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Research Submission

Transcranial Magnetic Stimulation for Migraine Prevention in Adolescents: A Pilot Open-Label Study

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Objective.—To assess the feasibility, tolerability, and patient acceptability of single-pulse transcranial magnetic stimulation (sTMS) for migraine prevention in adolescents in an open-label pilot study.

Background.—Migraine is common in adolescents and can be disabling. Well tolerated preventative therapies that are safe and effective are needed.

Methods.—This was an open-label prospective pilot feasibility study of sTMS for migraine prevention in adolescents aged 12-17 years. Participants used sTMS twice daily in a preventative fashion, as well as additional pulses as needed acutely. A 4-week baseline run-in period (weeks 1-4) was followed by a 12-week treatment period. Feasibility was the primary outcome. Secondary outcomes included tolerability and acceptability, as well as the change in headache days, number of moderate/severe headache days, days of acute medication use, and PedMIDAS (headache disability) scores between the run-in period (weeks 1-4) and the third month of treatment (weeks 13-16).

Results.—Twenty-one participants enrolled. Nineteen completed the baseline run-in, and 12 completed the study. Using sTMS proved feasible and acceptable with overall high compliance once treatment administration was streamlined. Initially, for preventive treatment, participants were asked to give 2 pulses, wait 15 minutes, then give 2 additional pulses twice daily. This 15-minute delay proved challenging for adolescents, particularly on school days, and therefore was dropped. Study completion rate went from 4/13 (31%) to 7/8 (88%) once this change was made, $P = .024$. On average, participants used the device preventively between 22 and 24 days over a 28-day block. There were no serious adverse events. Two participants reported mild discomfort with device use.

Conclusion.—sTMS appears to be a feasible, well-tolerated, and acceptable nonpharmacologic preventive treatment for migraine in adolescents. In designing future trials of sTMS for migraine prevention in adolescents, streamlined treatment administration will be essential to minimize drop-out. Efficacy needs to be assessed in a larger trial.

Key words: adolescents, migraine, transcranial magnetic stimulation, neuromodulation, headache

Abbreviations: CHAMP Children and Adolescent Migraine Prevention Study, CNS central nervous system, dB decibels, ESPOUSE eNeura SpringTMS Post-Market Observational US Study of Migraine, FDA Food and Drug Administration, SD standard deviation, sTMS single-pulse transcranial magnetic stimulation, T Tesla

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INTRODUCTION

Migraine is common in adolescents, with prevalence in the United States of approximately 5% in early adolescence, rising to approximately 8% in boys and 10% in girls by later adolescence.[1] The impact of migraine can be substantial, with many children and adolescents missing school or performing poorly in school.[2]

There is need for safe, well-tolerated, and effective migraine preventive treatments in this age group. The recent Childhood and Adolescent Migraine Prevention (CHAMP) study demonstrated that approximately 60% of children and adolescents with migraine who are treated with a preventive will improve, regardless of whether they are given prescription pharmacologic treatment or placebo.[3] As medications have more side effects than placebo,[3] it is important that first-line migraine preventive therapies in this age group have side effect profiles comparable to that of placebo.[4] Currently, the only Food and Drug Administration (FDA)-approved preventive treatment for adolescent migraine is topiramate, an antiepileptic drug with cognitive and systemic side effects.[5]

Transcranial magnetic stimulation (TMS) has a well-established safety record.[6-8] Magnetic field strengths generated by TMS devices are 1.5-2 T, comparable to the field strength of clinically used MRI scanners.[9] Similarly, the noise generated by single-pulse transcranial magnetic stimulation (sTMS) is no greater than what children might experience listening to music or from environmental exposures (100-120 dB).[10] In a review of over 850 infants and children exposed to sTMS, including both healthy children and those with neurologic disorders, there were no serious adverse events reported.[9] The use of sTMS in the treatment of migraine is supported by pathobiologic and clinical trial evidence,[6,11-15] and has the potential to be an effective, safe,[7] and well-tolerated nonpharmacologic preventive treatment option for migraine in children and adolescents.

At the time this study was designed, sTMS had been approved by the FDA for acute treatment of migraine with aura in adults following a study outlining safety and efficacy when used as abortive therapy in this population.[14]

The use of sTMS for migraine prevention was suggested in work by Bhola et al, wherein adults with migraine who used the device acutely were noted to have a decrease in their migraine frequency and duration of attacks over the course of 3 months of therapy.[13] This informed the design of the adult preventive sTMS study, ESPOUSE. Their recently published postmarketing data from 132 adults with migraine demonstrated a mean (SD) reduction of monthly headache days of 2.8 (0.4), greater than what would be expected from a historical placebo, with no serious adverse events.[12] This led to an extension of the FDA approval for sTMS in migraine in adults in July 2017 to include both acute and preventive treatment indications.

This study was designed as an open-label prospective migraine preventive study in adolescents, modeled after the ESPOUSE protocol, to determine the feasibility of sTMS, used in a preventive fashion, in the adolescent age group. The secondary aims were to assess tolerability, and acceptability, as well the efficacy of sTMS in reducing mean number of headache days per month, headache days of moderate to severe intensity, amount of acute medication used, and the PedMIDAS disability score.[16]

Conflict of Interest: Dr. Samantha Irwin is the cofounder and CEO of a company named HeadSoothe Nutraceuticals Inc, which is working to develop a combination nutraceutical for the treatment of headache in children. This company is not associated with this work. Dr. William Qubty, Dr. Isabel Elaine Allen, and Dr. Irene Patniyot have nothing to disclose. Dr. Peter J. Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; and personal fees from Alder Biopharmaceuticals, Cipla Ltd, Dr Reddy's Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc, Quest Diagnostics, Scion, Teva Pharmaceuticals, Trigemina Inc., Scion; and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Massachusetts Medical Society, Oxford University Press; and in addition, Dr. Goadsby has a patent for Magnetic stimulation for headache assigned to eNeura without fee. Dr. Amy Gelfand has received honoraria from UpToDate and consulting fees from Zosano, Eli Lilly, and Biohaven. eNeura provides consulting payments for work done by Dr. Gelfand to the UCSF Pediatric Headache program. Her spouse receives consults for Genentech, research support from Genentech, Quest Diagnostics, and MedDay, and personal compensation for medical-legal consulting.

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METHODS

For this open-label prospective feasibility study, 21 participants aged 12-17 were enrolled at the University of California, San Francisco (UCSF) Pediatric Headache center between May 2015 and December 2016. The rationale for this sample size is that investigators felt this was the number needed to enroll to ensure that the majority of issues that might impact adolescents' compliance with device use and feasibility were encountered. Participants met ICHD-3 beta criteria for migraine[17]; and diagnosis was confirmed by a pediatric headache specialist. Those with ≥15 headache days per month were considered to have chronic migraine; a formal review of whether ≥8 days per month met migraine criteria was not performed.

Adolescents provided assent and parents provided written informed consent. This study was approved by the UCSF Internal Review Board (IRB #14-14555).

To meet inclusion criteria, participants had to report 4-24 headache days per 28-day period. While those with chronic migraine could enroll, a maximum of 24 headache days out of 28 days was chosen to ensure participants did not have daily, or near daily, headache. Participants both with and without aura were included. Participants could be on a migraine preventive as long as the dosage had been stable for at least 4 weeks prior to enrollment. They could not have a history of epilepsy or a first degree relative with epilepsy, nor could they be on medications that lowered the seizure threshold (specifically antidepressants or neuroleptics, not including amitriptyline). Additionally, those with metal in the skull, head, or neck regions, and those with cardiac pacemakers or other implanted medical devices, such as a vagal nerve stimulator, were excluded. Girls who had their first menstrual period had to have a negative urine pregnancy test. Medication overuse, as defined in ICHD-3 beta,[17] was not an exclusion criterion.

Participants completed a 28-day baseline headache diary. Participants were instructed to complete their paper headache diary each evening. Diary compliance was assessed at 4-week intervals. If they had 4-24 days of headache and completed at least 24/28 diary entries (ie, ≥80% diary compliance) during the baseline run-in period (weeks 1-4), they were eligible to receive the device. The treatment period was 12 weeks long. Treatment outcomes were evaluated in the final 4 weeks of device use (weeks 13-16 of study) and were compared to the 4-week baseline run-in period (weeks 1-4).

The initial protocol instructed participants to use the device twice daily (morning and evening), as follows: Give 2 pulses, wait 15 minutes, then give 2 additional pulses. This was modeled on the adult ESPOUSE study.[12] For acute use, participants could give 3 pulses, wait 15 minutes, give another 3 pulses, wait 15 minutes and, if needed, give a final 3 pulses. During the study, it became evident that the 15-minute waiting period between pairs of preventive pulses was a challenge for the teenage participants to comply with, particularly on weekday mornings, as they were often rushing to get to school. The investigators discussed this issue and concluded there was no identifiable safety reason for this waiting period and, thus, the protocol was updated to allow participants to give the 4 preventive pulses all together.

After the initial study enrollment visit, participants were called every 4 weeks to check-in, query for adverse events, and to encourage continued study participation. Participants mailed their headache diaries back to the study center each month. Compliance with device use was by self-report in the headache diaries.

The primary outcome was feasibility. Feasibility was determined both by the length of time necessary to enroll study participants and the proportion of adolescents who found it possible to complete the study.

Secondary outcome measures included tolerability and acceptability. Tolerability was determined by querying for adverse events at the monthly check-in calls. Acceptability was defined as self-reported compliance with using the device twice a day. Self-report regarding degree of satisfaction with the device was also used as an indicator of acceptability. We also assessed efficacy by evaluating the following: (1) mean number of headache days in month 3 of active treatment (weeks 13-16) compared to the 28-day baseline run-in period

Table 1.—Baseline Demographic and Clinical Characteristics of 12- to 17-Year-Old Participants With Migraine ($n = 21$)

Age: average (SD), range (years)	15 (1.5), 12-17
Sex: females (% females), males	14 females (67%), 7 males
Age of first headaches: mode, average (range) (years)	5, 9 (3-15)
Age headaches became troublesome: mode, average (range) (years)	14, 11 (5-15)
Family history of headaches: *n* (%)	19 (90%)
Family history of migraine: *n* (%)	17 (81%)
Weight: mean (SD) (kg)	66.1 (20.3)
Frequency of headache days per month at baseline [(average (SD), self-reported]	11.8 (6.7)
Chronic migraine vs episodic migraine (*based on >15 headache days a month*)	7 vs. 14
PedMIDAS score (baseline): average (SD)	55 (40)
Medication overuse present: *n* (%)	0 (0%)
Migraine with aura	1 (5%)
Currently using acute headache medications: number of participants: *n* (%)	20 (95%)
Currently on a preventive migraine medication: number of participants: *n* (%)	11 (52%)

SD = standard deviation.

(weeks 1-4); (2) days of moderate/severe headache intensity; and (3) days of acute medication consumption between the third treatment month (weeks 13-16) vs the run-in (weeks 1-4). PedMIDAS scores from enrollment, representing the historical 3-month average, were compared to the third treatment month. PedMIDAS is a validated instrument for estimating headache-related disability in children and adolescents with migraine.[16]

Device Technical Specifications.—The weight of the device was 3.8 lbs (1.7 kg). The size of the device was 9 inches long × 5 inches wide × 3 inches deep (23 cm long × 13 cm wide × 8 cm deep). The magnetic pulse output was 0.9 Tesla at 1 cm from the center of the device's curved surface. The pulse rise time was 180 μs.

Statistical Analysis.—Data were analyzed using Stata version 15.0 (Statacorp, College Station, TX, USA). Descriptive statistics were calculated for all variables: means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Student's paired and unpaired 2-tailed *t*-tests were performed. Paired 2-tailed *t*-tests were used to see within subject changes with sTMS use for those participants who completed the entire 12-week treatment phase. All paired tests were also examined using nonparametric analyses (Wilcoxon rank sum test) because of the small sample size and the results did not change. Unpaired 2-group independent *t*-tests were included to outline the overall group changes, not excluding those participants who did not complete the study. A P value of $<.05$ was considered statistically significant. To avoid false precision, some results are given rounded to the level of precision with which they were measured (eg, PedMIDAS score is rounded to the nearest integer). Headache days are still reported to 1 decimal point as this is most commonly done in migraine treatment trials. A post hoc analysis comparing the proportion of study-completers before vs after the 15-minute pause between pairs of pulses was removed used Fisher's exact test.

RESULTS

Demographics.—Demographic data are summarized in Table 1. Twenty-one participants were enrolled. Nineteen completed the run-in period. Twelve completed the study. The average age (SD) was 15 (1.5), with a range of 12-17, and females represented 67% of the participants. Ninety percent had a family history of migraine. Seven participants had chronic migraine. Twenty participants were current users of acute medication. Eleven (52%) were on a preventive medication at time of enrollment.

Feasibility.—Twenty-one patients were enrolled at a single site over 1.5 years. Nineteen of 21 (91%) completed the baseline run-in period (weeks 1-4) and returned baseline headache diaries. Fifteen of 19 (79%) treated with sTMS during weeks 5-8, 11/19 (58%) treated with sTMS during weeks 9-12,

Table 2.—Examples of Comments From Participants and Parents on the Advantages and Disadvantages of Using the TMS Device for Headache Prevention

Advantages	Disadvantages
• Nice alternative to pills • No side effects • Easy to use • Prevented a few headaches if used in time • Reduced number of headaches overall • Reduced how long a headache lasted or the intensity of a headache if used acutely • Reduced intensity and less nausea • Better attendance in school	• Too long to use, would like to remove the 15-minute wait between uses • Did not like loud noise or the feeling of the pulse • Hard to transport and travel with • Unsure if device was in right place (no feedback/confirmation) • Hard to remember to use, especially at school • Cost to continue using the device post trial

and 12/19 (63%) treated with sTMS during weeks 13-16. Thus, 12/21 (57%) of those who enrolled in the study completed it, or 12/19 (63%) of those who completed the baseline run-in period.

Reasons for failure to complete the study ($n = 9$) included the following: (1) failure to complete the 4-week baseline headache diary ($n = 2$); (2) traveling without the device ($n = 1$); (3) protocol violation (changing preventive during treatment phase) ($n = 1$); (4) failure to return the diary during the treatment phase ($n = 3$); and (5) not wanting to remove metal earrings in order to use the device ($n = 1$). One participant withdrew due to headache worsening during the trial ($n = 1$).

Tolerability.—There were no serious adverse events. Of the 19 participants who completed the baseline run-in, a total 16 used the device for at least some period of time during weeks 5-13 of the treatment phase. Two of these 16 experienced mild adverse events (13%). One noted an unpleasant tingling sensation at the site after device use and found it difficult to tolerate the device's noise when using it as an acute treatment. This same participant also had a presumed viral upper respiratory tract infection during the study, deemed unrelated to device use by investigators. The second participant felt the device worsened her headache, leading to early study termination after 8 weeks of device use. The remaining 14/16 (88%) participants who used the device did not report any adverse events.

Acceptability.—Compliance with twice daily preventative use of sTMS was stable and consistent over the 12-week treatment period. During the first 8 weeks, participants on average used the device preventively on 22/28 days (79%) per 4-week time period, and it was used on average 24/28 (86%) days in the final 4-week block. Overall, feedback from participants and their parents support both feasibility and acceptability of use. Specific comments that may inform future study design are included in Table 2. Of note, this trial demonstrated that a 15-minute waiting period between administration of preventive pulses is not practical for adolescents and that in future trials, all preventive pulses should be given together to improve treatment adherence. For those who enrolled prior to this change in the protocol, only 4/13 (31%) participants completed the trial to week 16. Of those who enrolled after the change was instituted, 7/8 (88%) finished the trial. The proportion of study completers was significantly higher once treatment administration was streamlined ($P = .024$, Fisher's exact).

Other Secondary Outcomes.—Headache results are shown in Table 3 (paired data) and Table 4 (unpaired data). In the paired analysis (ie, completers analysis), the average (SD) number of headaches days per 28-day period was reduced from the run-in period, 13.3 ± 6.7, to the third month, 8.8 ± 6.7 (-4.5 days; $P = .019$) and the average ($\pm$SD) number of moderate/severe headache days

Table 3.—Baseline Data and Clinical Response to sTMS During 12 Weeks of Twice-Daily Preventive Treatment for Those Participants Who Completed the Entire Study

	Run-In Weeks 1-4 ($n = 12$) Mean (±SD)	Post TMS Use Weeks 13-16 ($n = 12$) Mean (±SD)	Paired *t*-Test Absolute Reduction (±SE of the Difference); *P* Value
Headache days/month	13.3 (±6.7)	8.8 (±6.7)	−4.5 (±1.7); $P = .019$*
Moderate/severe pain days	7.0 (±3.2)	4.2 (±3.0)	−2.8 (±1.3); $P = .052$
Acute medication days	5.3 (±3.7)	3 (±2.3)	−2.3 (±1.2); $P = .082$
PedsMIDAS score	63 (±46)†	27 (±27)	−36 (±14), $P = .026$*

*Significant *P* values comparing baseline run-in data to month 3 (weeks 13-16) of using sTMS.
†This PedsMIDAS is the baseline PedsMIDAS score for those who completed the entire study and who had paired data at study completion ($n = 10$), and was not completed during the run-in phase.

was also reduced from 7 ± 3.6 to 4.2 ± 3.0 ($P = .052$). No statistical difference was found for acute use of medication across the treatment period ($P = .082$) in the paired data, but when looking at overall group changes in the unpaired analysis, there was a statistically significant reduction in acute medication use from 5.5 ± 3.5 to 3 ± 2.3 days, a reduction of 2.5 days ($P = .036$). Finally, there was a significant reduction in mean (±SD) PedMIDAS scores from baseline to the last 4 weeks of treatment in the paired analysis from 63 ± 46 vs 27 ± 27, a reduction of 36 points ($P = .026$).

DISCUSSION

sTMS appears to be a feasible, well-tolerated, and acceptable preventive treatment option for adolescent migraine. Given that approximately 60% of pediatric and adolescent participants respond to first-line preventive therapy when it is delivered as part of a multidisciplinary approach accompanied by lifestyle counseling and optimal acute therapy,[18] it is important that our first-line therapies have side effect profiles no more dangerous than that of placebo.[4] From this small study, and the broader literature supporting the safety of sTMS use in migraine,[6-9] sTMS appears to meet this standard. Cost and insurance coverage remain separate issues. For adults, sTMS is now FDA approved for acute and preventative use in migraine.

Although this pilot study did not have a control arm, our results are encouraging in that there was a significant reduction in the number of headache

Table 4.—Baseline Data and Clinical Response to sTMS During 12 Weeks of Twice-Daily Preventive Treatment for All Participants, Regardless of Completion Status, to Show the Group Effect

	Run-In Weeks 1-4 ($n = 19$) Mean (±SD)	Post TMS Use Weeks 13-16 ($n = 12$) Mean (±SD)	Unpaired *t*-Test Absolute Reduction (±SE of the Difference); *P* Value
Headache days/month	12.4 (±6.3)	8.8 (±6.7)	−3.6 (±2.4); $P = .141$
Moderate/severe pain days	7.2 (±3.6)	4.2 (±3.0)	−3.0 (±1.2); $P = .023$*
Acute medication days	5.5 (±3.5)	3 (±2.3)	−2.5 (±1.2); $P = .036$*
PedsMIDAS score	55 (±40)†	27 (±27)	−28 (±14); $P = .050$*

*Significant *P* values comparing baseline run-in data to month 3 (weeks 13-16) of using sTMS.
†This PedsMIDAS is the baseline PedsMIDAS score ($n = 21$), and was not completed during the run-in phase.

days between the run-in period and the final 4 weeks of treatment. PedMIDAS disability scores were also significantly reduced.

Observations from this study will help to inform the design of future efficacy trials. Overall dropout in this trial was higher than expected. This appears to have been largely related to the time-consuming and burdensome nature of the initial treatment protocol design. When the adolescents were asked to wait 15 minutes between pairs of pulses, only 4/13 (31%) completed the trial. When treatment administration was streamlined, and this 15-minute delay was dropped, 7/8 (88%) completed the trial ($P = .024$). We believe the most likely reason for the high dropout experienced in our trial, specifically the difference in dropout premethodology and postmethodology changes, was due to the impracticality of waiting 15 minutes between the morning treatments while trying to get ready for school. In future trials, participants should be instructed to give all preventive pulses in this streamlined fashion. Finally, the difficulty of using the device when traveling was raised. The current device is larger than a typical pill bottle and weighs more. Practical issues such as the ease of transporting a treatment device will need to be considered in future trial design and may inform patient preferences in clinical use as well.

Other limitations include a small sample size with a relatively high dropout rate, which precludes a formal intention to treat analysis,[19] a heterogeneous sample and a heterogeneous protocol, no sham control group, and the possible recall bias if retrospective recording of headaches days occurred while using the paper diaries. In addition, it would be optimal in future studies if device use compliance could be assessed objectively by recording daily frequency of use within the device itself, to avoid recall bias by self-report.

Given these limitations, a larger efficacy study in children and adolescents is now needed. It will be important in trials powered for efficacy to include a control—be it a sham-device or active tablet comparator.

In conclusion, this pilot study suggests that sTMS appears to a feasible, well-tolerated, safe, and acceptable nonpharmacologic, nonbehavioral alternative for migraine preventive treatment in adolescents. The data are also suggestive of headache efficacy. Larger, controlled studies in the pediatric and adolescent age groups are needed.

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