treated successfully with non-pharmacologic intervention continued with their lifestyle modifications at follow-up.

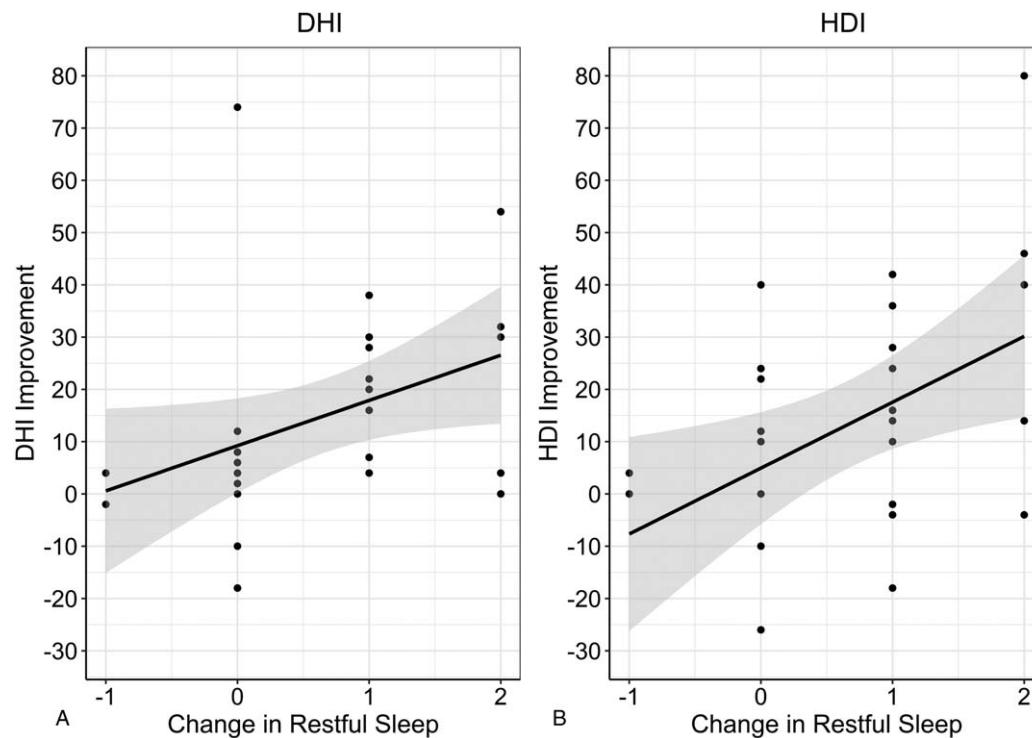


FIG. 3. Panel A. Relationship between Dizziness Handicap Inventory and lifestyle change scores. Panel B. Relationship between Headache Disability Inventory and lifestyle change scores. Significant relationships are indicated by grey shaded regions, whereas relationships that were not statistically significant have no shaded regions.

Importantly, our data demonstrate that the changes in lifestyle behaviors reduced dizziness symptoms and headache disability, consistent with previous literature (11,15). Using established criteria for clinically significant changes in handicap scores (21,22), 39% of our participants experienced a significant improvement in their DHI. This is much higher than other investigations wherein only 11% to 16% of patients were reported to be successfully treated with some version of lifestyle modification (12–14). Eighteen percent of our participants had significant improvement on the HDI which is similar to the findings published in other investigations.

None of the previous retrospective reports addressing lifestyle modification and VM utilized DHI or HDI as an outcome measure and pharmacological intervention studies did not report HDI changes. Fortunately, there are reports on pharmacological intervention for VM that have used the DHI which do allow comparison. Our results demonstrate average improvement in DHI score of ~14 points. DHI benefits reported in the literature of pharmacological interventions for VM demonstrate average DHI improvements of 24.5 points (40–160 mg of propranolol) (10), 31 points (37.5–150 mg of venlafaxine) (23), 41 points (40–60 mg propranolol) (31). Our results are in agreement for improvement in DHI with lifestyle modifications only, though our effect size was less on average (14.3-point change). Notably, when we consider only the individual participants who demonstrated improvement greater than an 18-point change on DHI, the mean change of 33 points was similar to pharmacologic intervention studies. This finding demonstrates that, among participants that report benefit, the improvement with lifestyle modifications only is similar to that reported for some more successful pharmacologic interventions.

It is worthwhile to note that not all pharmacological studies demonstrate such large changes in DHI scores. Liu et al. (8) reported significant DHI improvement for treatment groups who received 25 to 37.5 mg of venlafaxine (10.44 point improvement), 1,000 mg of valproic acid (8.1 point improvement), or 10 mg of flunarizine (6.82 point improvement). In this context, the current results demonstrate that lifestyle modification alone resulted in a greater effect on DHI, on average, than any of the pharmacologic interventions reported by Liu and colleagues.

Of the lifestyle modifications our study included, change in restful sleep was the only one significantly related to changes in DHI or HDI scores. This finding is consistent with the work of Smitherman and colleagues (17), who found that intervention for insomnia decreased headache frequency in almost half of the migraineurs in their experimental group. In the current study, all lifestyle factors were recommended simultaneously, so it is not clear if sleep alone would be sufficient or if sleep in combination with the other lifestyle modifications is critical. It is also worth noting that for individual participants, there could be variability in which lifestyle

modification(s) are most important at the individual level.

It is possible the inclusion of multiple lifestyle factors helped improve our results. Of the investigations reporting percentages of patients successfully managed for VM, only Johnson (12) mentioned regular sleep as a modification. Our results suggest a more comprehensive approach with multiple areas of lifestyle modification might be helpful for patients with definite VM, and restful sleep should be included in the intervention.

In addition to substantial benefits for many patients in the study, the lifestyle modification intervention is relatively low risk. Only one participant had a significant worsening of symptoms on the DHI. No participant had worsened symptoms on the HDI. None of the other published investigations report any worsening of symptoms related to lifestyle modifications (12–14). In the studies investigating pharmacologic management of VM, Salviz and colleagues (10) reported that 12% to 13% of participants had serious adverse effects necessitating treatment discontinuation. Using a lower dose of venlafaxine than Salviz et al., Liu and colleagues (8) reported no serious side effects aside from minor issues like nausea and somnolence, but they also reported a smaller intervention effect. Combined, the data support the clinical recommendation of lifestyle modification as an appropriate intervention option in patients with definite VM.

The current study is limited by the lack of a control group. Future investigations could incorporate crossover interventions to compare effects of no intervention to lifestyle modification, pharmacological intervention, and combinations. We do suggest that future intervention studies for definite VM incorporate validated instruments like DHI and HDI, as well as inclusion of individual participant outcomes, so that comparisons across studies are possible.

Another limitation for this study is that we relied solely on patient report to determine intervention compliance. It is possible that not every participant followed each lifestyle modification as directed and they also could have failed to report this accurately. Use of automated tracker technology may be helpful in future investigations to accurately measure sleep time and exercise activity, although compliance monitoring with other lifestyle modifications could be more difficult. It is possible this could also explain why, though we certainly saw improvement in symptoms of definite VM, we did not see the magnitude of effect size reported in some investigations of effects of isolated lifestyle modifications on migraine like avoidance of dietary triggers (63–93%) (16) or improved sleep (48.9%) (17).

CONCLUSION

Lifestyle modifications including restful sleep, mealtime regularity, exercise, and avoidance of dietary triggers offer an effective and low-risk intervention for patients with definite VM, as demonstrated by

improvement on the DHI and the HDI. As a group, reported improvements in restful sleep were associated with greater improvement in total DHI and HDI scores, but it is important to note individuals could have the greatest improvement on any one lifestyle factor or a combination of them. Individual participant improvement was greater than has been reported in other investigations that included at least some form of lifestyle modification for dizziness related to VM. Our results were similar to comparison studies for headache in VM. The lifestyle modification intervention had a greater effect on reduction of dizziness handicap than what has been reported in at least some investigations with pharmacological management. There are no serious side effects related to intervention with lifestyle modification in patients with definite VM. Further investigation is warranted to determine if intervention with lifestyle modification should be an initial consideration as reported in other investigations, an adjunct to pharmacological management, or if there are specific patient factors that may lead clinicians to choose this intervention over others.

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Research Submission

The Effect of Beginning Treatment With Fremanezumab on Headache and Associated Symptoms in the Randomized Phase 2 Study of High Frequency Episodic Migraine: Post-Hoc Analyses on the First 3 Weeks of Treatment

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Mirna McDonald, MS; Ronghua Yang, PhD; Marcelo E. Bigal, MD, PhD

Background.—Migraine has a substantial impact on daily living, affecting productivity and quality of life for patients and their families. Patients frequently discontinue preventive medications in part because of a delay in headache and symptom relief due to the long dose titration procedures necessary for some migraine preventives.

Objective.—To evaluate the efficacy of fremanezumab, a selective monoclonal CGRP ligand antibody, during the first 3 weeks of therapy in patients with high-frequency episodic migraine (HFEM) to relieve migraine headaches and associated symptoms and to reduce use of acute migraine medications.

Methods.—In a multicenter, randomized, double-blind, placebo-controlled, phase 2 study, patients with HFEM who met inclusion criteria and were 80% compliant with daily headache diary entry were randomized and treated once every 28 days for 3 months with either placebo or fremanezumab 225 or 675 mg. Compared to placebo, both doses of fremanezumab significantly reduced the primary endpoint of the HFEM study, change in the number of migraine days in month 3 relative to baseline. Herein, we performed post-hoc analyses to assess the efficacy of each dose during the first 3 weeks of treatment to reduce migraine headache parameters, associated migraine symptoms, and the consumption of acute migraine medications.

Results.—The sample consisted of 297 study participants. Compared to placebo, decreases in migraine days were seen during the first week of therapy for both fremanezumab doses with least square mean (LSM) differences between fremanezumab 225 mg and placebo of -0.93 (95% CI: -1.36 , -0.49) and between 675 mg dose and placebo of -1.02 (95% CI: -1.46 , -0.58), both $P < .0001$. This benefit was maintained through the second week of therapy for the 225 and 675 mg doses, respectively, (-0.76 (95% CI: -1.11 , -0.40) $P < .0001$; -0.79 (95% CI: -1.15 , -0.44) $P < .0001$) and the third week of therapy (-0.64 (95% CI: -0.97 , -0.30) $P = .0003$ and -0.64 (95% CI: -0.98 , -0.30) $P = .0003$). Likewise in the first week, patients recorded reductions in associated migraine symptoms such as nausea, vomiting, photophobia, and phonophobia, which continued through weeks 2 and 3. There were also reductions in days with acute medication use to treat migraine for the 225 and 675 mg fremanezumab doses compared to placebo. In the first week, LSM differences between 225 mg and placebo were -1.02 (95% CI: -1.39 , -0.64) and between 675 mg and placebo were -1.06 (95% CI: -1.39 , -0.64) $P < .0001$; for the second and third weeks (-1.01 (95% CI: -1.14 , -0.55) $P < .0001$; -0.90 (95% CI: -1.04 , -0.44) $P < .0001$; -0.91 (95% CI: -0.92 , -0.34) $P < .0001$; and -0.83 (95% CI: -0.84 , -0.26) $P = .0002$), respectively.

Conclusion.—Fremanezumab treatment resulted in a rapid preventive response in patients with HFEM, with reductions seen in several headache parameters and migraine symptoms within the first week after therapy initiation and continuing during the

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second and third weeks. Patients also were able to rapidly reduce their use of acute medications to treat migraine attacks. The trial is registered at Clinicaltrials.gov as NCT02025556.

Key words: migraine, fremanezumab, TEV-48125, calcitonin-gene-related peptide (CGRP), migraine preventive medication

Abbreviations: CGRP calcitonin-gene-related peptide, CM chronic migraine, EM episodic migraine, HFEM, high-frequency episodic migraine, HIT-6, Headache Impact test, IgG2Δa, immunoglobulin G2Δa, ITT, intent-to-treat, IWRS, interactive web response system, MMRM, mixed effect model of repeated measurement, M/S, moderate-to-severe; MSQ, Migraine-Specific Quality of Life Questionnaire

(*Headache*: 2019;59:383-393)

INTRODUCTION

Migraine is a debilitating neurologic disease that can transform from an episodic into a chronic form.¹⁻³ Migraine frequency can be conceptualized as a continuum from low-frequency episodic into high-frequency episodic and then into chronic migraine; one goal of preventive treatment is to avoid this transformation. This is achieved by reducing headache frequency and lowering disability and impact.⁴ Risk factors for progression, as well as factors protecting transformation from episodic into chronic migraine, have been identified.⁵

Current preventive treatments for migraine often have unwanted adverse events or contraindications, limiting their use. In addition, they often require slow titration to achieve tolerable dosing and can take up to 4–6 weeks at a minimum to provide relief to patients.⁶⁻⁹ Adherence to preventive migraine medications is low⁸ and lack of initial efficacy, accompanied by adverse events, often results in discontinuation.

Conflict of Interest: Dr. Silberstein reports receiving consulting fees from Alder BioPharmaceuticals, Allergan, Amgen, Automatic Technologies, Avanir Pharmaceuticals, Curelator, Depomed, Dr. Reddy's Laboratories, electroCore, Eli Lilly, eNeura, Insys Therapeutics, Supernus Pharmaceuticals, Teva Pharmaceuticals, Theranica BioElectronics, and Trigemina. Dr. Rapoport reports that he is on the speakers bureau for Amgen, Depomed, Dr. Reddy's, electroCore, Teva, and has been a consultant for Amgen, Autonomic Technologies, Dr. Reddy's, Electrocore, Impax, Teva, and Zosano. P. Loupe and R. Yang are full-time employees of Teva Pharmaceuticals and M. McDonald is a former employee of Teva Pharmaceuticals.

Dr. Aycardi is a full-time employee of Xenon Pharmaceuticals Inc.; he was an employee of Teva Pharmaceuticals at the time of this study.

Dr. Bigal is a full-time employee of Purdue. He was a full-time employee of Teva and of Labrys Biologicals at the time of this study.

Calcitonin-gene related peptide (CGRP) is a neuropeptide involved in the pathophysiology of migraine; it induces trigeminal sensitization and activation of second-order sensory neurons in the brain stem.¹⁰⁻¹³ By its effect on trigeminal sensitization, CGRP may be a risk factor for increased headache frequency, predisposing the progression of migraine from an episodic to chronic form.¹⁴⁻¹⁶ Its blockage may be associated with a rapid decreased frequency or remission of migraine, which has been demonstrated for chronic migraine.¹⁷

Fremanezumab (Ajovy, Teva Pharmaceuticals, Ltd) is a fully humanized immunoglobulin G subclass 2 (IgG2Δa) monoclonal antibody with two mutations in the hinge that reduce effector function.¹⁸ This antibody selectively targets the CGRP ligand and is well-tolerated and effective as a preventive treatment for episodic and chronic migraine in phase 2 and 3 studies.¹⁹⁻²² Fremanezumab resulted in significant reductions in migraine and headache days within the first month of treatment; additionally, as post-hoc analyses in the phase 2 chronic migraine study suggested, improvement in headache hours occurs as early as 3 days after dosing.¹⁷

Herein, we conduct similar analyses in the episodic migraine study, to determine the effect of 2 doses of fremanezumab (225 and 675 mg) during the first 3 weeks of therapy on reducing headache parameters and associated symptoms in the phase 2, high-frequency episodic migraine (HFEM) study.

METHODS

Study Design.—The methods for the fremanezumab phase 2 HFEM study have been previously reported.¹⁹ Briefly, the study was performed from January 2014

to January 2015 in 62 US sites, including headache centers, neurology clinics, and primary care facilities. The study was conducted in accordance with Good Clinical Practice and US FDA guidelines, and was registered at clinicaltrials.gov as NCT02025556. All protocols were approved by the institutional review boards for each site and patients provided written informed consent before participating in the study.

For patients to be considered eligible participants in the study they had to be men or women aged 18–65 years with confirmed diagnoses of migraine as per the International Classification of Headache Disorders (ICHD III beta).²³ Inclusion criteria consisted of having 8 or more headache days per month for at least 3 months and confirmation of this headache frequency during the 28-day study run-in period. Patients had to have 8–14 days of headache per month fulfilling one of the following criteria (migraine day, headache preceded or accompanied by migraine aura, or headache relieved by an ergot or triptan). Patients were allowed to have used one standard migraine preventive drug at stable doses for at least 2 months prior to study onset and acute migraine medications up to 14 days per month (maximum of 4 days of opioids or barbiturates per month). Patients were excluded if they used onabotulinumtoxinA for migraine or for any medical or cosmetic reasons during the 6 months prior to study entry. They were excluded if they had discontinued >2 medication categories or >3 more preventive medications (within 2 medication categories) due to lack of efficacy or had treatment with an investigational drug or device within 30 days of study entry or had any prior exposure to a monoclonal antibody targeting the CGRP pathway. They were allowed to treat a migraine attack as usual.

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 16-week clinical trial consisting of a 28-day screening period, and a 3-month double-blinded treatment period. Patients who met eligibility criteria were trained during the 28-day screening period to provide daily headache and migraine symptom data using an electronic headache diary. Diary entry involved patients logging into the web-based interactive system (IWRS) every day and answering questions on the occurrence of headache, migraine, associated symptoms, and the use of acute medications during the previous 24 hours period. The IWRS allowed patients to back

enter 1 day of information and was locked thereafter. If patients demonstrated 80% compliance with diary entry during the screening period, they were stratified based on sex and preventive medication use and then randomized into either one of the two fremanezumab arms (225 and 675 mg) or placebo arm by study site coordinators using the IWRS and eClinical Operating System portal. The randomization scheme was developed by a staff member of the contract research organization managing the study (NCGS, Charleston, SC, USA) who had no further role in the study.

As the HFEM study was conducted without prior proof-of-concept for this or other antibodies, in agreement with government regulators, an interim analysis was initially suggested. For randomization, participants were first stratified by sex and use of concomitant preventive drugs. Once the stratification group was determined, randomization was done by block (men using preventive drugs, men not using preventive drugs, women using preventive drugs, women not using preventive drugs). Participants ($n = 192$) were initially randomized 1:1 to 675 mg or placebo. After the fulfillment of this first cohort, participants ($n = 105$) were randomized 9:1 to 225 mg or placebo, yielding an approximately 1:1:1 final randomization schedule and an interim analysis for the highest dose. However, since no safety concerns emerged in the chronic migraine study that was being conducted in parallel to this HFEM study (and which enrolled higher doses) and due to the fast rate of enrollment on the current study, it was agreed that the interim analysis was no longer justified, since it would not transfer into any protocol modification while inducing the potential for unblinding and Type I error. IRBs had access to the protocol and SAP. To help keep the blinding, IRBs requested that the patient consent forms indicate a randomization of approximately 1:1:1 ratio.

Study sites had 2 blinded study coordinators at each clinic visit to protect the treatment blind. One study coordinator performed the clinical assessment which included reviewing electronic diary data entry procedures and safety assessments with patients. The second study coordinator performed the treatment administration. Patients were blinded to whether they were receiving placebo or one of the fremanezumab doses; they all received 4 injections at each 28-day treatment visit and the injections

were identical in packaging and appearance regardless of treatment arm. Each active injection contained 225 mg of fremanezumab. Patients in the fremanezumab arms received one of two dosing strategies: once monthly subcutaneous injections of 225 or 675 mg for 3 months.

Outcomes and Statistical Analyses.—The primary efficacy endpoint of the phase 2 HFEM study was the mean change from baseline in the number of migraine days during the third study month. A migraine day was defined as a headache day lasting at least 4 consecutive hours and meeting the criteria for migraine with aura, migraine without aura, or probable migraine; it could also be a headache day of any duration treated with migraine specific medications, such as a triptan or ergot. Key secondary and exploratory endpoints included the change from baseline to month 3 in the number of headache days and hours with headaches of any severity. The number of days with moderate-to-severe (M/S) headaches was an exploratory endpoint in the HFEM and was defined as a day with at least 4 consecutive hours of moderate to severe headache. Other exploratory endpoints included assessment of treatment-related changes in migraine associated symptoms (nausea, vomiting, photophobia, and phonophobia) and a change in the use of acute medications during the study. Patients provided daily information on the use of acute medication consumption by responding to questions in the e-diary regarding the previous day usage and selecting from a list of the most frequently used medications to treat migraine attacks. Patients could enter the name of a used medication if it was not included in the list and could enter information on acute medication use at any hour in the e-diary. For purposes of these post-hoc analyses, missing weekly data were prorated to 7-day rate based on available data within that week.

As one of the questions remaining from the original study was how soon after starting fremanezumab did treatment effects become apparent, we conducted mixed effect model repeated measurement (MMRM) analysis to investigate the earliest significant separation from placebo. The post-hoc analyses included the change from baseline in the efficacy variables at week 1, 2, and 3 as the dependent variable; preventive medication use, sex, visit, and treatment as fixed factors, treatment by visit as

an interaction term, acute medication use and years since onset of disease were defined as covariates, with patients treated as random. An unstructured covariance matrix for repeated observations within patients was used and 95% CIs for the least square mean differences between each fremanezumab group and placebo were constructed. All variables were analyzed by the intent-to-treat (ITT) principle, which included all randomized participants who received at least one dose of study drug and provided at least one measurement. One patient received study drug and discontinued prior to providing one measurement and was not included in the ITT cohort analysis. All statistical tests were 2-sided at alpha level of 0.05. As these are post-hoc analyses, the reported *P* values should be interpreted with caution as there were no adjustments for multiplicity. The analyses were conducted with SAS (Version 9.2).

Role of the Funding Source.—The analyses of this paper were designed by all authors, some of whom are employees of the funding source, Teva Pharmaceuticals Ltd. One of the authors, Mirna McDonald, a former employee of Teva Pharmaceuticals conducted the statistical analyses. All authors were involved in writing the manuscript. They had access to all data in the study and there were no agreements with the sponsor which would preclude the authors' ability to analyze and interpret data and publish manuscripts independently when and where they choose.

RESULTS

Patient Disposition.—The HFEM study was conducted in parallel to a study investigating the efficacy of fremanezumab in chronic migraine (CM), thus screening included 1170 patients with a migraine diagnosis. Of these, 264 patients met eligibility criteria for CM and were enrolled in the parallel CM study. An additional 609 patients did not qualify for either the HFEM or CM study and were excluded. A total of 297 individuals were eligible for the HFEM study and were randomized to receive placebo ($n = 104$), 225 mg ($n = 96$), or 675 mg ($n = 97$). Of the patients in the HFEM study randomized into treatment arms, 2 participants did not receive any study medication and so were not included in the ITT or safety cohorts (1 in the 225 mg group and 1 in the 675 mg group) and one

Table 1.—Patient Baseline Demographic and Disease Characteristics

Patient Characteristics ^{†‡}	Placebo (n = 104)	Fremanezumab 225 mg (n = 96) [§]	Fremanezumab 675 mg (n = 97) [§]
Age – mean (SD) years	42.0 (11.6)	40.8 (12.4)	40.7 (12.6)
Sex			
Male	12 (12%)	9 (9%)	15 (15%)
Female	92 (88%)	87 (91%)	82 (85%)
Ethnic origin			
White	85 (82%)	74 (77%)	74 (76%)
Black or African American	13 (13%)	19 (20%)	18 (19%)
Asian	2 (2%)	1 (1%)	1 (1%)
Other	0	0	0
Years of migraine	21.1 (14.1)	18.9 (12.9)	16.9 (12.3)
Migraine days/month	11.5 (2.2)	11.5 (1.9)	11.3 (2.2)
Migraine days/week	2.9 (.6)	2.9 (.5)	2.8 (.6)
M/S headache days/month [¶]	9.8 (2.7)	10.0 (3.1)	9.6 (2.9)
M/S headache days/week	2.4 (.7)	2.5 (.8)	2.4 (.7)
Headache days/month	12.4 (2.3)	12.6 (3.1)	12.5 (2.7)
Headache days/week	3.1 (.6)	3.1 (.8)	3.1 (.6)
M/S headache hours/month	53.7 (45.7)	45.9 (27.2)	48.4 (27.9)
M/S headache hours/week	13.4 (11.5)	11.5 (6.8)	12.1 (7.0)
Headache hours/month	82 (49.3)	76.1 (36.7)	80.4 (36.6)
Headache hours/week	20.5 (12.4)	19.0 (9.2)	20.1 (9.2)
Days with nausea or vomiting/month	5.8 (4.3)	6.2 (4.1)	5.9 (4.0)
Days with nausea or vomiting/week	1.4 (1.1)	1.5 (1.0)	1.5 (1.0)
Days with photophobia and phonophobia/month	7.6 (4.7)	7.8 (4.3)	7.6 (4.2)
Days with photophobia and phonophobia/week	1.9 (1.2)	1.9 (1.1)	1.9 (1.0)
Days using acute medications/month	10.4 (3.6)	10.4 (3.6)	9.8 (4.0)
Days using acute medications/week	2.6 (.9)	2.6 (.9)	2.4 (1.0)

[†]All P values for treatment comparisons of demographic characteristics were >.05.

[‡]Data are mean (SD) of days or hours per month or per week, or number (percentage) of patients.

[§]The intent-to-treat mixed effect model of repeated measurement (ITT MMRM) analyses included 95 patients from fremanezumab 225 mg and 96 from fremanezumab 675 mg groups as one patient from each group withdrew from the study prior to drug treatment.

[¶]M/S, moderate-to severe.

patient was lost to follow-up after the first injection of study medication so there were no diary records; she was included in the safety cohort but not in the ITT cohort of the 225 mg group.

As shown in Table 1, baseline demographics and clinical disease characteristics were similar across treatment arms with a mean (SD) of 11.4 (2.1) migraine days per month. Compliance with diary entry was high throughout the study and similar across groups; for instance, during the first treatment month, 91% of placebo, 89% of 225 mg, and 84% of 675 mg patients provided daily entries at ≥80% compliance rate (≥22 days per 28 day treatment period).

Efficacy—Headache Parameters.—The study has been described in detail.¹⁹ As displayed in Figure 1 and Table 2, the number of migraine days for patients treated with fremanezumab was reduced compared to those treated with placebo in *the first week of therapy* for both fremanezumab doses; LSM differences between placebo and active treatment at week 1 for the 225 mg fremanezumab dose is -0.93 migraine days per week (95% CI: -1.36, -0.49); and for the 675 mg dose -1.02 migraine days per week (95% CI: -1.46, -0.58), both $P < .0001$. This benefit was maintained through the second and third weeks of therapy (all $P < .001$). Likewise there were consistent reductions in

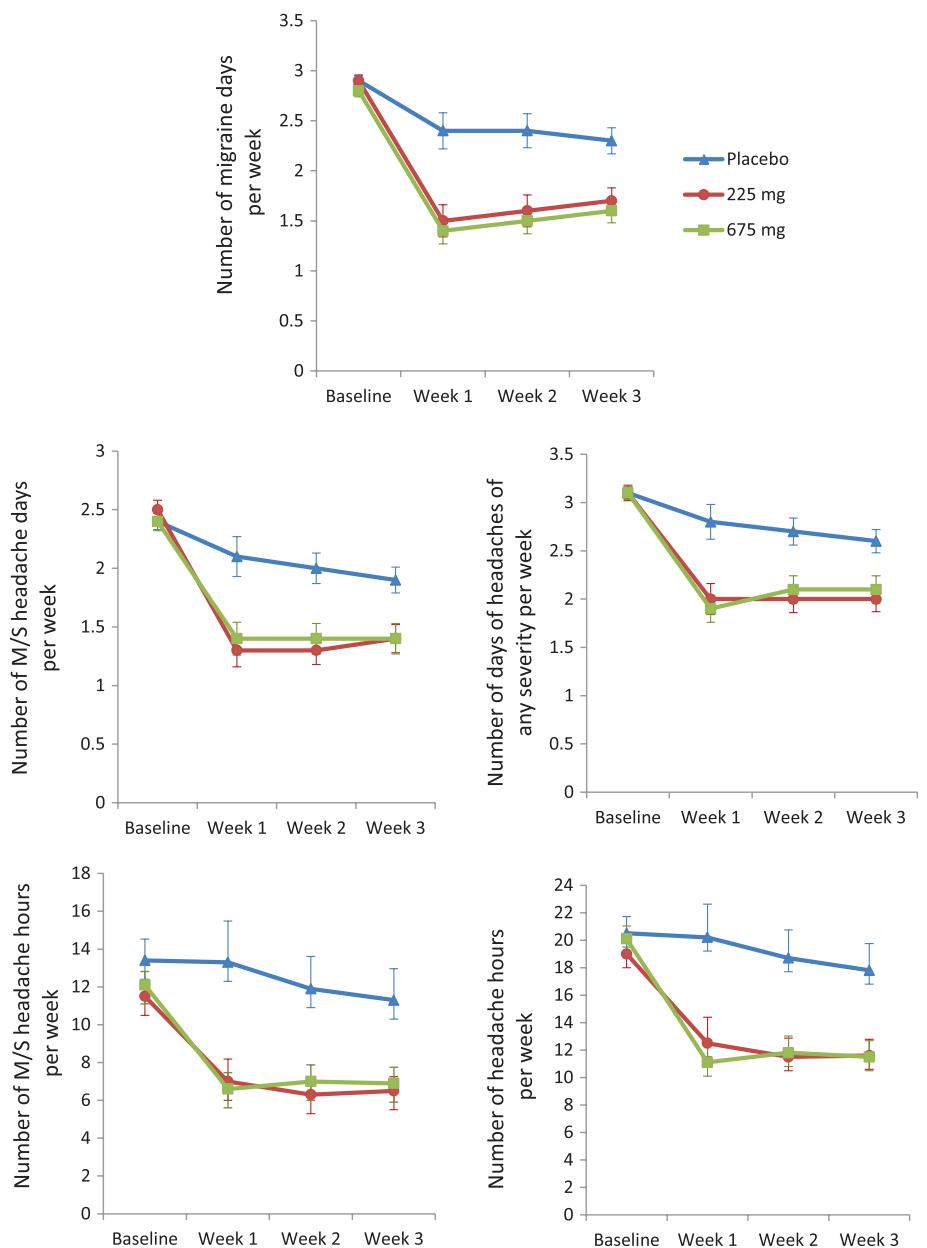


Fig. 1.—Reductions in headache parameters (mean \pm SE) during the first 3 weeks of fremanezumab treatment.

weekly M/S headache days and days of headache of any severity within the first 3 weeks of fremanezumab administration (all $P < .01$). For M/S headache hours and headache hours of any severity, the same pattern of efficacy emerged; the mean number of headache hours per week for 225 and 675 mg fremanezumab groups decreased by 6.50 and 8.99 hours in week 1, 5.69 and 6.52 hours in week 2, and 4.90 and 5.96 hours in week 3 compared to decreases of 0.78, 1.08, and 1.90 hours per week in the placebo group (all $P < .01$).

Migraine associated symptoms: Nausea, Vomiting, Photophobia, and Phonophobia.—In addition to questions concerning headaches, we also assessed whether fremanezumab caused reductions in symptoms associated with migraine such as nausea, vomiting, photophobia, and phonophobia (Table 2 and Fig. 2).

Compared to patients on placebo, decreases from baseline in the numbers of days per week with nausea or vomiting occurred in the first week of therapy for

Table 2.—Change from Baseline in the Occurrence of Headache Parameters and Migraine Symptoms During the First 3 Weeks of Frenametuzumab Treatment

Parameters [†]	Change from Baseline to Week 1			Change from Baseline to Week 2			Change from Baseline to Week 3		
	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)
Migraine days	-0.36 (.18)	-1.28 (.18)	-0.44 (0.15)	-1.20 (.16)	-1.24 (.15)	-0.52 (.15)	-1.16 (.15)	-1.17 (.15)	
	-0.93 (.22)	-1.02 (.22)	-0.76 (.18)	-0.79 (.18)	(-1.15, -0.44)	(-1.15, -0.44)	-0.64 (.17)	-0.64 (.17)	
	(-1.36, -0.49)	(-1.46, -0.58)	(-1.11, -0.40)	(-1.15, -0.44)	<i>P < .0001</i>	<i>P < .0001</i>	(-0.97, -0.30)	(-0.98, -0.30)	
	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>			<i>P = .0003</i>	<i>P = .0003</i>	
M/S headache days	-0.26 (.16)	-1.08 (.16)	-0.37 (.14)	-1.07 (.14)	-0.92	-0.45 (.14)	-1.00 (.14)	-0.93 (.14)	
	-0.83 (.20)	-0.72 (.20)	-0.70 (.16)	-0.55 (.16)	(-1.11, -0.33)	(-1.01, -0.38)	(-0.87, -0.22)	(-0.86, -0.24)	
	(-1.22, -0.44)	(-1.22, -0.44)	(-1.01, -0.38)	(-1.01, -0.38)	<i>P = .0003</i>	<i>P < .0001</i>	<i>P = .0009</i>	<i>P = .0005</i>	
	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>			<i>P = .0028</i>	<i>P = .0028</i>	
Headache days	-0.16 (.17)	-1.08 (.17)	-0.30 (.15)	-1.08 (.15)	-0.96 (.15)	-0.40 (.14)	-1.03 (.15)	-0.95 (.14)	
	-0.92 (.21)	-0.92 (.21)	-0.78 (.17)	-0.66 (.17)	(-1.11, -0.44)	(-1.11, -0.44)	(-0.63, .17)	(-0.55, .17)	
	(-1.34, -0.50)	(-1.34, -0.50)	(-1.34, -0.50)	(-1.34, -0.50)	<i>P < .0001</i>	<i>P < .0001</i>	<i>P = .0002</i>	<i>P = .0011</i>	
	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>			<i>P = .0002</i>	<i>P = .0002</i>	
M/S headache hours	.96 (1.3)	-3.64 (1.34)	-4.90 (1.32)	-0.68 (1.05)	-4.38 (1.08)	-4.49 (1.05)	-1.16 (1.01)	-4.55 (1.00)	
	-4.60 (1.67)	-5.85 (1.67)	-3.70 (1.25)	-3.82 (1.25)	(-9.15, -2.56)	(-6.16, -1.25)	(-6.28, -1.35)	(-5.36, -0.75)	
	(-7.88, -1.31)	(-9.15, -2.56)	(-9.15, -2.56)	(-9.15, -2.56)	<i>P = .0062</i>	<i>P = .0032</i>	<i>P = .0025</i>	<i>P = .0042</i>	
	<i>P = .0062</i>	<i>P = .0005</i>	<i>P = .0005</i>	<i>P = .0005</i>			<i>P = .0094</i>	<i>P = .0094</i>	
Hours of headaches of any severity	0.78 (1.73)	-8.20 (1.75)	-1.08 (1.42)	-6.77 (1.46)	-7.60 (1.42)	-1.90 (1.34)	-7.86 (1.33)	-7.86 (1.33)	
	-6.50 (2.21)	-8.99 (2.22)	-5.69 (1.69)	-6.52 (1.70)	(-13.36, -4.62)	(-9.03, -2.36)	(-9.87, -3.17)	(-5.70, -1.07)	
	(-10.85, -2.14)	(-13.36, -4.62)	(-13.36, -4.62)	(-13.36, -4.62)	<i>P = .0036</i>	<i>P < .0001</i>	<i>P = .0009</i>	<i>P = .0017</i>	
	<i>P = .0036</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>			<i>P = .0002</i>	<i>P = .0002</i>	
Days with nausea/vomiting	-0.17 (.13)	-0.62 (.14)	-0.68 (.13)	-0.29 (.11)	-0.67 (.12)	-0.59 (.11)	-0.31 (.11)	-0.54 (.11)	
	-0.46 (.17)	-0.51 (.17)	-0.38 (.13)	-0.30 (.13)	(-0.54, -0.11)	(-0.56, -0.03)	(-0.57, -0.06)	(-0.49, .02)	
	(-0.78, -0.13)	(-0.84, -0.19)	(-0.84, -0.19)	(-0.84, -0.19)	<i>P = .0061</i>	<i>P = .0022</i>	<i>P = .0005</i>	<i>P = .0146</i>	
	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>			<i>P = .0002</i>	<i>P = .0002</i>	
Days with photophobia and phonophobia	-0.08 (.15)	-0.91 (.15)	-0.89 (.15)	-0.26 (.13)	-0.82 (.13)	-0.81 (.13)	-0.34 (.13)	-0.77 (.13)	
	-.82 (.18)	-0.81 (.18)	-0.56 (.15)	-0.54 (.15)	(-1.18, -0.47)	(-0.85, -0.26)	(-0.84, -0.25)	(-0.73, -0.14)	
	(-1.18, -0.47)	(-1.17, -0.46)	(-1.17, -0.46)	(-1.17, -0.46)	<i>P < .0001</i>	<i>P < .0001</i>	<i>P = .0003</i>	<i>P = .0047</i>	
	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>			<i>P = .0047</i>	<i>P = .0047</i>	
Days with acute medication use	-0.05 (.15)	-1.07 (.16)	-1.06 (.15)	-0.16 (.13)	-1.01 (.13)	-0.90 (.13)	-0.28 (.13)	-0.83 (.13)	
	-1.02 (.19)	-1.02 (.19)	-0.84 (.15)	-0.74 (.15)	(-1.39, -0.64)	(-1.39, -0.64)	(-1.04, -0.44)	(-0.92, -0.34)	
	(-1.39, -0.64)	(-1.39, -0.64)	(-1.39, -0.64)	(-1.39, -0.64)	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	<i>P < .0001</i>	

[†]Parameter values provided include the change from baseline in least square means (LSMs) for each treatment group and in **bold font**, the LSM difference (SE) in change from baseline between placebo and active treatment group. *P* values and 95% confidence intervals are from the mixed effect model of repeated measurement (MMRM) analyses conducted on the change from baseline at weeks 1, 2, and 3 between the placebo and the frenametuzumab dose groups. M/S refers to moderate to severe.

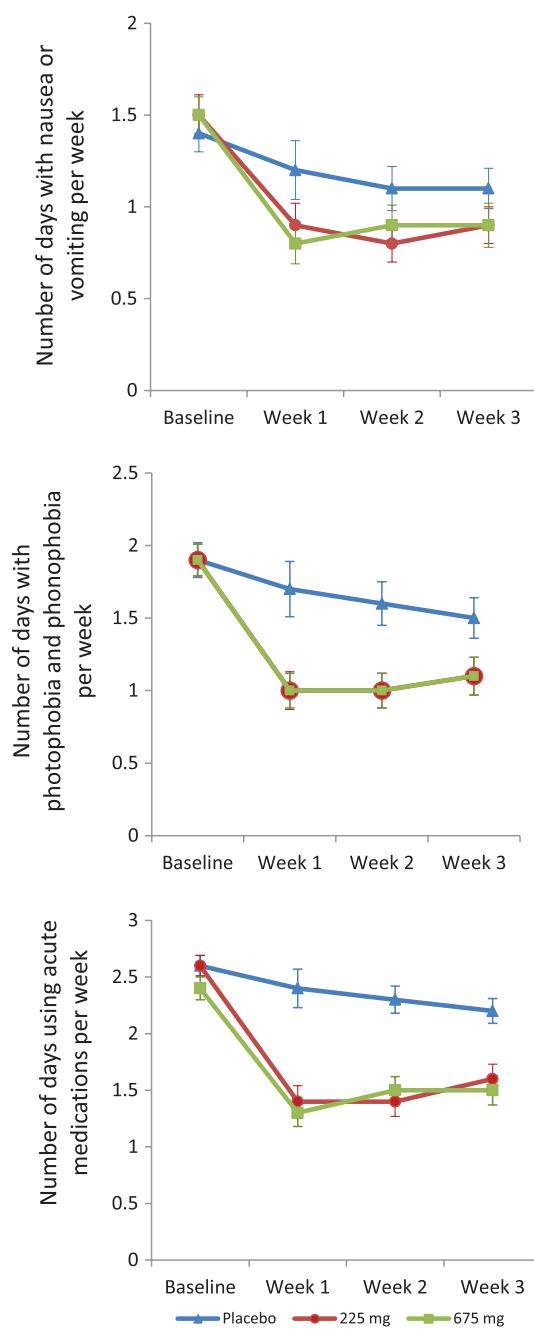


Fig. 2.—Reductions in migraine symptoms (mean \pm SE) during the first 3 weeks of fremanezumab treatment.

fremanezumab 225 and 675 mg doses (LSM differences of -0.46 (95% CI: -0.78 , -0.13) $P = .0061$ and -0.51 (95% CI: -0.84 , -0.19) $P = .0022$, respectively). Decreases continued in second (LSM difference -0.38 (95% CI: -0.64 , -0.11) $P = .005$) and third week (LSM difference -0.32 (95% CI: -0.57 , -0.06) $P = .0146$) for the 225 mg fremanezumab dose. For the 675 mg dose, decreases continued in the second week (LSM

difference -0.30 (95% CI: -0.56 , -0.03) $P = .0274$) and less so in the third week (LSM difference -0.24 (95% CI: -0.49 , 0.02) $P = .0696$).

Similarly, decreases in the number of days per week with photophobia and phonophobia occurred within the first week for the fremanezumab 225 and 675 mg doses (LSM differences of -0.82 (95% CI: -1.18 , -0.47), and -0.81 (95% CI: -1.17 , -0.46) both $P < .0001$). These decreases continued in the second week ($P = .0003$ and $P = .0004$) and third week ($P = .0044$ and $P = .0047$) of fremanezumab treatment.

Reduction in Acute Medication Use.—There was also a difference between the placebo and fremanezumab groups in the number of days of acute medication use per week in the first 3 weeks (Table 2 and Figure 2). The use of acute medications decreased for the fremanezumab 225 and 675 mg doses compared to placebo during the first week (LSM differences of -1.02 (95% CI: -1.39 , -0.64), and -1.02 (95% CI: -1.39 , -0.64) both $P < .0001$); second week (LSM differences of -0.84 (95% CI: -1.14 , -0.55) and -0.74 (95% CI: -1.04 , -0.44) both $P < .0001$); and third week (LSM differences of -0.63 (95% CI: -0.92 , -0.34) $P < .0001$ and -0.55 (95% CI: -0.84 , -0.26) $P = .0002$).

Safety.—The safety results for the HFEM have been fully described earlier.¹⁸ The most common adverse events were injection site reactions (pain, erythema, and/or pruritus) and there were no relevant changes in vital signs or blood pressure between groups and no treatment emergent anti-drug antibody response occurred.

DISCUSSION

Fremanezumab treatment, in a post-hoc analysis of the phase 2 HFEM study, resulted in a rapid preventive response in patients with episodic migraine. Improvements in multiple headache parameters and migraine symptoms, as well as acute medication use were seen in the first few weeks of treatment. Monthly doses of fremanezumab, 225 and 675 mg, demonstrated decreases in the number of migraine days and other headache parameters in the first week of treatment. These findings are consistent with the phase 2 chronic migraine study¹⁷ in which patients on fremanezumab had decreases in headaches within the first 3 days of treatment.

Collectively these data suggest that the onset of effect for fremanezumab as a preventive treatment for migraine may correct some of the issues associated with currently available oral migraine preventive treatments. Oral therapies often require gradual dose titration and their efficacy may not be apparent for several months; this along with their adverse event profile may lead to patients discontinuing treatment before their therapeutic effect is apparent.^{7,24} Fremanezumab, with its rapid onset of effect, together with a low rate of adverse events, may improve patient adherence and compliance with a preventive medication.

In this study, patients at baseline had an average of 11 migraine days per month, or 3 migraine days per week. Within the first week of treatment, patients on fremanezumab reported a decrease in 1 migraine day per week compared to patients on placebo; thus patients rapidly began to feel better. A reduction of 1 migraine day per month, and a 30% reduction in headache frequency from baseline have previously been suggested as 2 of the criteria necessary for a clinically meaningful effect for a preventive treatment for chronic migraine.²⁵ The study was not designed to assess the clinical meaningfulness of changes in migraine days and the other headache parameters. Despite this, it is reassuring that both doses of fremanezumab met these 2 criteria in the first week of therapy. The effects seen on migraine days and the other headache parameters continued through the second and third week of the first month and were maintained during the entire 3 months of the study.¹⁹

We examined the early effects of fremanezumab on associated migraine symptoms, since they are a major contributor to the burden of migraine.^{26,27} Many patients have self-reported problems with taking oral preventive migraine medications because of nausea and vomiting.²⁷ Photophobia and phonophobia are very common and are thought to result from enhanced sensitivity to light and sound occurring in both the premonitory (prodrome) and headache phases of migraine.²⁸ Treatment-related reductions in associated migraine symptoms occurred in the first few weeks and continued throughout the three month study (all comparisons between fremanezumab dose groups and placebo were significantly different with the exception of reduction in days of nausea or vomiting for the 675 mg dose, $P < .069$).¹⁹

Fremanezumab also reduced the use of acute migraine medications during the study. Patients with frequent migraine attacks carry a nearly daily burden,²⁹ and since excessive use of acute medication is a risk factor for migraine worsening,³⁰ the early decrease in acute care medication consumption is important.

This study has limitations. First, the analyses were not defined a priori, since quick onset of action was not anticipated. Given that these were post-hoc analyses, adjustments for multiple comparisons are not appropriate³¹ and the findings should be considered exploratory in nature. Another limitation is that we are unable to provide specific drug information on the decreases in acute medications. We also lack quality of life measures, such as the Migraine-Specific Quality of Life Questionnaire (MSQ) and impact data, such as the Headache Impact Test (HIT-6), which could have also helped in understanding the clinical meaningfulness of treatment effects occurring within the first few weeks of therapy.²⁵ There was also no long term follow-up of patients in this study; so we do not know the effectiveness of the treatment beyond 12 weeks. That being said, the findings of these post-hoc analyses suggest the very early onset of effectiveness of migraine prevention of fremanezumab.

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RESEARCH ARTICLE

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The prevalence of primary headache disorders and their associated factors among nursing staff in North China

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Abstract

Background: Epidemiological data on the prevalence of headache in nursing staff in Mainland China are lacking. We therefore performed a study to assess the prevalence of headache, and factors associated with headaches, in nursing staff in three hospitals in North China.

Methods: Stratified random cluster sampling was used to select 1102 nurses from various departments in three hospitals. A structured questionnaire was used to collect epidemiological data, headache characteristics and associated factors.

Results: The response rate was 93.0%. Among nursing staff, the 1-year prevalence of primary headache disorders was 45.3%, of migraine 14.8% (migraine with aura 3.4%, migraine without aura 11.4%), of tension-type headache (TTH) 26.2%, of chronic daily headache (CDH) 2.7%. Multivariate analysis showed that seniority (≥ 5 years) was a risk factor for migraine (OR 2.280), obesity (BMI ≥ 25) was a risk factor for TTH and CDH (OR 1.684 and 3.184), and age (≥ 40 years) was a risk factor for CDH (OR 8.455). Nurses working in internal medicine were more likely to suffer CDH than those in other departments. Working a greater number of night shifts was also associated with increased prevalence of headache.

Conclusion: The prevalence of primary headache disorders in nurses is higher than that in the general population in China, and occupational factors may play an important role. Therefore, the prevalence of headache in nurses should be a focus of attention, and coping strategies should be provided. Such measures could contribute to improving patient care.

Keywords: Prevalence; Headache; Migraine; Tension-type headache; Chronic daily headache; Nursing staff

Background

Primary headache, especially migraine and tension-type headache (TTH) are common in the general population worldwide [1,2]. The current headache prevalence is 46% in the adult population worldwide [1]; Asians have a lower prevalence than European and North American populations due to racial differences [3,4]. In a door-to-door population-based survey in China, the 1-year prevalence of primary headache disorders was 23.8%, and was higher in females [5]. Headache can affect work

and other activities, with most migraine sufferers and around half of tension-type headache sufferers reporting limitation of activities during a headache attack [6,7]. Due to the high prevalence of headaches and the associated disability, the presence of headaches in specific professional groups should be investigated.

Nursing staff, who are primarily female, experience a huge source of stress as a result of caring for suffering and dying patients, and through challenging physician-patient relationships, more easily to suffer headache than general population [8,9]. Studies have explored nurses' occupational stress and coping [10,11] but no study has investigated the headache prevalence in nurses in mainland of China. Studies conducted in Taiwan and Japan

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revealed that the prevalence of headaches in nurses is higher than in the general population [8,9]. There has been limited research in this area worldwide, and, at present, little is known about the prevalence of headache among nursing staff in Mainland China.

The purpose of this epidemiological study was to investigate the prevalence of primary headache and factors associated with headache among nursing staff in China. The diagnostic criteria were based on the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3-beta) [12]. In addition, we evaluated the impact of nursing occupational factors on the prevalence of primary headache.

Methods

Ethics

The study protocol was approved by the Ethics Committee of the Chinese PLA General Hospital, Beijing. All participants provided written informed consent after receiving a detailed explanation of the purpose and design of the study.

Questionnaire

Participants filled out a structured questionnaire to gather demographic and socioeconomic data, headache characteristics over the previous year, and occupation-related factors. The demographic and headache profile sections of the questionnaire were the same items as used in a Chinese national epidemiology study, and were validated for headache assessment and diagnosis in the general population [5,13].

Demographic questions included age, ethnicity (Han versus Non-Han), marital status (Unmarried versus Married/Divorced, we merged the latter two as the number of divorced people was low), educational attainment (Junior college or lower versus University or above), body-mass index (BMI, graded as underweight, normal weight, overweight, obese); socioeconomic status including nursing specialty (internal medicine, surgical department and others), work seniority (<5 years versus ≥5 years), title (primary nurse, nurse practitioner, nurse-in-charge or above).

The headache profile section included items on headache duration, frequency, location, quality, intensity, aura, and characteristics of accompanying symptoms (nausea, vomiting, photophobia and phonophobia), and the impact of physical activity on headache. The diagnoses of migraine and TTH were made according to the criteria of ICDH-3-beta, respondents reporting headaches lasting more than 4 h per day on 15 or more days per month were given the label CDH and questioned on medication usage in order to identify medication-overuse headache (MOH) [14]. Trigeminal autonomic cephalgia, other primary headaches and secondary headaches were not included in this questionnaire.

The working patterns of nursing staff are unique. We therefore assessed occupation-related factors, including work arrangements (rotational shifts) and number of night shifts (for those completing shift work).

Sample and survey

The study was conducted in three 3A hospitals in North China from December 2013 to June 2014. The hospitals were the Chinese PLA General Hospital, The General Hospital of Chinese Armed Police Forces and the Hebei General Hospital. We adopted a stratified random cluster sampling method. In each hospital, we randomly selected eight clinical departments from which all nurses were invited to participate. Each participant was interviewed face-to-face by neurologists who were systematically trained with the ICHD-3-beta tool and the survey, then completed and retrieved the structured questionnaire. Participants who reported headache were followed up in a telephone interview to confirm diagnosis. Prior to this, a pilot study surveyed one department in each hospital to test the epidemiological methods.

Statistics

Data were processed using EpiData 3.1 and analysed using SPSS 17.0. Continuous variables which did not comply with the normal distribution were summarised as median, and categorical variables as numbers and percentages. Chi-square tests were used to compare the distributions of categorical variables between groups. Multivariate logistic regression was applied to identify odd ratios (ORs) with 95% confidence intervals (CIs) for different types of headache, according to social-demographic characteristics. Statistical significance was set at $p < 0.05$.

Results

Among the 1102 nurses invited to participate, 58 declined to complete of the survey, and 18 submitted incomplete questionnaires. The response rate was 93%. 1023 respondents completed the survey, all female. The age ranged from 20–57 years with a median of 27 years.

The 1-year prevalence of primary headache was 45.3% (95% CI 42.4–48.4%), with 14.8% (95% CI 9.2–20.4%) experiencing migraine (3.4% for migraine with aura, 11.4% for migraine without aura), 26.2% (95% CI 21.1–31.3%) TTH, and 2.7% (95% CI 0–8.7%) CDH. Only 10 respondents reported two types of primary headache, and 5 had unclassifiable headache. Only 2 nurses were diagnosed with both CDH and MOH. The prevalence of TTH peaked during middle age (30–39 years) (30–39: 33%; 20–29: 24%; ≥40: 29.3%), while migraine and CDH increased gradually with age (migraine: 20–29: 13.8%, 30–39: 17.2%, ≥40: 18.7%; CDH: 20–29: 1.7%, 30–39: 3.4%, ≥40: 10.7%).

The demographic data comparisons between different types of headaches and non-headache are shown in

Table 1. Univariate analysis suggested that the prevalence of all three types of headache differed significantly with age, marital status, and seniority. Education was associated with the likelihood of experiencing headache but not with a particular kind of headache. Nursing specialty correlated with CDH, job title and BMI were linked to TTH and CDH but not migraine. Being married or divorced increased the probability of suffering all three headache types (migraine: married/divorced: 25.8%, unmarried: 18%, $P < 0.05$; TTH: married/divorced: unmarried: 38.6%, 27.4%, $P < 0.01$; CDH: married/divorced: 7.8%, unmarried: 2.6%, $P < 0.01$). More highly educated participants were prone to having more headaches, especially migraine (University or above: 25.3%, Junior college or lower: 18.9%, $P < 0.05$). Those with seniority of greater than 5 years were more likely to suffer all types of headache than were less-senior staff (migraine: seniority ≥ 5 : 27.5%,

seniority < 5 : 15.2%, $P < 0.01$; TTH: seniority ≥ 5 : 37.1%, seniority < 5 : 27.8%, $P < 0.01$; seniority ≥ 5 : 7.5%, seniority < 5 : 2.3%, $P < 0.01$). The prevalence of TTH and CDH was significantly higher in some roles (TTH: nurse 28.6%, nurse practitioner 33%, nurse-in-charge or above 42.8%, $P < 0.05$; CDH: nurse 2.9%, nurse practitioner 4.2%, nurse-in-charge or above 13.3%, $P < 0.01$). The prevalence of migraine and total headache did not significantly differ with work arrangements (day shift vs. rotating shift with day, evening and night shifts). However, nurses working day shifts were significantly more likely to suffer from TTH (TTH: day-shift 36.7%, rotating-shift 30%, $P < 0.05$).

Figure 1 shows the trends in the prevalence of primary headache associated with BMI. The prevalence of TTH increased with increasing BMI. In migraine and CDH, the prevalence initially marginally decreased and then increased with increasing BMI. Participants classified as

Table 1 The demographic characteristics comparisons between different types of headaches and non-headache among nursing staff

Variable	Non-headache N	Total headache		Migraine		Tension-type headache		Chronic daily headache	
		N(%)	P value	N(%)	P value	N(%)	P value	N(%)	P value
Total	560	463(45.3)		152(21.3)		268(32.4)		28(4.8)	
Age		0.000		0.028		0.002		0.000	
20-29	437	308(41.3)		103(19.1)		179(29.1)		13(2.9)	
30-39	92	111(54.7)		35(27.6)		67(42.1)		7(7.1)	
≥ 40	31	44(58.7)		14(31.1)		22(41.5)		8(20.5)	
Nationality		0.407		0.047		0.309		0.843(adjusted)	
Han	535	440(45.1)		139(20.6)		260(32.7)		26(4.6)	
Non-Han	25	23(47.9)		13(34.2)		8(24.2)		2(7.4)	
Marital status		0.000		0.012		0.001		0.004	
Unmarried	336	220(39.6)		74(18)		127(27.4)		9(2.6)	
Married/Divorced	224	243(52)		78(25.8)		141(38.6)		19(7.8)	
Education		0.009		0.044		0.073		0.067	
Junior colleague or lower	356	257(41.9)		83(18.9)		153(30.1)		13(3.5)	
University or above	204	206(50.2)		69(25.3)		115(36.1)		15(6.8)	
Nursing specialty		0.825		0.559		0.701		0.046	
Internal Medicine	237	207(46.6)		63(21)		120(33.6)		18(7.1)	
Surgical Department	198	162(45)		60(23.3)		87(30.5)		8(3.9)	
Others	125	94(42.9)		29(18.8)		61(32.8)		2(1.6)	
Seniority(year)		0.000		0.000		0.004		0.003	
<5	302	186(38.1)		54(15.2)		116(27.8)		7(2.3)	
≥ 5	258	277(51.8)		98(27.5)		152(37.1)		21(7.5)	
Title		0.002		0.559		0.017		0.001	
Primary nurse	267	177(39.9)		54(16.8)		107(28.6)		8(2.9)	
Nurse practitioner	229	204(47.1)		75(24.7)		113(33)		10(4.2)	
Nurse-in-charge or above	64	82(56.2)		23(26.4)		48(42.9)		10(13.5)	
Work arrangement		0.145		0.82		0.046		0.067	
Day-shift	186	174(48.3)		49(20.9)		108(36.7)		14(7)	
Rotating-shift	374	289(43.6)		103(21.6)		160(30)		14(3.6)	

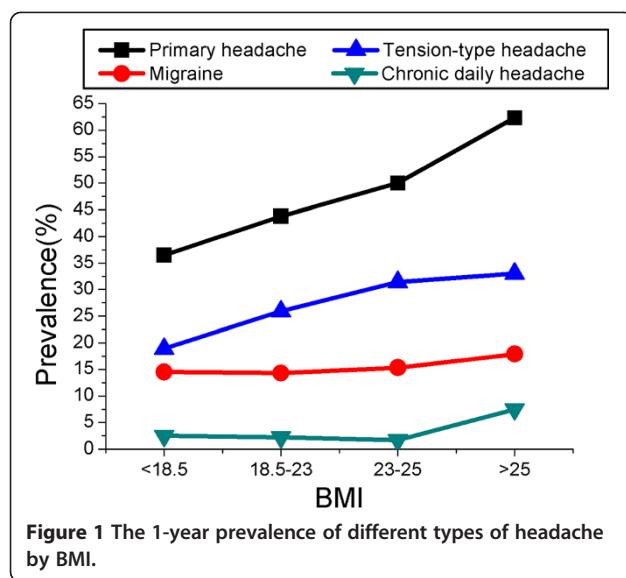


Figure 1 The 1-year prevalence of different types of headache by BMI.

obese (BMI >25) had a significantly increased prevalence of all types of headache compared with those of a normal weight (migraine: OR = 1.86, 95% CI 1.04 to 3.34, P < 0.05; TTH: OR = 1.9, 95% CI 1.17 to 3.08, P < 0.01; CDH: OR = 5.14, 95% CI 2.21 to 11.99, P < 0.01).

Then the above factors were analyzed by enter method of multivariate logistic regression (Table 2), revealing that seniority ≥5 years and BMI ≥25 remained independent risk factors for total headache, as did seniority ≥5 years for migraine, BMI ≥25 for TTH, age ≥40 years and BMI ≥25 for CDH. Nurses of other specialties were less likely to suffer CDH than internal medicine and surgical department nurses, but the number of other them was very low. Age

for migraine and TTH, seniority for TTH and CDH, marital status and title for all three types of headache, work arrangement for TTH, and obesity for migraine were not identified as risk factors by multivariate logistic regression analysis.

We investigated whether frequency of night shift affects the prevalence of headache by grouping nurses above or below the median of eight (see Table 3). Nurses working greater than eight night shifts were significantly more likely to suffer all types of headache than those working less than eight night shifts (Migraine: 29.4% vs. 18.9%; TTH: 35.5% vs. 28.1%).

Discussion

This study is the first to assess the prevalence of headaches among nursing staff in Mainland China. We found that the 1-year prevalence of primary headaches was 45.3% (95% CI 42.4-48.4%). This is higher than the prevalence in females in the general population in Mainland China (36.8% [95% CI 34.9-38.7%]) according to data from a previous nationwide population-based study conducted using the same screening questionnaire [5]. Our findings were similar to those of previous studies in Taiwan and Japan, which also found that the prevalence of primary headache was higher in nursing staff compared to the general population. In Taiwan, the prevalence of primary headache was 49.6% [9,15], while in Japan, the prevalence of recurrent headache was 40.9% [8]. Compared to the general population, nurses, as a special occupational group with basic medical knowledge, took medicine more rationally, which could be the reason for low prevalence of MOH. This side-fact indicated the importance of popularization of medical knowledge. Multivariate analysis

Table 2 Multivariable adjusted odds ratios (95% confidence interval) for total headache, migraine, tension-type headache (TTH), and chronic daily headache (CDH)

	Total headache	Migraine	Tension-type headache	Chronic daily headache
Age				
20-29	Reference	Reference	Reference	Reference
30-39	1.166(0.751-1.809)	1.070(0.585-1.959)	1.242(0.742-2.078)	1.464(0.371-5.780)
≥40	1.401(0.667-2.944)	1.732(0.617-4.857)	1.043(0.438-2.482)	8.455(1.138-62.848)*
Seniority (years)(≥5 VS <5)	1.468(1.013-2.126)*	2.280(1.323-3.929)**	1.122(0.718-1.752)	3.724(0.890-15.579)
Nursing specialty				
Internal Medicine	Reference	Reference	Reference	Reference
Surgical Department	0.989(0.741-1.320)	1.121(0.740-1.699)	0.914(0.649-1.289)	0.464(0.187-1.152)
Others	0.848(0.605-1.188)	0.766(0.459-1.279)	0.998(0.676-1.474)	0.136(0.027-0.673)*
BMI				
Normal weight (18.5 to <23)	Reference	Reference	Reference	Reference
Underweight (<18.5)	0.804(0.557-1.160)	0.982(0.582-1.659)	0.704(0.447-1.110)	1.685(0.507-5.603)
Overweight (23 to <25)	1.082(0.719-1.626)	0.959(0.525-1.752)	1.177(0.736-1.883)	0.509(0.105-2.473)
Obese (≥25)	1.814(1.165-2.823)**	1.515(0.802-2.863)	1.684(1.011-2.806)*	3.184(1.116-9.089)*

*P < 0.05, **P < 0.01.

Table 3 The impact of number of night shifts per month on the prevalence of different types of primary headache

Night shift number	Total headache		Migraine		Tension-type headache	
	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)
	1.59(1.13-2.23)		1.79(1.12-2.85)		1.41(0.93-2.12)	
≤8	40.5		18.9		28.1	
>8	51.9		29.4		35.5	

revealed that seniority of greater than 5 years was a risk factor for migraine; obesity was a risk factor for TTH; and age, obesity, and internal medicine specialty were risk factors for CDH.

The 1-year prevalences of migraine, TTH and CDH in our study were 14.8%, 26.2% and 2.7%. These were higher than reported in the general female population in which the prevalence was 12.8% for migraine, 14% for TTH, and 1.4% for CDH. The difference in prevalence between the two populations was greatest for TTH. The reason for this might be that nurses were exposed to a greater number of occupational stressors due to a large workload, poor work environment, and difficult patients [8,10,11,16,17]. High work stress is a risk factor for primary headache, especially TTH [8,18-23]. The previous national population-based study in Mainland China revealed that the prevalence of TTH and migraine peaked during middle age (40-49 years), and CDH gradually increased with age [5]. Japanese and Taiwan studies have reported that the highest prevalence of migraine in females occurs at the age of 30-39 years [14,24]. The peak in prevalence of migraine in our study was 40-49 years; this is consistent with the population-based study, but later than in the two other Asian studies. Takeshima et al. reported that the peak age for TTH in Japan was 40-59 years [25]. Studies conducted in Malaysia and Hong Kong reported younger peak ages of 16-35 and 25-34 years, respectively [26,27], which were similar to our findings (30-39 years). The younger peak age in TTH compared to the Japanese study might be because of the relatively large proportion of young nurses. The prevalence of CDH increased as individuals aged, which is consistent with the findings of the general population study in Mainland China.

In the present study, a trend indicated that higher prevalence of TTH was associated with higher BMI; this is contrary to the commonly held belief that BMI is a risk factor for the frequency, but not prevalence, of headache [28,29]. Although previous studies suggested that migraine prevalence was significantly associated with obesity in reproductive-age individuals [30,31], the relationship between obesity and prevalence of episodic tension-type headache was first revealed in our clinic-based study, which found that obese participants were almost twofold more likely to have TTH than the healthy

weight controls. As data regarding the association between TTH and obesity are limited, the underlying reasons are unclear. The difference may be the result of different BMI classifications; we adopted the guideline specifically for the Asia-pacific population [32], which define obesity as $BMI \geq 25 \text{ kg/m}^2$, and did not separately calculate morbid obesity in nursing staff as the numbers were low. We believe that the characteristics of our study group may be in part responsible for this difference. Nurses, who are predominantly female, tend to pay more attention to their own appearance and might develop anxiety and depression if obese, this anxiety and depression may lead to TTH [23,33]. In addition, obesity and TTH have an overlapping pathophysiology. Low serotonin levels may increase food intake and development of obesity, and are also thought to play an important role in TTH [34]. Levels of several inflammatory mediators, including IL-1, IL-6, and tumour necrosis factor (TNF)- α , are increased in obese individuals [35], and these have been proposed to contribute to the development of TTH [36,37]. Multivariate logistic regression indicated no significant association between migraine and obesity, which was not consistent with previous studies [29,38]. The difference in findings might be due to the small sample size in our study. Obese participants ($BMI > 25$) were more than threefold more likely to suffer CDH than the participants of a healthy weight. This conclusion is consistent with previous reports of an association between obesity and the frequency of episodic headache [29]. Individuals with episodic headache and obesity develop chronic daily headache (CDH) at more than fivefold the rate of normal-weight individuals [39].

It revealed that the nurses of other specialties were less likely to suffer CDH than internal medicine and surgical department nurses, however, there were only 2 nurses of other specialities suffering CDH, so this finding maybe not so believable. In our study, seniority of greater than 5 years was significantly associated with a greater prevalence of primary headache, especially migraine, indicating that occupational factors affect the prevalence of headache among nursing staff. As the seniority increased, nurses would shoulder a greater work pressure and face more complicated personal relationship, which all could lead to the attack of migraine. Among the rotating-shift group, working greater than eight night shifts per month was

associated with a higher incidence of primary headache. In previous observational studies, it was found that night shift work was associated with an increased risk of cancer and cardiovascular disease [40–42], but the effect of night shift work on the risk of headache had not been assessed previously. More night shift work may lead to increased sleep disturbance and chronic fatigue, which are triggers of headaches.

Our study had several strengths. First, it was the first study in Mainland China to assess the prevalence and associated factors of primary headache in nursing staff. Second, the random cluster sampling method utilised combined with the high response rate eliminated selection bias. Furthermore, the diagnosis of headache met the latest ICDH-3-beta guidelines, and a follow-up telephone interview conducted by a neurologist guaranteed the accuracy of the diagnosis.

This study had several limitations. Despite our ability to control for a large number of potential confounders, we could not assess these comprehensively, and did not investigate other psychosomatic diseases that might be confounding variables. We did not investigate life-style factors, such as lack of exercise, smoking, drinking, sleeping late, all of which could increase the prevalence of headache. We used a structured questionnaire to collect data, we can't know in detail the headache profile before, then it is difficult for us to judge what types of headache the chronic daily headache was transformed from, so we cannot distinguish the chronic migraine from chronic tension-type headache. The sample was relatively small, involving only three hospitals and 1023 nurses in North China, therefore the number of outcome events in some subgroups, especially chronic daily headache with low prevalence, is small. Further work is needed.

Conclusion

This epidemiological study was performed to assess the prevalence of primary headache in nursing staff in Mainland China. The prevalence was high, which suggests that occupational health problems of nurses should be focused upon. Awareness and avoidance of trigger factors can not only decrease the frequency of headache but also reduce the possibility of chronic headache and medication overuse, guaranteeing the working health of nurses and thus improve their output. Greater attention to, and better management of, primary headache among nursing staff could improve health care in China.

Abbreviations

TTT: Tension type headache; CDH: Chronic daily headache; MOH: Medication-overuse headache; ICHD-3-beta: International Classification of Headache Disorders, 3rd edition (beta version).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Dr YW was responsible for reviewing the literature and writing the manuscript. Dr JK was responsible for data statistics. Dr FY co-organized this survey. Drs SW, HW were regional leaders of this survey. Ms. XZ, HL, XD was responsible for issuing and recalling the questionnaires. Dr SY was the principal investigator who was responsible for study design, data analysis and interpretation, and revision of the manuscript. As the corresponding author, Dr Y had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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ASSOCIATION STUDIES ARTICLE

Serum calcium and risk of migraine: a Mendelian randomization study

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Abstract

Migraine affects ~14% of the world's population, though not all predisposing causal risk factors are known. We used electronic health records, genetic co-heritability analysis, and a two-sample Mendelian Randomization (MR) design to determine if elevated serum calcium levels were associated with risk of migraine headache. Co-morbidity was evaluated using electronic health records obtained from the PennOmics database comprising >1 million patient entries. Genetic co-heritability and causality via MR was assessed using data from the International Headache Consortium (23,285 cases, 95,425 controls) and circulating serum calcium levels (39,400 subjects). We observed co-occurrence of migraine and hypercalcaemia ICD-9 diagnoses ($OR = 1.58$, $P = 4 \times 10^{-13}$), even after inclusion of additional risk factors for migraine ($OR = 1.23$, $P = 2 \times 10^{-3}$). Second, we observed co-heritability ($r_g = 0.191$, $P = 0.03$) between serum calcium and migraine headache, indicating that these traits have a genetic basis in common. Finally, we found that elevation of serum calcium levels by 1 mg/dl resulting from our genetic score was associated with an increase in risk of migraine ($OR = 1.80$, 95% CI: 1.31–2.46, $P = 2.5 \times 10^{-4}$), evidence supporting a causal hypothesis. We also present multiple MR sensitivity analyses in support of this central finding. Our results provide evidence that hypercalcaemia is comorbid with migraine headache diagnoses, and that genetically elevated serum calcium over lifetime appears to increase risk for migraine. Further studies will be required to understand the biological mechanism, pathways, and clinical implication for risk management.

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Introduction

Migraine is the most common neurological disorder in the world with over a billion afflicted (1), with elevated prevalence in women versus men of European ancestry (2). A highly debilitating disorder, it ranks among the costliest in terms of economic impact and lost productivity (3). Migraine is classified into two common forms: migraine with and without aura, an associated perceptual distortion that occurs before or close to the onset of migraine (4). Genome-wide association studies have demonstrated numerous genetic factors that underlie susceptibility to migraine generally (5), suggestive of a common aetiology between migraine with and without aura. An important next step is to translate these data into clinically relevant insights of causal mechanisms underlying the disorder.

Identification of causal factors for migraine is critical to success in translational medicine. Specifically, interventions based on causal factors have the best chance for success in ameliorating disease. While the Randomized Control Trial is the standard to assess causal relationships, such trials are expensive, time-consuming, and ultimately require knowledge of an intervention hypothesized to be clinically beneficial. Thus, research efforts generating compelling evidence for causal hypotheses offer the best chances for translational clinical outcomes to emerge.

Epidemiological studies can provide evidence of association between measurable biomarkers and risk to disease. However, these studies often require knowing what biomarker will be studied at the start of the study, and often cannot survey all possible traits. For example, a tumour within parathyroid glands can cause primary parathyroidism (6), resulting in excess secretion of parathyroid hormone and circulating levels of serum calcium, with severe headache as a common symptom. Given the sporadic nature of this disease, it is challenging to evaluate the relationship between elevated parathyroid hormone or serum calcium levels with a disposition to headache, with only anecdotal reports scattered in the literature (7–9). While not perfect, biomedical informatics mining of electronic health records could provide one complementary source of data to identify potential and plausible candidate traits like these for further study (10).

Once correlated risk factors have been identified, a suite of computational methods can provide direct evidence for and against causal hypotheses using human genomics data (11–13). One approach, termed Mendelian Randomization, uses genetic variants associated with a biomarker of interest in an instrumental variable analysis to estimate a causal effect of the biomarker on a disease endpoint. The approach has some analogy to the classic Randomized Control Trial, where genotype operates as the randomized intervention (14,15). Because alleles are sorted randomly at birth and the assumption that trait endpoints do not change germline variation, the approach avoids issues due to reverse causality. In addition, careful selection of genetic variation for testing can address issues of confounding. While these methods require several key assumptions to hold, application of the approach has been used extensively to generate evidence for (16) and against (17) specific causal hypotheses, importantly where clinical trial data is not readily available. A second, recently described approach estimates genetic correlation – joint heritability – between a pair of traits (18). Application of the approach recapitulates expected causal associations such as low-density lipoprotein cholesterol and heart disease, as well as obesity and T2D, though one limitation of the approach is that this does not provide a direction of effect between the trait and endpoint. Nonetheless, both approaches are

complementary towards evaluating causal hypotheses using genomics data.

Serum calcium level is a continuous, quantitative biomarker that is maintained within a homeostatic range. The prevalence of extreme levels of circulating serum calcium (diagnosed as hypercalcaemia) has a range of underlying causes in the general population and is difficult to estimate given its frequency, though has been observed in 0.5–1% of patients who visit emergency departments (39). Genetic variation associated with population-level variability in serum calcium levels have also been reported (19), allowing the opportunity to apply the above approaches—mining electronic health records, estimation of genetic heritability, and direct causal inference testing—to evaluate the hypothesis that serum calcium is a causal risk factor for migraine headache. Here, we use biomedical electronic health records to show a correlation between elevated calcium levels and migraine, and subsequently large-scale genetic data sets to test the hypothesis that genetically elevated serum calcium levels increase risk for migraine headache.

Results

Hypercalcaemia and migraine headache are diagnoses that occur together frequently

Large-scale epidemiological association studies have not systematically examined a potential correlation between serum calcium levels and migraine headache. Thus, we aimed to test the hypothesis that Migraine headache diagnoses are associated with elevated serum calcium levels, diagnosed as hypercalcaemia. To do this, we obtained ICD-9 diagnosis codes in over 1 million de-identified health records curated as part of the PennOmics resource (Methods), quantifying the odds that a Migraine Headache diagnoses (MHD) co-occurs in the patient record with another ICD-9 diagnosis code (Methods). We observed co-occurrence between MHD ICD-9 codes and ICD-9 codes for Hypercalcaemia ($OR = 1.58$, $P = 4.75 \times 10^{-13}$, [Supplementary Material, Table S2](#)), including adjustments for age, sex, and ancestry. These data are consistent with the hypothesis that migraine and elevated serum calcium levels (diagnosed as hypercalcaemia) occur together frequently in the electronic registry of our patient cohort.

A migraine headache may have additional contributing factors or co-diagnoses that might occur, potentially confounding our initial analysis. Consequently, we looked for additional diagnoses that frequently occurred along with migraine headache in our patient records. We found that MHD was co-diagnosed with hypothyroid, hypertension, and hyperlipidemia ($OR = 1.44$, 1.48 , and 1.80 , each $P < 10^{-50}$, [Table 1](#)), as well as hyperparathyroid ($OR = 0.75$, $P = 1.25 \times 10^{-3}$, [Table 1](#)). After including all of these additional factors into the previous model, we again observed co-occurrence for MHD with a diagnosis of hypercalcaemia ($OR = 1.23$, $P = 1.75 \times 10^{-3}$, [Table 1](#)). These data are consistent with the hypothesis that migraine headache and elevated serum calcium levels are frequently diagnosed together, independently of other important diagnoses that also occur with migraine.

Evidence of a common genetic basis between serum calcium levels and migraine headache

If serum calcium has a genetic link to migraine headache, genetic risk factors should be shared in common across the entire genome, and therefore, both traits would share genetic

Table 1. Phenotypic co-occurrence between migraine headache, demographics, hypercalcaemia, and other risk factors. Adjusted odds ratio (OR) and estimates from logistic regression, including Age, Sex, hypertension, hyperlipidemia, hypothyroidism, hyperparathyroidism, and hypercalcaemia

Variables	Overall n=1038457	with MHD n=29607	Without MHD n=1008850	Adjusted OR of MHD (95% CI)	P-value
Age (overall) ^a				0.85 (0.84–0.86)	<0.001
Mean (SD)	48.7 (21.7) % ^b	45.9 (15.5) % ^c	48.7 (21.9) % ^c		
Sex					
Male	439862 (42.4%)	5272 (1.2%)	434590 (98.8%)	1.00	
Female	598595 (57.6%)	24335 (4.1%)	574260 (95.9%)	3.69 (3.58, 3.80)	<0.001
Race					
Black	314045 (30.2%)	7850 (2.5%)	306195 (97.5%)	1.00	
White	724412 (69.8%)	21757 (3.0%)	702655 (97%)	1.38 (1.34, 1.42)	<0.001
Diagnosis, Yes					
Hyperlipidemia	203393 (19.6%)	7812 (3.8%)	195581 (96.2%)	1.80 (1.74, 1.87)	<0.001
Hypertension	234285 (22.6%)	8042 (3.4%)	226243 (96.5%)	1.48 (1.43, 1.54)	<0.001
Hypothyroid	57846 (5.6%)	2976 (5.1%)	54870 (94.8%)	1.44 (1.38, 1.50)	<0.001
Hyperparathyroid	5190 (0.5%)	148 (2.9%)	5042 (97.1%)	0.75 (0.64–0.90)	1.25×10^{-3}
Hypercalcaemia	6306 (0.6%)	270 (4.3%)	6036 (95.7%)	1.23 (1.08–1.40)	1.75×10^{-3}

^aReference is for computation of OR per 10-year increase in age.

^bProportions are within the columns.

^cproportions are across rows.

heritability. To test this hypothesis, we obtained genome-wide association data for both serum calcium levels and migraine headache (5,19), and estimated genetic correlation between both traits (all subjects, Methods). In this analysis, we observed a moderate genetic correlation between migraine and calcium levels ($r_g = 0.19$, 95% CI: 0.02–0.36, $P = 0.03$), rejecting the hypothesis that these traits are independent of one another, and evidence that serum calcium levels and migraine headache may have a genetic basis in common.

Genetically elevated serum calcium levels are associated with migraine headache

We next turned to directly test the hypothesis that elevated serum calcium levels cause increased susceptibility to migraine headache, using a two-sample Mendelian Randomization study design. We constructed a risk score using all eight genetic factors associated with serum calcium levels (Fig. 1, Supplementary Material, Table S3, Methods). This genetic instrument explained 1.25% of the variability in serum calcium levels, and was sufficient strength to minimize effects from weak instrument bias for our analysis of migraine headache ($F\text{-statistic} = 118.9$). Based on 23,285 migraineurs and 95,425 controls (5), we found that elevation of serum calcium levels by a hypothetical 1 mg/dl resulting from our genetic score was associated with an increase in risk of migraine ($OR = 1.80$, 95% CI: 1.31–2.46, $P = 2.5 \times 10^{-4}$, Table 2). Furthermore, when stratified by aura status, we found that elevation of serum calcium levels by a hypothetical 1 mg/dl resulting from our genetic score was associated with an increase in risk of migraine with ($OR = 2.66$, 95% CI: 1.41–5.02, $P = 2.6 \times 10^{-3}$, Table 2) or without aura ($OR = 2.57$, 95% CI: 1.49–4.43, $P = 6.6 \times 10^{-4}$, Table 2).

Next, we identified four genetic risk factors exclusively associated with serum calcium levels and their effects (Supplementary Material, Table S3, Methods). This genetic instrument explains 0.87% of the variability in serum calcium levels and has sufficient strength to minimize effects from weak instrument bias for our analysis of migraine headache

($F\text{-statistic} = 82.5$). We estimated the causal effect of genetic elevation of serum calcium levels with migraine headache, using a genotype risk score method (Methods). We found that elevation of serum calcium levels by a hypothetical 1 mg/dl resulting from this exclusive genetic score was associated with an increase in risk of migraine ($OR = 1.81$, 95% CI: 1.24–2.63, $P = 2 \times 10^{-3}$, Table 2). Furthermore, when stratified by aura status, we found that elevation of serum calcium levels by a hypothetical 1 mg/dl resulting from our genetic score was associated with an increase in risk of migraine with ($OR = 2.72$, 95% CI: 1.27–5.81, $P = 9.8 \times 10^{-3}$), or without aura ($OR = 2.84$, 95% CI: 1.50–5.40, $P = 1.4 \times 10^{-3}$, Table 2). As the confidence intervals for these aura-stratified analyses included the causal effect estimate based on the entirety of the data, we conclude that the estimates stratified by aura status are not statistically different from the unstratified analysis.

Sensitivity analysis for the serum calcium genetic instruments using alternative causal inference methods

We next evaluated the robustness of our primary observation by applying a suite of sensitivity analyses. First, an unweighted risk score based on all serum-calcium variants was associated with an increased risk of migraine in all samples ($P = 2.9 \times 10^{-3}$, Table 2) or stratified by aura ($P = 0.011$ with aura, $P = 0.037$ without aura, Table 2), suggesting that our result is robust to the choice of weights used in our risk score. We next obtained a weighted-median estimate for the causal effect using all variants, an approach that generates a causal estimate analogous to the risk score method used above. This approach is unbiased asymptotically but only requires 50% or more of the weight for the score to derive from valid instruments, a less stringent requirement compared to the GRS score method (40). The weighted-median estimated for 1 mg/dl genetic elevation of serum calcium on migraine risk agreed with estimates from the analysis above which included all samples ($OR = 1.92$, 95% CI: 1.30–2.84, $P = 1.6 \times 10^{-3}$, Table 2), or analysis that stratified either with aura ($OR = 2.73$, 95% CI: 1.29–5.97, $P = 9.6 \times 10^{-3}$, Table 2) or

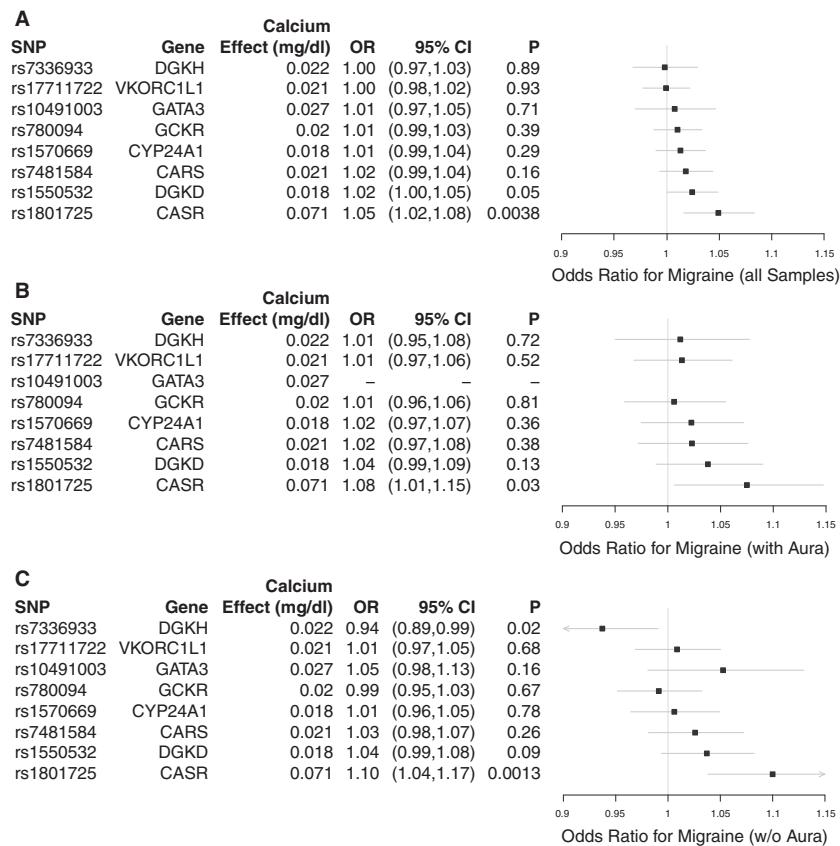


Figure 1. Summary SNP association data for each serum calcium variant for migraine. The effect size of the effect on serum calcium is given in units of mg/dl. (A) All samples. (B) Subset of migraine patients with aura. (C) Subset of migraine patients without aura. OR, Odds Ratio; CI, Confidence Interval.

Table 2. Summary statistics for genetic instruments used for causal inference analysis for serum calcium for migraine traits

	All Samples		With Aura		Without Aura	
	Odds Ratio ^a (95% CI)	P	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Analyses using All Variants (n=8)						
Cumulative GRS ^b	1.80 (1.31–2.46)	2.5×10^{-4}	2.66 (1.41–5.02)	2.6×10^{-3}	2.57 (1.49–4.43)	6.6×10^{-4}
Unweighted GRS ^b	1.66 (1.19–2.31)	2.9×10^{-3}	2.43 (1.22–4.82)	0.011	1.87 (1.04–3.38)	0.037
Weighted-median GRS ^c	1.92 (1.30–2.84)	1.6×10^{-3}	2.73 (1.29–5.79)	9.6×10^{-3}	3.60 (1.81–6.85)	$<2.0 \times 10^{-4}$
Egger Regression (Causal Effect) ^c	1.97 (1.05–3.69)	0.037	2.70 (0.78–8.75)	0.11	5.42 (1.73–16.19)	2.2×10^{-3}
Egger Regression (Bias Term) ^d	-0.003 (-0.025–0.019)	0.74	-0.0007 (-0.048–0.046)	0.97	-0.026 (-0.065–0.013)	0.16
SIMEX MR-Egger (Causal Effect) ^d	2.01 (1.05–3.80)	0.037	2.85 (1.32–6.17)	0.021	5.80 (0.91–37.0)	0.066
SIMEX I^2 (weighted)	0.933		0.943		0.938	
Analyses using Serum Calcium Exclusive variants (n=4)						
Cumulative GRS ^b	1.81 (1.24–2.63)	2.0×10^{-3}	2.72 (1.27–5.81)	9.8×10^{-3}	2.84 (1.50–5.40)	1.4×10^{-3}
Unweighted GRS ^b	1.61 (1.06–2.45)	0.025	2.45 (1.06–5.64)	0.036	1.86 (0.88–3.93)	0.10

^aOdds ratios are given in units of fold increase in migraine risk per unit increase in serum calcium (1 mg/dl).

^bP-value and 95% CI from the normal distribution.

^cP-value and 95% CI calculated by bootstrapping (n = 10,000).

^dP-value and 95% CI calculated from the Student's t distribution.

without aura (OR = 3.60, 95% CI: 1.81–6.85, $P < 2 \times 10^{-4}$, Table 2). To evaluate the potential for systematic bias in our data, we applied Egger regression to estimate bias and a causal effect in the context of bias (25). However, we did not observe evidence of bias ($P > 0.15$ for all instruments, Table 2), and found a modest association for the score that included all migraine-affected subjects ($P = 0.037$, Table 2). To further evaluate the potential of bias and violation of the no measurement error (NOME)

assumption, we applied the recently reported SIMEX approach (41). We found that each of our scores had a high I^2 (Table 2) indicative of a robust genetic instrument, and our estimated causal effects were similar to that obtained by Egger Regression, with modest association for scores using all migraine-affected or those with aura ($P < 0.05$, Table 2). Finally, we excluded our strongest variant from our constructed instrument (rs1801725, CASR). We observed modest nominal association using all

migraineurs ([Supplementary Material, Table S4](#)), consistent with an attenuated, residual contribution to migraine across all serum calcium loci. Taken collectively, these analyses suggest that inference is robust to the weights we selected for our genetic instruments, and our inference that genetically elevated serum calcium levels increase susceptibility to migraine headache does not seem to have evidence of clear violations in several specific assumptions made in our Mendelian Randomization analysis.

Discussion

Causal inference is one of the most challenging and important problems in biology and medicine. To achieve impactful translational outcomes efficiently, identification of causal risk factors is crucial. Computational approaches that rapidly facilitate causal hypothesis testing using the approaches we describe here are designed to begin the process of building a compelling, evidence-based case for causality, complementing or perhaps even motivating future experimental activities in models systems and in humans. We present three lines of support for an association between serum calcium levels and susceptibility to migraine headache: (i) comorbidity analysis using electronic health records indicates that diagnoses for migraine and serum calcium (using hypercalcaemia as a proxy) occur in patient records together more than expected, (ii) genetic heritability analysis indicates that serum calcium and susceptibility to migraine headache may have a genetic basis in common, and (iii) a genetic risk score analysis in the Mendelian Randomization framework indicates that a hypothetical 1 mg/dl genetic increase in serum calcium levels is associated with a 1.8-fold increase in risk to migraine headache. Taken collectively, these data support an epidemiological and genetic correlation, and a potentially causal connection between levels of circulating calcium and susceptibility to migraine.

As an alternative to epidemiological data, which in our case was not available, we extracted diagnosis ICD-9 codes from >1M electronic health records as a proxy. This design does have some limitations that should be acknowledged. First, the diagnosis codes of migraine that we obtained may not reflect a true clinical diagnosis of migraine headache obtained from a trained neurologist. Because the data are de-identified, we are not able to go back and 'verify' the diagnoses that are listed, or check specific biomarker measurements in patients (i.e. levels of serum calcium) in a comprehensive way. It may be important in the future to consider systematic, computational diagnosis of migraine headache using known affected subjects within the health record data to train a model to make accurate predictions of which subjects have clinically defined migraine headache. Second, because the collection of diagnoses begins at 2008, we are not able to determine the order of diagnoses. Thus, our analysis here may be susceptible to reverse causality, as is the case with other types of correlational studies, as well as confounding from factors that we did not include in our analysis.

Despite these limitations, there is some indication that our association does match previous epidemiological reports. Features of metabolic syndrome (hypertension, hyperlipidemia), as well as sex and hypothyroid are all positively associated with migraine ([27–30](#)), and our findings match these previous observations. As hyperparathyroidism is a frequent cause of hypercalcaemia, it is somewhat curious why the adjusted co-occurrence is in the opposite direction. At face, this implies that in the context of a patient presenting metabolic syndrome traits and features of headache, hyperparathyroid

is less often diagnosed. Further work would be required to rule out ascertainment against the diagnosis.

We also performed a genetic correlation analysis, to provide additional evidence supporting a relationship between these two traits. We note that this type of correlation evidence is different from, but complementary to, the Health record comorbidity analysis. Genetic correlation not only connects directly to the quantitative trait measured (serum calcium levels), but also directly estimates correlation between traits due to genetics, which should be correlated if a causal hypothesis is true. However, this analysis does not immediately give a direction for the relationship between traits, and still could be subject to confounding due to directional bias from unknown, pleiotropic associations.

Using the framework of Mendelian Randomization, large-scale genetic studies provide one of many pieces of evidence in support of consistent and robust causal relationships between measurable biomarkers and risk of clinical endpoints. However, the Mendelian Randomization analyses we performed here also have limitations that should be acknowledged. First, our analysis requires (i) a potent genetic instrument and effect on serum calcium, (ii) that the serum calcium genetic variants are not associated with one or more unmeasured confounding variables which also increase risk of migraine, and (iii) that the effect of change in migraine through our selected genetic instruments are mediated entirely through serum calcium levels. We assessed several of these assumptions in turn. While our genetic instrument explained ~1% of the variability in serum calcium levels, this was a sufficiently strong to minimize weak residual bias, assessed by F-statistic. While we cannot completely rule out additional confounding, we did examine the association of our SNP panel against a number of cardiometabolic traits, identifying a subset that was free of metabolic associations. We also generated causal effect estimates using both unweighted and weighted-median risk scores, and our results were consistent with the full genotype risk score approaches and suggest our inference is robust to potentially invalid instrument contributing to our score. Furthermore, we utilized Egger's regression and the SIMEX approach to evaluate systemic bias from our genetic instruments, and did not reject the null hypothesis of no bias. However, our negative results here do not completely rule out all forms of potential biases. While the MR analysis of the sub-strata estimated a higher causal effect than the entire population ([Table 2](#)), this could be reasonably explained by the fact that the 'all sample' migraine meta-analysis data includes studies that were not present in either of the aura stratified analyses.

Calcium channel blockers (CCBs) are often used as a migraine prophylactic, thus possibly implicating Ca^{2+} into the aetiology of migraine. However, the mechanism of action of these drugs is thought to target the vascular aetiology of migraine, e.g. lower cerebral vasoconstriction by reducing Ca^{2+} cellular influx ([31,32](#)). A recent meta-analysis of clinical trials data from a range of CCBs found no difference in reduction of migraine headaches relative to placebo ([33](#)), though clearly more data on specific drugs are required. Furthermore, CCBs may not ultimately impact levels of serum calcium, except in extreme cases, as changes in serum calcium levels are probably compensated by changes in levels of parathyroid hormone to maintain homeostasis. One possibility is that certain CCBs may act to raise parathyroid hormone by lowering serum calcium through hypercalciuria ([34](#)), which would be a possible, additional mechanism of action for some of these drugs that is consistent with our findings. Overall, our results suggest that direct targeting of

Ca^{2+} levels – in addition to the known vasodilatory effect of CCBs – may offer additional therapeutic benefits.

One of the variants we studied was rs1801725, a coding missense mutation (Ala986Ser) in the calcium sensing receptor gene, CASR. Indeed, the observed association at this genetic variant contributes heavily in our Mendelian Randomization result, in addition to the aggregated contribution of weaker serum calcium association in our risk score analysis. CASR is expressed in the parathyroid gland and kidney where it detects changes in circulating calcium levels and relays this information back to intracellular signalling pathways to regulate calcium homeostasis via secretion or absorption (35). Rare mutations in CASR can cause Mendelian forms of either hypercalcaemia (if loss of function) or hypocalcaemia (activating mutations). Here, the alanine residue at this site is a conserved amino acid (back to the model fish, Stickleback); carriage of the serine allele is associated with elevated serum calcium levels, consistent with a hypomorphic function CASR with carriage of serine at this position. Given the evidence from Mendelian disease studies, evolutionary constraint at this site, and that this presumed hypomorphic allele is coding, a strong hypothesis is that this variant is indeed causal, though functional assays are necessary to demonstrate the effect of this variant formally.

Because the serine allele is also associated with increased susceptibility to migraine headache ($P = 3.8 \times 10^{-3}$), one hypothesis is that modest pharmacological CASR agonism would both lower serum calcium and protect against migraine headache. Cinacalcet, an FDA approved agonist of CASR marketed as Sensipar, is approved in treatment for the limited indications of secondary hyperparathyroidism or hypercalcaemia in patients with parathyroid carcinoma. While the drug has a narrow applicability owing to the potential risk of hypocalcaemia, along with additional adverse side effects (nausea, muscle or chest pain, and osteoporosis), it still may be worthwhile to explore the repurposing potential of this compound for treatment of migraine headache in specific instances.

Our comorbidity analysis, while providing some correlation between hypercalcaemia and migraine, suggest the potential clinical impact. While patients with hypercalcaemia are potentially rare diagnoses overall (0.6% in our cohort), 1% of migraine subjects were also diagnosed with hypercalcaemia. If we assumed that elevated calcium levels were causal for migraine susceptibility, the implication is that this small population of migraineurs (~1%) could be managed by returning their serum levels to homeostatic levels. There could also remain a larger population of subjects who have undiagnosed hypercalcaemia, or even levels of serum calcium that are higher than the population average but who are otherwise sub-clinical, who could be tested (and potentially treated) in a similar manner. An important consideration here is if the amount of change in serum calcium we note is actually obtainable to achieve a clinical benefit. We demonstrate that genetic elevation of serum calcium by 1 mg/dl increase was associated with increased odds of migraine headache by 1.8-fold. One study has shown that >85% of patients taking Sensipar had their serum calcium levels decreased by >1 mg/dl (36); a second study demonstrated a median difference of ~1 mg/dl for treated versus placebo controls (37). These clinical trials indicate that the level of change in serum calcium associated with migraine risk is, in fact, clinically obtainable.

In summary, we provide evidence supporting the correlation in diagnoses of serum calcium levels (quantified as hypercalcaemia) and migraine headache, independent of additional, potentially confounding risk factors. In addition, we provide

evidence for shared narrow-sense genetic heritability, using large-scale data from human populations studied separately for serum calcium levels and migraine headache. Finally, we found that genetic variants exclusively associated with circulating calcium levels are associated with migraine headache, providing evidence of a causal relationship between elevated serum calcium levels over a lifetime and migraine headache.

Materials and Methods

Description of the PennOmics resource

PennOmics is a data warehouse that integrates research and clinical data from several separate data storage resources from area hospitals affiliated with the University of Pennsylvania Health System (UPHS). This includes records stored at the Penn Data Store (PDS), the Cancer Center tumour registry, the Velos Clinical Trial Management System, and genomics data from contributing clinical and research labs throughout UPHS. Records and clinical data contained in PennOmics are continually updated (>3 million potential patient records are contained there as of this writing) and are completely de-identified, meaning all direct patient identifiers have been removed, including adjustment of patient age information to further obfuscate the identification of individual subjects. Details for the prevalence of each ICD-9 diagnosis codes and demographic data used in this study are provided in Table 1.

Comorbidity analysis for ICD-9 codes using the PennOmics resource

ICD-9 diagnoses and demographic patient information from the PennOmics resource, comprising 1,098,023 subjects with records collected after 2008, was queried on November 6th, 2015. Initially, we obtained all diagnoses for subjects where sex and age (in years) was present, in non-hispanic and White ($n=724,412$) and Black ($n=314,045$) reported ethnicities. Hispanic white samples were excluded here, owing to the small number of reported MHD diagnoses given the total number of samples present in this extracted collection. For each individual, binary variables for each phenotype group were constructed, which included (i) migraine headache, (ii) hypercalcaemia, (iii) hypertension, (iv) hyperlipidaemia, (v) hypothyroid, and (vi) hyperparathyroid, based on available ICD-9 codes in the resources (Supplementary Material, Table S1). A subject was labelled '1' for the given variable if any of these assigned ICD-9 codes were present in the record, otherwise '0'. We used logistic regression (implemented in R (3.13), using `glm()`, binomial link function) to report the odds of co-occurrence of the migraine headache ICD-9 status diagnosis code with ICD-9 code variables for hypercalcaemia, including hypertension, hypothyroid, hyperparathyroid or hyperlipidaemia, age, and sex as additional covariates. These factors were selected given previous reports of correlation with migraine (27–30). Results are presented for the analysis that included ancestry as an additional covariate in the model, which were qualitatively similar when each ethnicity was analyzed individually (Supplementary Material, Table S2).

Heritability analysis for migraine headache and serum calcium levels

We used the bivariate heritability estimation method implemented in LDSC (v1.0.0) to estimate the genetic correlation

between migraine and serum calcium levels. The details of the method are described elsewhere (18). Briefly, assuming a polygenic model, the genetic correlation between two traits can be estimated using the summary association statistics (i.e. p-values converted to Z-scores via inverse-normal transformation) for both traits and for all tested genetic variants included in a genome-wide association panel, and the ‘LD score’, which measures the amount of genetic variation tagged (i.e. in linkage disequilibrium) by the SNP (38). Under some assumptions, the slope of the regression of the product of the association Z-scores on the LD score can be used to estimate the genetic correlation between the two traits. Precise details of the method, its efficiency, and accuracy are described elsewhere (38). For this analysis, we utilized common variants that were present in the Hapmap3 reference (20), which were also genotyped across most of the sample: specifically, the number of analyzed samples not less than two-thirds of the 90th percentile of the total in each meta-analysis. We obtained summary GWAS data for serum calcium levels from a recent report (19), which involve an inverse-variance fixed-effects Hapmap reference panel-based imputation meta-analysis of 17 population-based cohorts of European descent, all measured for circulating serum calcium levels. For migraine headache, we utilized association data from a recent report, based on an inverse-variance fixed-effects Hapmap reference panel-based imputation meta-analysis including 29 cohorts of European ancestry (5). In brief, contributing cohorts derived mostly from northern European (Finland, Germany, Netherlands, UK, Iceland, Sweden, Norway, Estonia, etc.), with cases/controls were matched within each study. Stratification was further controlled by inclusion of principal components for genetic similarity as covariates in the association analysis by each study. From these data, all subjects diagnosed with migraine headache included 23,285 individuals with migraine (cases defined from both population and clinically defined cohorts) and 95,425 population-matched controls.

Construction of genetic instruments for Mendelian randomization analysis

We used our previous reported tool, MeRP, to perform instrument construction and testing (21). Briefly, the National Human Genome Research Institute (NHGRI) maintains a compilation of data from GWAS publications (22), and was used as our starting point. All ($n=8$ total) serum calcium single nucleotide polymorphic (SNP) associations that were genome-wide significant ($P < 5 \times 10^{-8}$) were obtained. These SNPs then went through filtering steps for LD and confounding trait associations. First, associations with potential confounding traits were assayed from within the NHGRI GWAS catalog and a summary file containing association p-values for >2 million SNPs and 15 cardio/metabolic traits (these included blood pressure, cholesterol, anthropometric and obesity, glucose/insulin, along with type 2 diabetes and coronary heart disease) obtained from the public domain, and violating SNPs were removed. The remaining SNPs were grouped together based on pairwise LD ($r^2 > 0.05$) and the SNPs with the lowest trait associated p-value value from each LD group were selected to comprise the serum calcium genetic variants for MR analysis. This resulted in four ($n=4$: rs7336933, rs1801725, rs10491003, rs1570669) SNPs exclusively associated with serum calcium levels that comprised our final, serum calcium instrument for MR testing. The list of exclusive and non-exclusive serum calcium ($n=4$: rs780094, rs17711722, rs7481584, and rs1550532) associated SNPs along with annotations for

nearest genes are provided (Supplementary Material, Table S3). Phenotypic associations for non-exclusive variants includes the following: rs780094 has multiple established trait associations ($P < 5 \times 10^{-8}$) with triglycerides, total cholesterol, Height, fasting glucose; rs17711722 was nominally associated ($P < 0.05$) with triglycerides, body mass index (BMI), 2-hour glucose, fasting insulin, and HOMA-IR; rs7481584 was nominally associated with high-density lipoprotein cholesterol, BMI, and type 2 diabetes; rs1550532 was nominally associated with fasting insulin, HOMA-IR, and coronary heart disease.

Causal inference analysis between serum calcium levels and migraine headache

We utilized a statistical method for estimating causal effects based on multi-SNP genetic instruments using summary data alone, using a two-sample Mendelian Randomization (MR) design based on summary statistics. In the two-stage design, association data from both the intermediate trait (in this case, serum calcium levels) and the endpoint (migraine headache) are obtained from two separate genome-wide studies. This study design is a valid approach to infer causal effects (23). Briefly, if genetic variants (SNPs) are unlinked, and further if the effects of each SNP on levels of serum calcium levels are log-additive, a causal effect (alpha-hat) and the error between a biomarker and outcome can be estimated by (24):

$$\hat{\alpha} = \frac{\sum_j w_j \hat{\beta}_j \sigma_j^{-2}}{\sum_j w_j^2 \sigma_j^{-2}} \quad (1)$$

$$SE(\hat{\alpha}) = \sqrt{\frac{1}{\sum_j w_j^2 \sigma_j^{-2}}} \quad (2)$$

where for all j SNPs, $\hat{\beta}_j$ represents the estimated natural log odds effect of the j -th SNP on the endpoint of interest, σ_j represents the standard error on the log odds effect of the j -th SNP on the endpoint, and w_j represents a weight for the SNP on the outcome. Each SNP was weighted using the reported estimated effect of the SNP on serum calcium levels (in units of mg/dl). The significance of the estimate was assessed via the ratio of the above quantities (i.e. alpha-hat/SE(alpha-hat)), which is chi-squared distributed with 1 degree of freedom. Effects of each variant used in our genetic risk score on migraine headache were obtained from the genome-wide association data set from the International Migraine Headache Genetics Consortium (5), the same used in the heritability analysis described above, and we also included additional stratified analyses with (5,118 cases, 74,239 controls) and without (7,107 cases and 69,427 controls) aura. Our two-stage design assumed that samples are non-overlapping between the endpoint (Migraine Headache Genetics consortium) and the intermediate trait (the Serum Calcium). Only one study (TwinsUK) was common to both, and only contributed to replication for serum calcium associated variants, thus, we used estimates from the primary scan which did not include this study.

We conducted additional sensitivity analysis to examine potential bias in our instruments and robustness of our analyses. This includes (i) Egger regression using all eight associated serum calcium variants to evaluate systematic bias (25), and (ii)

the recently reported SIMEX method designed evaluate the ‘no measurement error’ assumption (41). We also computed a causal estimate using an unweighted genotype scores (i.e. weights set to one for all variants). As for the weighted scores, the migraine log-odds was polarized to the serum calcium-increasing allele. In addition, we performed a weighted-median method, which can also assess a causal effect (unbiased asymptotically as sample size increases) and only requires at least 50% of the weight for the score to derive from valid instruments (40). Weighted median estimation was carried out using the sample code previously made available (40). Standard error and 95% CI were estimated by bootstrapping for the median-weighted and Egger regression approaches. To measure the strength of the genetic instruments, we calculated F-statistics for each score as previously described (26), based on the total symmetric sample size of the asymmetric migraine study design ($N = 2 * (n_{\text{aff}} * m_{\text{controls}}) / (n_{\text{aff}} + m_{\text{controls}})$).

Supplementary Material

Supplementary Material is available at HMG online.

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Conflict of Interest statement. None declared.

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Investigation of distinct molecular pathways in migraine induction using calcitonin gene-related peptide and sildenafil

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Abstract

Objective: Migraine displays clinical heterogeneity of attack features and attack triggers. The question is whether this heterogeneity is explained by distinct intracellular signaling pathways leading to attacks with distinct clinical features. One well-known migraine-inducing pathway is mediated by cyclic adenosine monophosphate and another by cyclic guanosine monophosphate. Calcitonin gene-related peptide triggers migraine via the cyclic adenosine monophosphate pathway and sildenafil via the cyclic guanosine monophosphate pathway. To date, no studies have examined whether migraine induction mediated via the cyclic adenosine monophosphate and cyclic guanosine monophosphate pathways yields similar attacks within the same patients.

Methods: Patients were subjected to migraine induction on two separate days using calcitonin gene-related peptide (1.5 µg/min for 20 minutes) and sildenafil (100 mg) in a double-blind, randomized, double-dummy, cross-over design. Data on headache intensity, characteristics and accompanying symptoms were collected until 24 hours after drug administration.

Results: Thirty-four patients were enrolled and 27 completed both study days. Seventeen patients developed migraine after both study drugs (63%; 95% CI: 42–81). Eight patients developed migraine on one day only (seven after sildenafil and one after calcitonin gene-related peptide). Two patients did not develop migraine on either day. Headache laterality, nausea, photophobia and phonophobia were similar between drugs in 77%, 65%, 100%, and 94%, respectively, of the 17 patients who developed attacks on both days.

Conclusion: A majority of patients developed migraine after both calcitonin gene-related peptide and sildenafil. This supports the hypothesis that the cyclic adenosine monophosphate and cyclic guanosine monophosphate intracellular signaling pathways in migraine induction converge in a common cellular determinator, which ultimately triggers the same attacks.

Trial registration: ClinicalTrials.gov Identifier: NCT03143465.

Keywords

CGRP, headache, provocation, cAMP, cGMP, intracellular signaling pathway

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Introduction

Migraine is a complex neurological disease with remarkable clinical heterogeneity of attacks and attack triggers (1–3). A range of pharmacological headache-inducing substances are established and commonly used in human migraine models for the study of migraine attacks and their underlying

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pathophysiological mechanisms (4). These triggers produce migraine attacks by stimulating different cellular signaling pathways (4).

Studies in migraine patients have revealed at least two signaling pathways causing migraine attacks. The first pathway is mediated via cyclic adenosine monophosphate (cAMP), which can be activated by calcitonin gene-related peptide (CGRP) infusion (5). The second pathway is mediated via the cyclic guanosine monophosphate (cGMP) pathway (6). It has been suggested that sildenafil triggers migraine attacks via inhibition of intracellular phosphodiesterase-5 which normally breaks down cGMP (6). This is in contrast to CGRP, which exerts its effects from the extracellular space, binding to its G-protein coupled receptor and resulting in upregulation of cAMP (5).

The question is whether clinical heterogeneity of migraine attacks may be explained by distinct signaling pathways. Another explanation is that a common, and more downstream, determinant of cAMP- and cGMP signaling pathways of migraine ultimately conjoins the two cascades and leads to initiation of the same attacks. In that case, CGRP and sildenafil would be capable of inducing migraine attacks with similar clinical features in the same patients. To date, no studies have explored this facet of the migraine pathophysiology using mediators of two different cellular signaling pathways of attacks in a head-to-head comparison. For this purpose, we administered CGRP and sildenafil in a paired, randomized, double-blinded, double-dummy, two-way cross-over study design.

Methods

Recruitment

We recruited patients with migraine without aura via a Danish recruitment website (www.forsogsperson.dk) and advertisements at hospitals and educational institutions. Patients were eligible for inclusion if they were male or female with a diagnosis of migraine without aura based on the IHS criteria (7), aged 18–50 years, weighed 50–100 kg and experienced migraine attacks at least once every other month. Exclusion criteria included inconsistent headache laterality, chronic migraine, any other primary headache disorder (apart from tension-type headache), daily medication intake (apart from oral contraceptives), being pregnant or breastfeeding females, daily smoking, a history of serious somatic or psychiatric disease, and hypo- or hypertension (systolic blood pressure >150 mmHg or <90 mmHg and/or diastolic blood pressure >90 mmHg or <50 mmHg). This study was part of a larger parent study with specific exclusion

criteria including contraindications for MRI. Patients were enrolled from August 2017 to November 2018.

All patients underwent a medical examination and pregnancy tests were performed for female patients.

All patients provided written informed consent in agreement with the Declaration of Helsinki of 1964 with revisions until 2013.

Approval and data availability

The study was approved by the Ethical Committee of the Capital Region of Denmark (H-15019063) and registered at www.clinicaltrials.gov (NCT03143465). Data from the study can be made available upon reasonable request to the corresponding author. Other parts of the parent study have been and/or will be published elsewhere.

Design and data acquisition

Patients reported to the clinic headache free for at least 48 hours, having fasted for 4 hours; coffee, tea, alcohol, cocoa and tobacco were not allowed for 12 hours prior to study start. All patients were randomly allocated to receive a tablet of 100 mg sildenafil (TEVA pharmaceutical industries Ltd., Petah Tikva, Israel) or CGRP (Tocris Bioscience, Bristol, United Kingdom) as an IV infusion (1.5 µg/min for 20 minutes) on two separate study days. Randomization was balanced between drugs. Double blinding was obtained by administering both tablet and IV infusion on both days, with either tablet or IV formulation containing the active substance.

Patients were instructed about possible side effects of both CGRP and sildenafil on both study days. Before study start, the patients were informed about the possible outcomes of headache on both, one, or none of the study days, independent from each other.

Patients rested in the supine position until 90 minutes after drug administration and were monitored with a purpose-developed headache interview along with blood pressure, heart rate, blood oxygenation and respiratory frequency every 10 minutes. After the monitoring period, patients stayed in the clinic until 8 hours after study start and were discharged thereafter with a headache questionnaire (Figure 1). During this period, an MRI scan was performed from 6 hours to 7 hours (for another part of the parent study). Information obtained in the headache interview and questionnaire included intensity of headache pain using the numerical rating scale (NRS) from 0–10 ('0' denoting no pain and '10' maximum imaginable pain) as well as headache characteristics and associated symptoms (pain location, aggravation by physical activity, nausea/vomiting, sensitivity to light and sound and mimicking usual

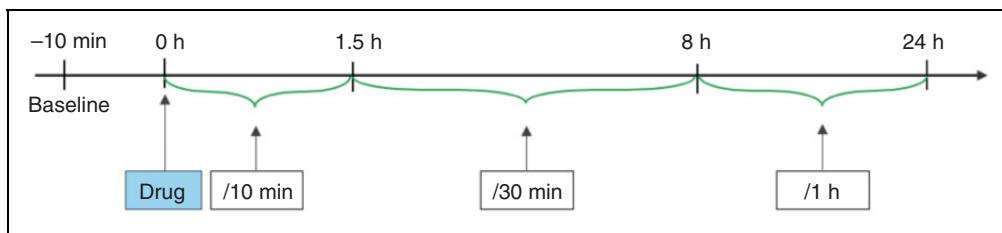


Figure 1. Overview of study design with depiction of headache evaluation intervals. Study design was double-blind, randomized, double-dummy, two-way cross-over. Drug: Calcitonin gene-related peptide and sildenafil.

migraine). The headache interview and questionnaire contained data on the same parameters and were merged upon study completion. Information on habitual migraine triggers was obtained from each patient before study start.

Data analysis

Headache data were evaluated by SY and CEC, who were blinded to study drug randomization. Diagnosis of migraine-like attacks (hereinafter referred to as migraine attacks) was based on the following criteria (8):

Migraine attack fulfilling either (i) or (ii):

- (i) Headache fulfilling criteria C and D for migraine without aura according to the IHS criteria: C. Headache has at least two of the following characteristics: Unilateral location; pulsating quality; moderate or severe pain intensity (≥ 4 on NRS); aggravation by cough (in-hospital phase) or causing avoidance of routine physical activity (out-hospital phase); D. During headache at least one of the following: Nausea and/or vomiting; photophobia and phonophobia.
- (ii) Headache described as mimicking the patient's usual migraine attack and treated with acute migraine medication.

Statistical analyses

Our main outcome parameter was incidence of migraine attacks, reporting the proportion of patients with attacks on both days. We calculated the binomial proportion confidence interval with comparisons to placebo responses in previous human migraine studies (9–11).

Pain intensity (NRS) over time was compared between the CGRP and sildenafil days using the Wilcoxon signed-rank test on the area under the curve using the trapezoidal rule. Area under the curve for pain intensity was calculated until 7 hours, as patients were allowed rescue medication from that

time point. Time to onset of migraine and difference in peak NRS are reported as median with range and compared between the CGRP and sildenafil days using the Wilcoxon signed-rank test. In explorative analysis, binomial proportion confidence interval of patients who reported the same clinical characteristics on both days were calculated using sign test due to sample size. Mean arterial blood pressure is reported as mean with standard error from time 0 to 90 min. Sample size was determined based on other measurements, which were part of the larger parent study.

R (Version 3.5.2) was used to conduct the statistical analyses. P values are reported as two-tailed with a 5% level of significance.

Results

Migraine incidence and intensity

We recruited 34 patients, of whom 27 completed both study days (25 females; mean age 25 years, range 20 to 47) (Figure 2). Median time between the two study days was 14 days.

Seventeen patients developed migraine attacks on both study days (63%; 95% CI: 42–81). Eight patients developed an attack on one day (30%) (seven after sildenafil and one after CGRP) (Figure 2) and finally, two patients did not develop an attack on either day (7%) (Figure 3). Twenty-four of 27 patients (89%) developed an attack after sildenafil and 18 (67%) after CGRP (Figure 3).

Area under the NRS curves for CGRP and sildenafil yielded no difference between drugs ($p=0.348$) (Figure 4). For the 18 attacks after CGRP, median time until onset of attack was 165 min (range 30–540), while median time to onset was 285 min (range 60–480) in the 24 sildenafil-induced attacks ($p=0.057$). Peak NRS was 5 (range 0–8) after CGRP and 7 (range 0–10) after sildenafil, $p=0.004$.

Clinical characteristics and symptoms

The characteristics of headache after CGRP and sildenafil are presented in Table 1. Migraine symptoms

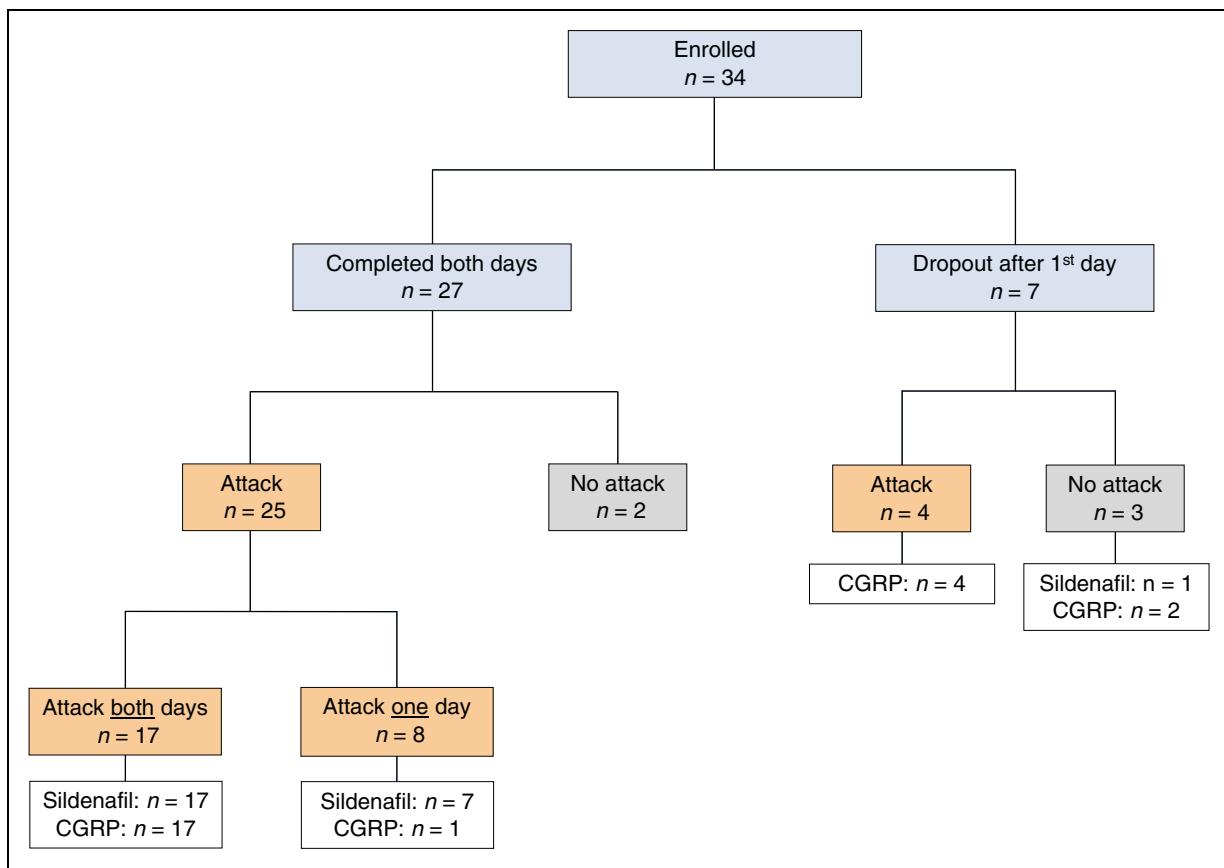


Figure 2. Flowchart of inclusion process and distribution of migraine attacks in each group separated into study drug. Reason for drop-out for those who developed an attack after the first study day: Withdrawal of consent ($n = 1$), study termination ($n = 2$) and exclusion due to daily medication after day 1 unrelated to study ($n = 1$). Reason for drop-out for those who did not develop an attack: Withdrawal of consent ($n = 1$) and lost to follow-up ($n = 2$).

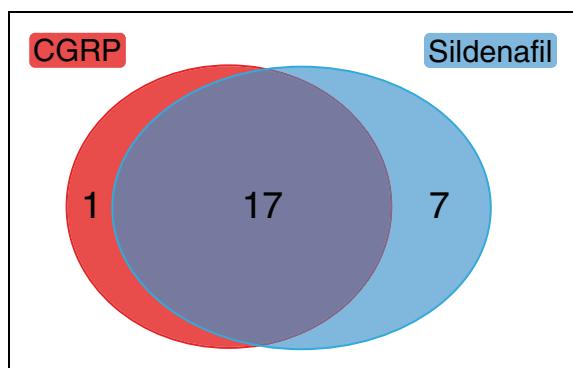


Figure 3. Number of patients who developed migraine attacks after calcitonin gene-related peptide (CGRP) and sildenafil. Overlap represents number of patients who developed attacks on both days. Twenty-five of 27 patients developed migraine attacks on either or both study days.

were compared between drugs for the 17 patients who experienced an attack on both study days and comparability in attack characteristics is reported in Table 2 and depicted in Figure 5.

Mean arterial pressure on each study day is visualized in Figure 6.

Discussion

The major finding of the present study was that the majority of patients experienced a migraine attack after both CGRP and sildenafil with similar clinical features of attacks.

Incidence and clinical characteristics of migraine attacks

We found that 17 patients (63%; 95% CI: 42–80) developed migraine attacks after both CGRP and sildenafil. In comparison, the largest previously reported placebo rate for migraine induction was 16.7% (11). If CGRP and sildenafil attacks were mutually exclusive in patient subgroups; that is, if some patients were only responsive to CGRP and others only to sildenafil, we would expect the overlap to be similar to the previous placebo response. However, 16.7% is far from the boundaries

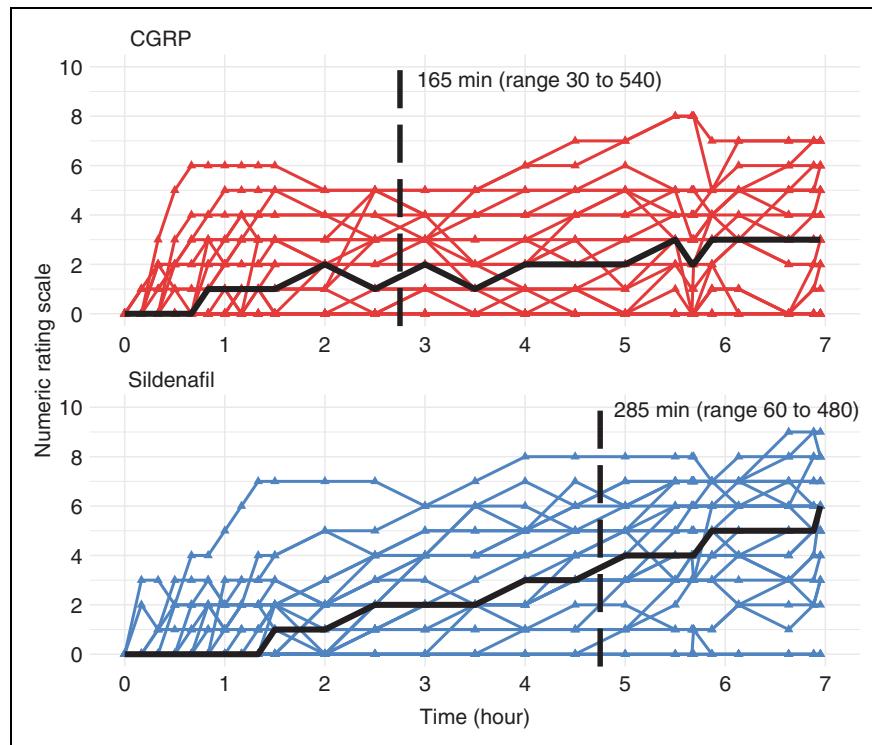


Figure 4. Individual red and blue lines represent headache pain intensity by time after calcitonin gene-related peptide (CGRP) and sildenafil for patients who completed both study days ($n = 27$). Solid horizontal black lines show median pain intensity. Dashed vertical lines with time and range annotation depict median time to onset of migraine.

of our confidence interval. These findings suggest that the two different signaling pathways, activated by CGRP and sildenafil respectively, both cause migraine attack induction in migraine patients in general, challenging the notion of distinct dominant signaling pathways between patients (4).

Migraine attacks are heterogeneous across all clinical characteristics such as location of headache, severity and quality of pain (throbbing and/or pressing) and associated symptoms (photophobia, phonophobia and nausea) (1,12). A majority of patients commonly report that attacks can be triggered by at least one non-pharmacological trigger, such as stress and mental tension, menstruation, alcohol consumption and sleep disturbances (1,13). Diversity of the inter-individual features of migraine attacks and sensitivity to natural migraine triggers are reflected in our study sample as well (Table 1). We showed that characteristics of attacks were alike across the two study drugs (Figure 5). Most of the patients reported that the pharmacologically induced attacks mimicked their usual migraine attacks and were treated by their usual abortive medication (Table 1). Based on these observations, it is highly unlikely that variability of clinical heterogeneity of migraine attacks between patients is elucidated by different signaling pathways.

Cellular mechanisms of CGRP and sildenafil

The effects of infused CGRP are fostered via binding to its receptor, which activates the intracellular signaling pathways including formation of cAMP leading to activation of protein kinase A (5,14). Sildenafil, as a lipophilic drug, directly inhibits intracellular phosphodiesterase-5, and thus cancels the breakdown of cGMP, which in turn activates protein kinase G (6). Altogether, our findings of a large overlap of migraine induction after both CGRP and sildenafil as well as similarity of those attacks within patients support the existence of a more downstream common determinant where the two signaling pathways converge, ultimately leading to initiation of the same migraine attacks (15).

Preclinical studies have demonstrated that sildenafil is capable of inhibiting degradation of cAMP via increased cGMP levels (16). Furthermore, studies in animal coronary and pulmonary arterial tissues have shown that activation of cAMP can also promote the cGMP pathway (17,18). Collectively, this indicates interaction in both directions between the cAMP and cGMP pathways as an alternative explanation to the common outcome of migraine attack after CGRP and sildenafil. Thus, cAMP may drive the key signaling pathway of migraine attacks, noting that other well-established headache-inducers

Table 1. Clinical characteristics of headache and associated symptoms after calcitonin gene-related peptide (CGRP) and sildenafil.

ID	Gender, age	Drug	Time to peak pain	Headache characteristics	Associated symptoms	Mimics usual attacks	Migraine attack (onset)	Treatment (time)/efficacy	Migraine triggers
1	M 25 Y								
	CGRP	6 hours		Bilat (left)/4/T/-	-/-/+	Yes	Probable ^a	NA	Stress
	Sildenafil	NA		NA	NA				
	Spon			Right/NA/T/+	-/+/+				
2	F 23 Y								
	CGRP	1 h		Bilat (left)/5/T/+	+/-/+	Yes	Yes (40 min)	NS	Stress, sleep,
	Sildenafil	7 hours		Bilat (left)/5/T/+	+/-/+	Yes	Yes (5 hours)	S1 50 mg (10 hours)/No; I+P (23 hours)/NA ^b	irregular meals
	Spon			Left/7/T/+	+/-/+				
3	F 28 Y								
	CGRP	NA		No headache	NA	NA	No (NA)	NA	Stress, sleep
	Sildenafil	3 hours		Bilat (left)/5/T/+	-/+/+	Yes	Yes (60 min)	NA	menstruation,
	Spon			Right/9/T/+	+/-/+				alcohol
4	F 22 Y								
	CGRP	40 min		Right/6/T/+	-/+/+	Yes	Yes (40 min)	No treatment	Stress, sleep, alcohol,
	Sildenafil	10 hours		Right/8/T/-	-/+/+	Yes	Yes (8 hours)	I+P (10 hours)/Yes	dehydration, physical
	Spon			Right/7/T/+	+/-/+				activity, light
5	F 24 Y								
	CGRP	10 min		Bilat/1/T/+	-/-/-	No	No (NA)	No treatment	Stress, sleep,
	Sildenafil	7 hours		Bilat (left)/4/T/+	-/+/+	Yes	Yes (7 hours)	P (13 hours)/NS ^c	menstruation,
	Spon			Bilat/8/T/+	+/-/+				physical activity
6	F 29 Y								
	CGRP	NA		No headache	NA	NA	No (NA)	No treatment	Stress, alcohol,
	Sildenafil	8 hours		Right/9/T+P/+	+/-/+	Yes	Yes (4.5 hours)	S1 100 mg (7 hours)/No; NS (8 hours)/ No;	dehydration
	Spon			Right/NA/T/+	+/-/+			NS (9 hours)/Yes	
7	F 27 Y								
	CGRP	7 h		Bilat/2/P/+	-/-/-	No	No (NA)	No treatment	Loud sounds
	Sildenafil	7 h		Right/8/T/+	-/+/+	Yes	Yes (80 min)	NS	
	Spon			Right/NA/T/+	-/+/+				
8	F 21 Y								
	CGRP	80 min		Bilat (left)/4/T+P/+	-/+/+	Yes	Yes (2.5 hours)	No treatment	Stress, sleep,
	Sildenafil	8 hours		Bilat/8/T+P/+	-/+/+	Yes	Yes (6 hours)	2 Kodipar (9 hours)/Yes	menstruation,
	Spon			Left/9/T/+	+/-/+				alcohol, physical
									activity, light
9	F 25 Y								
	CGRP	7 hours		Bilat/7/T/+	+/-/+	Yes	Yes (3 hours)	S1 50 mg (8 hours, 14 hours, 22 hours)/	
	Sildenafil	NA		NA	NA			No, NS ^c , Yes	Stress, sleep
	Spon			Right/8/T/+	+/-/+			NA	
10	M 24 Y								
	CGRP	11 hours		Left/3/T/+	-/-/+	Yes	Probable ^c	I (21 hours)/Yes	
	Sildenafil	6 hours		Left/6/T/+	-/+/+	Yes	Yes (6 hours)	I (6 hours)/NS	Stress, sleep,
	Spon			Left/7/T/+	+/-/+				dehydration

(continued)

Table I. Continued.

ID	Gender, age Drug	Time to peak pain	Headache characteristics	Associated symptoms	Mimics usual attacks	Migraine attack (onset)	Treatment (time)/efficacy	Migraine triggers
I1								
F 25 Y								
CGRP	7 hours	Bilat (right)/5/T+P/+	-/-/+	Yes	Probable ^a	No treatment		
Sildenafil	6 hours	Bilat (left)/7/T/+	-/-/+	Yes	Probable ^a	No treatment		
Spon		Unilat/8/T/+	+/-/+					
I2								
F 23 Y								
CGRP	10 hours	Left/3/T/+	+/-/+	No	Yes (3.5 hours)	No treatment		
Sildenafil	50 min	Bilat (left)/3/P/-	-/+/-	No	No	No treatment		
Spon		Left/10/T/+	+/-/+					
I3								
F 25 Y								
CGRP	7 hours	Bilat (right)/5/T/+	+/-/+	Yes	Yes (6 hours)	2 AC+P (8 hours)/Yes		
Sildenafil	7 hours	Bilat/3/T/+	-/+/-	Yes	Yes (7 hours)	2 AC (8 hours)/Yes		
Spon		Right/7/T/+	+/-/+					
I4								
F 23 Y								
CGRP	70 min	Bilat/4/T/+	+/-/+	Yes	Yes (70 min)	No treatment		
Sildenafil	10 hours	Bilat/7/T/+	+/-/+	Yes	Yes (2.5 hours)	I (11 hours)/No		
Spon		Bilat/8/T/+	+/-/+					
I5								
F 22 Y								
CGRP	1 hours	Bilat (left)/3/P/-	-/-/-	No	No	No treatment		
Sildenafil	NA	NA	NA	NA	NA	NA		
Spon		Left/8/T/+	-/+/-					
I6								
F 20 Y								
CGRP	7 hours	Bilat (right)/6/T/+	+/-/+	Yes	Yes (4.5 hours)	I+P (8 hours)/Yes; 2AC (12 hours)/Yes		
Sildenafil	4.5 hours	Bilat (right)/7/T/+	+/-/+	Yes	Yes (2.5 hours)	Diclodan+O (7 hours)/Yes		
Spon		Right/9/T/+	+/-/+					
I7								
M 25 Y								
CGRP	6 hours	Bilat (right)/7/T+P/+	+/-/+	Yes	Yes (70 min)	S2+O (6 hours)/Yes		
Sildenafil	NA	NA	NA	NA	NA	NA		
Spon		Left/7/T/+	+/-/+					
I8								
F 24 Y								
CGRP	4.5 hours	Bilat/4/T+P+	-/+/-	No	Yes (6 hours)	2 AC (7 hours)/Yes		
Sildenafil	8 hours	Left/7/T/+	-/+/-	Yes	Yes (5.5 hours)	I+P (7 hours)/No; I (8 hours)/Yes		
Spon		Bilat/9/T/+	+/-/+					
I9								
F 30 Y								
CGRP	5.5 hours	Left/8/T/+	+/-/+	Yes	Yes (3 hours)	2 AC+O (7 hours)/No;		
Sildenafil	6 hours	Left/2/P/+	-/+/-	Yes	Yes (6 hours)	I+P (9 hours) /No;		
Spon		Left/10/T/+	+/-/+			2 AC (12 hours)/Yes; AC (23 hours) /No		
						1.5 AC (9 hours)/Yes		
I20								
F 23 Y								
CGRP	NA	NA	NA	NA	NA	NA		
Sildenafil	5.5 hours	Bilat (left)/4/P/-	-/-/-	Yes	No	NA		
Spon		Bilat/7/T/+	-/+/-					

(continued)

Table 1. Continued.

ID	Gender, age	Time to peak pain	Headache characteristics	Associated symptoms	Mimics usual attacks	Migraine attack (onset)	Treatment (time)/efficacy	Migraine triggers
21								
F 23 Y								
CGRP	7 hours	Bilat (left)/7/T/+	+/-/+	Yes	Yes (30 min)	S1 50 mg (7 hours,		
Sildenafil	7 hours	Bilat/9/T/+	+/-/+	Yes	Yes (5 hours)	9 hours)/No, Yes		
Spon		Left/9/T/+	+/-/+			S2 (7 hours)/Yes	Stress, menstruation, odors	
22								
F 27 Y								
CGRP	6 hours	Left/4/P/+	-+/-	Yes	Probable ^a	No treatment		
Sildenafil	7 hours	Bilat (left)/10/P/+	+/-/+	Yes	Yes (5.5 h)	O+Diclodan (8 h)/Yes	Stress, light, menstruation, odors, hunger, anticipation	
Spon		Left/10/T/+	+/-/+					
23								
F 20 Y								
CGRP	5.5 hours	Bilat/8/T/+	+/-/+	Yes	Yes (2.5 hours)	S1 25 mg (7 hours,		
Sildenafil	5 hours	Bilat/7/P/+	+/-/+	Yes	Yes (4.5 hours)	10 hours)/No, Yes		
Spon		Bilat/8/T/+	+/-/+			S1 25 mg (7 hours)/Yes	Stress, sleep, alcohol	
24								
F 22 Y								
CGRP	50 min	Bilat/I/P/+	-+/-	No	No	No treatment		
Sildenafil	NA	No headache	NA	NA	NA	NA	Stress, sleep, alcohol, heat	
Spon		Bilat/7/T/+	+/-/+					
25								
F 20 Y								
CGRP	5 hours	Bilat/6/T/+	-+/-	Yes	Yes (5.5 hours)	AC (7 hours)/Yes		
Sildenafil	4 hours	Bilat/8/T+P/+	+/-/+	Yes	Yes (3 hours)	AC+O (7 hours)/Yes	Menstruation, sleep, dehydration, acute changes in temperature	
Spon		Bilat/9/T/+	+/-/+					
26								
F 28 Y								
CGRP	6 hours	Bilat (left)/5/T/+	+/-/+	Yes	Yes (5.5 hours)	AC (8 hours)/NS ^c ;		
Sildenafil	6.5 hours	Left/9/T+P/+	+/-/+	Yes	Yes (2.5 hours)	2 AC (17 hours)/Yes		
Spon		Left/9/T/+	+/-/+			S2+O (7 hours)/Yes	Stress, sleep, menstruation, alcohol, light, anticipation	
27								
F 30 Y								
CGRP	7 hours	Left/4/P/+	-+/-	Yes	Yes (5 hours)	AC (8 hours)/No		
Sildenafil	NA	NA	NA	NA	NA	NA	Stress, menstruation	
Spon		Right/7/T/+	+/-/+					
28								
F 47 Y								
CGRP	6.5 hours	Left/6/T/+	-+/-	Yes	Yes (3 hours)	S1 50 mg (7 hours,		
Sildenafil	6.5 hours	Left/8/T/+	-+/-	Yes	Yes (3 hours)	10 hours) /No, NS ^c		
Spon		Left/7/T/-	-+/-			No treatment	Stress, sleep, alcohol, light	
29								
F 33 Y								
CGRP	6 hours	Bilat/10/T+P/+	-+/-	Yes	Yes (3.5 hours)	S2 (7 hours)/Yes		
Sildenafil	NA	NA	NA	NA	NA	NA	Stress, sleep, odour	
Spon		Bilat+Unilat ^d /10/T/+	-+/-					
30								
F 25 Y								
CGRP	8 hours	Left/5/T/+	-+/-	Yes	Yes (5.5 hours)	No treatment		
Sildenafil	6 hours	Left/4/T/+	-+/-	Yes	Yes (6 hours)	No treatment	Stress, sleep	
Spon		Left/9/T/-	-+/-					

(continued)

Table 1. Continued.

ID	Gender, age Drug	Time to peak pain	Headache characteristics	Associated symptoms	Mimics usual attacks	Migraine attack (onset)	Treatment (time)/efficacy	Migraine triggers
31								
F 25 Y	CGRP	7 hours	Bilat/6/T/+	-/+/-	Yes	Yes (50 min)	I+P (7 hours)/NA; P (8 hours) /Yes	
	Sildenafil	4 hours	Bilat/6/T/+	+/-/+	Yes	Yes (3 hours)	I+P (7 hours)/NA; AC (10 hours)/No	Stress, sleep, menstruation
	Spon		Right/8/T/+	+/-/+				
32								
M 26 Y	CGRP	9 hours	Left/5/P/-	+/-/+	No	Yes (9 hours)	No treatment	
	Sildenafil	9 hours	Bilat (left)/8/P/+	+/-/+	Yes	Yes (3 hours)	SI 50 mg (7 hours)/No	Stress, concentration
	Spon		Bilat (left)/7/T/+	+/-/+				
33								
F 23 Y	CGRP	NA	No headache	NA	NA	NA	NA	Stress, sleep
	Sildenafil	8 hours	Bilat (unilat ^e)/4/P/+	-/+/-	Yes	Yes (6 hours)	No treatment	
	Spon		Bilat (left)/7/T/+	-/+/-				
34								
F 24 Y	CGRP	7 hours	Bilat (right)/6/T+P/+	-/+/-	Yes	Yes (50 min)	SI 50 mg+I (7 hours) /Yes	
	Sildenafil	6 hours	Bilat (right)/5/T/+	+/-/+	Yes	Yes (4 hours)	SI 50 mg+I (8 hours) /Yes	Menstruation, alcohol, chocolate, physical activity
	Spon		Right/9/T/+	+/-/+				

The criteria for a migraine attack are described in 'Methods'. Treatment efficacy: 50% decrease of headache intensity within 2 hours. Headache characteristics: Localization/intensity/quality/aggravation. Associated symptoms: Nausea/photophobia/phonophobia.

Bilat: bilateral; Uni: unilateral; T: throbbing; P: pressing; NS: not specified (missing data).

Spon: spontaneous migraine attack; M: male; F: female; Y: years of age.

Diclodan: diclofenac 100 mg (suppository); I: ibuprofen 400 mg; Kodipar: codeine 30.6 mg + paracetamol 500 mg; P: paracetamol 1 g. SI: sumatriptan (tablet); S2: sumatriptan 12 mg (injection); AC: aspirin 500 mg + caffeine 50 mg; O: ondansetron 16 mg (suppository).

^aDoes not fulfill the associated symptoms criteria, but the attack is reported to mimic the patient's usual attack.

^bNo data from > 24 hours.

^cWent to sleep.

^dNo side preference.

^eShifted from left to right at 7 hours.

Table 2. Clinical features of migraine attacks after calcitonin gene-related peptide and sildenafil in patients who developed attacks on both days.

Clinical feature	CGRP-induced attacks	Sildenafil-induced attacks	Same feature both days
Unilateral location	12/17	10/17	13/17 ^a 95% CI: 0.50–0.93
Throbbing quality	16/17	14/17	15/17 ^a 95% CI: 0.64–0.99
Peak pain ≥ 4 on NRS	17/17	15/17	15/17 95% CI: 0.64–0.99
Aggravation by exertion	16/17	16/17	15/17 95% CI: 0.64–0.99
Nausea	11/17	10/17	11/17 ^a 95% CI: 0.38–0.86
Photophobia	17/17	17/17	17/17 95% CI: 0.81–1.00
Phonophobia	17/17	16/17	16/17 95% CI: 0.71–1.00

^aIncludes patients who experiences bilateral location, pressing quality or no nausea as same features on both days.

CI: confidence interval.

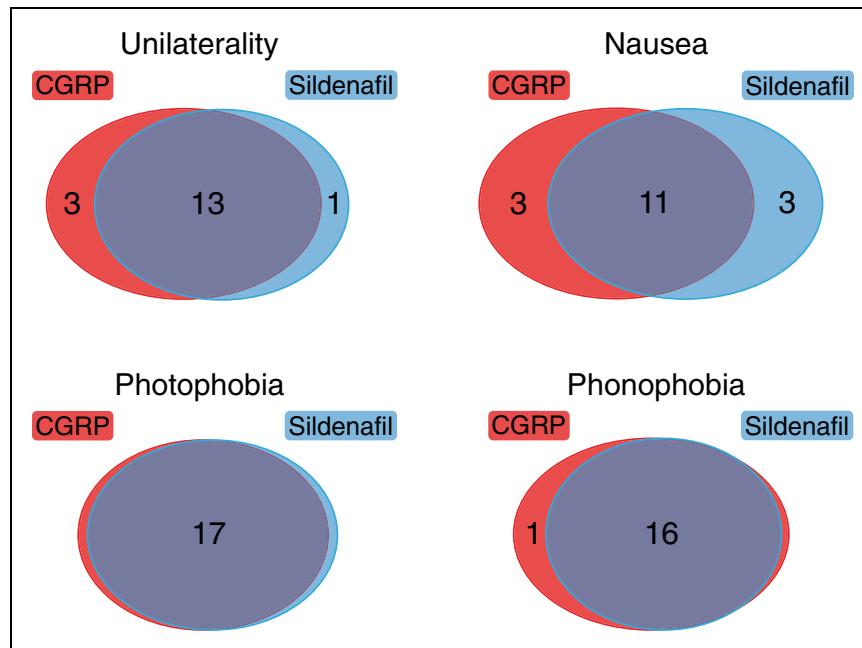


Figure 5. Number of patients who developed each migraine characteristic during attacks after calcitonin gene-related peptide (CGRP) and sildenafil. Overlaps represent patients who developed the same characteristic after both study drugs. Figure includes patients who experienced an attack on both days ($n = 17$).

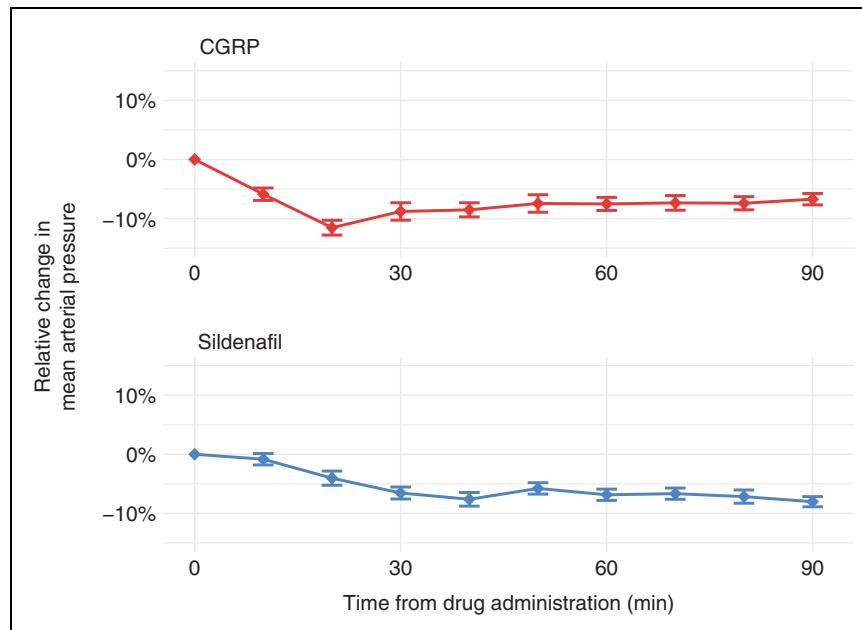


Figure 6. Relative change in mean arterial pressure (MAP) after calcitonin gene-related peptide (CGRP) and sildenafil from time of study drug administration (0 min). Values depicted as median \pm standard error.

such as PACAP-38 and cilostazol carry their effects via the cAMP signaling pathway as well (19,20). Pharmacological headache-inducers are believed to act on the trigeminovascular system. CGRP, when infused, is unable to cross the blood brain barrier, and thus most likely activates peripheral CGRP receptors, which are

available in both trigeminal neurons (e.g. ganglion, fibers) and cranial vascular cells (21,22). On the other hand, sildenafil freely crosses cellular membranes due to its lipophilic properties, and may therefore exert central effects, in addition to the well-known peripheral vascular effects (23,24).

Seven of the eight patients who developed an attack on one study day only reported the migraine attack after sildenafil administration, yielding migraine induction rates of 67% after CGRP and 89% after sildenafil. Mean induction rates across previous studies, in varying cohorts, amount to similar results with 64% for CGRP (8–10,25,26) across five studies and 83% for sildenafil (11). The relatively higher migraine attack induction after sildenafil is indicative of a more potent migraine-inducing ability. This might be attributed to its more downstream effects, thus being closer to the common determinator compared to CGRP in the migraine initiating cascade.

Due to the study design, there was no placebo control in addition to the active drugs, and the patients were not exposed to the same agent twice. However, we aimed to reduce expectation bias by informing the patients about possible outcomes, which would be independent of study day. As median time between the two study days was 14, and half-lives of CGRP and sildenafil were ~7–10 min (27) and ~4 h (28), the risk of carry-over effect was minimum. Furthermore, previous studies found similar induction rates both in placebo-controlled and open-label studies alike (8–11,25,26). The consistent reproducibility of CGRP and sildenafil migraine induction rates further suggests that false positive induction and day-to-day variation is unlikely to influence overlap. As CGRP induction rates are lower than for sildenafil, the overlap of patients developing attacks after both agents will be limited by CGRP as the lowest denominator.

Time to onset of migraine

We found that CGRP induced migraine faster than sildenafil (Figure 4). These differences in initiation of

migraine might be explained by the fact that CGRP was administered intravenously, while sildenafil was administered as an oral formulation with $t_{max} \sim 1.5$ hours (28). With this quicker access to target cells and subsequent faster activation of protein kinase, CGRP initiation of the migraine cascade might reach the proposed common determinator faster than sildenafil; however, the end result is the same.

The difference in “time-to-effect” is also demonstrated in studies showing immediate vascular responses to CGRP infusion (29), while response to oral sildenafil treatment occurs within 30 minutes of administration (30). The same effect is visualized in Figure 6, showing an immediate response after CGRP. The middle cerebral artery is dilated after CGRP during migraine attacks (26), while previous study showed no dilation of the middle cerebral artery after 100 mg sildenafil during attacks (31). However, this was assessed using transcranial Doppler (31) in contrast to MRI (26).

Conclusion

A majority of migraine patients developed attacks after both CGRP and sildenafil, with similar attack characteristics that mimicked their habitual attacks and were largely treatable by their usual abortive medication. A possible explanation of these findings is that migraine could be initiated by a common cellular determinator in which the cGMP and cAMP pathways converge. Future studies should focus on this commonality of migraine attack initiation as it could prove a prospective cellular target for new preventive therapeutics.

Clinical implications

- Calcitonin gene-related peptide induces migraine via the cyclic adenosine monophosphate pathway, and sildenafil via the cyclic guanosine monophosphate pathway, as two distinct cellular signaling pathways mediating migraine mechanisms.
- Calcitonin gene-related peptide and sildenafil induced the same attacks within the majority of patients, despite attack initiation via distinct intracellular signaling pathways.
- Our findings suggest that modulation of migraine initiation via the two signaling pathways ultimately converge in a common cellular determinator.

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Author contributions

SY and CEC: Study concept and design, acquisition, analysis, and interpretation of data, and drafting of manuscript. NMT and TS: Acquisition and processing of data. FMA, AH and MA: Study concept and design, interpretation of data and overall supervision of study.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MA is a consultant or scientific advisor for Allergan, Amgen, Alder, Eli Lilly, Novartis and Teva, and principal investigator for Alder, Amgen, ElectroCore, Novartis and Teva trials. MA has no ownership interest and does not hold stock in any pharmaceutical company. MA serves as co-editor of the *Journal of Headache and Pain*, associate editor of *Cephalalgia* and associate editor of *Headache*. FMA is principal investigator for a Novartis Phase IV trial and member of advisory boards for Eli Lilly and Novartis. CEC has received lecturing fees from Teva. The remaining authors report no competing interests.

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