Remote Electrical Neuromodulation for Acute Procedural Pain in Chronic Migraine Patients Receiving onabotulinumtoxinA

NCT05730556

30November2023

RESEARCH PROTOCOL

Remote electrical neuromodulation for acute procedural pain in chronic migraine patients receiving onabotulinumtoxinA

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Version 1.7 November 2023

SYNOPSIS

Study Title	**Remote electrical neuromodulation for acute procedural pain in chronic migraine patients receiving onabotulinumtoxinA**
Objectives	To assess the effectiveness of remote electrical neuromodulation with the Nerivio ® device at relieving acute procedural pain in patients receiving onabotulinumtoxinA per PREEMPT protocol for chronic migraine prevention.
Study Period	24 weeks
Subjects	80 subjects ages 18 - 75 who meet criteria for chronic migraine receiving onabotulinumtoxinA for chronic migraine
Study Treatment	Nerivio ® (Remote Electrical Neuromodulation) applied to the upper extremity prior to the procedure and removed following procedure.
Study Design	Single-center, randomized, single-blind, sham-controlled, crossover study to evaluate the effectiveness of Nerivio ® for treatment of acute procedural pain in patients receiving onabotulinumtoxinA for the treatment of chronic migraine. During phase 1, 80 adults with a diagnosis of chronic migraines will be surveyed on their pain levels during routine procedure and then randomized to receive either intervention vs sham treatment at week 12 +/- 7 days (buffer time to accommodate rescheduling) for phase 2. For phase 3, subjects will then transition to receive the alternate therapy at week 24 +/- 7 days. Pain levels will be compared across time points
Inclusion and Exclusion Criteria	Inclusion Criteria 1. Adults aged 18 to 75 years old 2. Meet the criteria for *1.3 chronic migraine* based on ICHD3 criteria 3. Currently receiving onabotulinumtoxinA per PREEMPT protocol for the treatment of chronic migraine 4. Patient is willing and able to comply with the protocol to the satisfaction of the investigator 5. Patient has the capacity to provide written, informed consent for themselves Exclusion Criteria 1. Participants with an active implanted electrical and/or neurostimulator device (e.g., cardiac pacemaker, cochlear implant). 2. Participants with congestive heart failure (CHF), severe cardiac or cerebrovascular disease. 3. Participants with uncontrolled epilepsy. 4. Pregnant, trying to get pregnant or breastfeeding female participants 5. Subjects participating in any other interventional clinical study. 6. Participants with other significant pain, medical or psychological problems that in the opinion of the investigator may confound the study assessments 7. Participants who have previous experience with the device 8. Patients with cranial deformities, prior cranial surgeries with violation of the calvarium, or shunt placement 9. Patients receiving concurrent nerve blocks or trigger point injections within the same visit
Measurements	Subjects will be surveyed on their pain intensity using a Visual Analog Scale pre-, intra- and post-procedure (approximately 0 – 5 minutes post-procedure). Additionally, patient demographic information (sex, age, race, ethnicity), BMI, arm circumference, depression/anxiety screen, medical comorbidities, headache qualities (location, duration, intensity, frequency, associated symptoms), previous rounds of onaboulinumtoxinA received, current treatment regimen (beyond onabotulinumtoxinA) including other preventive and abortive treatments will be recorded. Migraine-specific quality measures (MIDAS) will also be recorded throughout the study period. Patients will be contacted on the day following each treatment of onabotulinumtoxinA to follow-up on post-procedural headache.
Outcomes	**Primary:** Pain intensity with a Visual Analog Scale, pre- , intra-, and post-procedure **Secondary:** 1. Presence of post-procedural headache 2. Any adverse events.

1. Background and Rationale:

Migraine is a condition that impacts a large segment of the global population (~958.8 million) and is exceeded only by stroke with regards to its overall burden of neurological disease (**GBD 2015 Neurological Disorders Collaborator Group).** It has been estimated that the prevalence of total migraine (episodic and chronic) is about 20.7% in women and 10.7% in men in the United States (**Burch 2020**). Of the patients with episodic migraine, it has been shown that around 2.5% will progress or "transform" into chronic migraine, defined as headache that occurs ≥15 days per month with at least 8 headaches with features of migraine based on the International Classification of Headache Disorders 3rd Edition (ICHD-3) criteria (**Buse 2012, see ICHD-3 criteria in supplemental material**).

The injection of onabotulinumtoxinA (BoNT-A) is common treatment for patients with a wide variety of conditions such as chronic migraine, cervical dystonia, spasticity, strabismus, neurogenic bladder, and hyperhidrosis. Proper implementation of this treatment modality can involve the injection of BoNT-A into many different sites per procedural visit and must be repeated to ensure continued effect. BoNT-A for the treatment of chronic migraine is administered per PREEMPT protocol, which involves the injection of 5U into 31 injection sites (total 155U) with the option for additional injections (up to 40-45U) based on a follow-the-pain strategy and must be administered every 10 to 12 weeks to maintain effect (**Aurora, 2010; Diener, 2010**). While levels of procedural discomfort do not appear to predict therapy continuation (**Anderson, 2020**), steps should be taken to reduce needle-related pain to minimize stress and anxiety surrounding the procedure.

Management of acute procedural pain is an area of considerable interest, typically with relation to pediatric populations. Many modalities have been found to be effective at reducing procedural needle-related pain, including immersive virtual reality distraction, cognitive-behavioral therapy, hypnosis, breathing interventions, clown therapy, and ethyl chloride spray; however, the effective implementation of these strategies tends to require hiring additional personnel or dedication of time that may not be feasible in a busy, clinical setting. The utilization of devices for management of acute procedural pain has been investigated for needle-related procedures in children (**Ballard, 2019**), but further investigation is required to understand the potential benefits of using for acute needle-related procedural pain in adults.

The Nerivio® device (Theranica Bio-Electronics Ltd., Israel) is a wearable, remote electrical neuromodulation (REN) device controlled by smartphone application that has been cleared for the acute treatment of migraine in adults and adolescents (**Yarnitsky 2019, Tepper 2020, Ailani 2022**). The proposed mechanism of action involves stimulation of peripheral nerves within the upper extremity, thereby inducing conditioned pain modulation (CPM) and reduction of acute pain. While this device is cleared for the treatment of paroxysmal pain in migraine, little is known about whether it could demonstrate effectiveness at reducing pain in the head and neck that occurs in response to procedural intervention. The aim of the current study is to compare acute procedural pain intensity among chronic migraine patients receiving Nerivio ® vs sham device treatment during treatment with onabotulinumtoxinA per the PREEMPT protocol.

2. Objectives

The goal of this research proposal is to establish remote electrical neuromodulation with Nerivio ® as an efficacious therapy for acute procedural pain in patients receiving onabotulinumtoxinA

for the treatment of chronic migraine. We hope to demonstrate an improvement in procedural pain when patients receive remote electrical neuromodulation with Nerivio ® compared to no treatment and sham treatment. We will record acute procedural pain utilizing a numerical 0-10 rating scale and will compare this number across phases to determine efficacy. We will test the hypotheses that: 1) Patients receiving transcutaneous remote electrical neuromodulation with Nerivio ® will experience significantly lower levels of acute procedural pain compared to when they received either no treatment or sham treatment and that (2) patients receiving remote electrical neuromodulation with Nerivio ® will experience a reduced incidence of post-procedural headache compared with either no treatment or sham treatment. For the purpose of the study, "post-procedural headache" will be defined as a headache 24-hours post-procedure in which head pain lasts 4 hours or more and is at least moderate in severity or during which abortive medications are used to treat the patient's head pain.

We believe that enacting strategies to reduce acute procedural pain provides benefits for the patient experience and if results indicate that remote electrical neuromodulation provides significant benefits, this method of treatment may be considered for wider use where injection of local anesthetic is unable to be performed, contraindicated, or not feasible, e.g., onabotulinumtoxin for dystonia/spasticity or cosmetic use, electromyography, or acupuncture.

3. Preliminary Data

The utilization of devices for acute procedural pain has been investigated in the past. One such device, the Buzzy ®, relies on a vibrating motor and cold sensation to interfere with discomfort related to the procedure. A meta-analysis published in 2018 compiled the results of 9 studies (n=1138) and found that the device significantly reduced self-reported pain levels (standardized mean difference [SMD]: −1.11; 95% confidence interval [CI]: −1.52 to −0.70; P < 0.0001), observer-reported pain levels (SMD: −1.19; 95% CI: −1.90 to −0.47; P = 0.001), and procedural anxiety (SMD −1.37; 95% CI: −1.77 to −0.96; P < 0.00001). The proposed mechanism of action of the Buzzy ® device is the Gate Control Theory, whereby non-noxious stimuli interfere with the transmission of painful stimuli at the level of the dorsal horn of the spinal cord (**Ballard, 2018**).

The proposed mechanism of action of Nerivio ® differs from the Buzzy ® device. Per the device's manufacturers, Nerivio ® produces its effects via remote electrical neuromodulation (REN). REN acts by stimulating peripheral nerves of the upper extremity with electrical stimulus that is not painful. These signals induce a conditioned pain modulation (CPM) response at the level of the brainstem, specifically at the periaqueductal gray and rostral ventromedial medulla (**Yarnitsky, 2019**). Nerivio ® has been found to be effective for the acute treatment of migraine headache compared to sham stimulation with significant benefits in pain relief (66.7% [66/99] vs 38.8% [40/103]; therapeutic gain of 27.9% [$CI_{95\%}$, 15.6-40.2]; *P* < .0001), pain-free (37.4% vs 18.4%, *P* = .003), and most-bothersome-symptom relief (46.3% vs 22.2%, *P* = .0008) at 2 hours post-treatment. The device also has device-related adverse events (4.8% [6/126] vs 2.4% [3/126], *P* = .499) with the most common adverse events being warmth sensation (2.4% treatment vs 0.8% sham; redness 1.6% treatment vs 0.8% sham; and pain in the arm (1.6% treatment vs 0% sham) (**Yarnitsky, 2019**).

While this device has been studied for acute migraine, further studies are required to determine its effectiveness at treating other types of pain. Of interest to this study, we will be investigating acute procedural pain in the cranial-cervical region.

4. Patient Selection

Subjects will be recruited from the patient population at the Headache Medicine clinic at the Mayo Clinic Scottsdale, Arizona location. Subjects will initially be approached in the clinic in person or by phone. Prior to study initiation, written informed consent or electronic consent will be obtained from the subject. Goal enrollment is 80 adults (18 - 75 years old) who meet the criteria for a diagnosis of chronic migraine that have been stable on their current headache medication for a minimum of 8 weeks. Definition of chronic migraines will be defined per the International Classification of Headache Disorders (ICHD3) as a headache occurring on 15 or more days/month for more than 3 months, which have the features of migraine headache on at least 8 days/month. Subjects should be approved and scheduled to received onabotulinumtoxinA for the treatment of chronic migraine for recruitment.

4.1. *Inclusion Criteria*

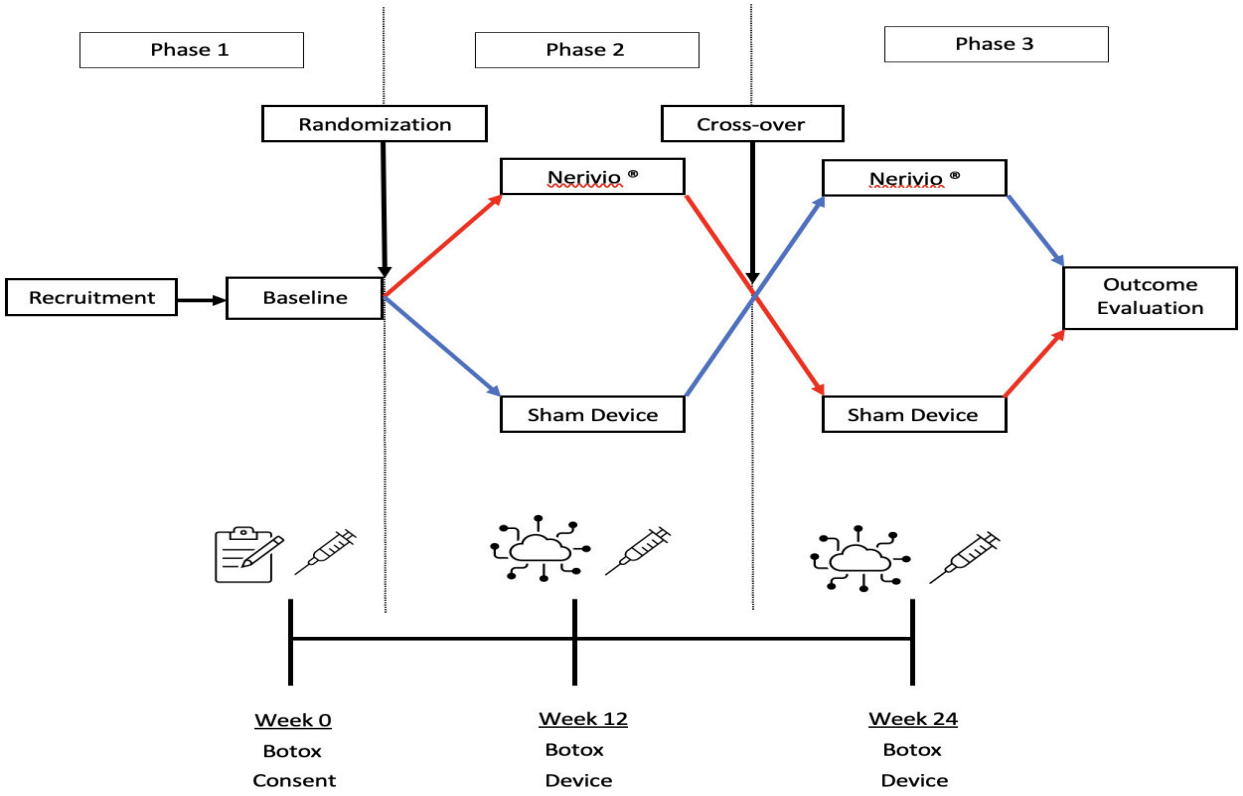
4.1.1 Adults aged 18 to 75 years old
4.1.2 Meet the criteria for *1.3 chronic migraine* based on ICHD3 criteria
4.1.3 Currently receiving onabotulinumtoxinA per PREEMPT protocol for the treatment of chronic migraine
4.1.4 Patient is willing and able to comply with the protocol to the satisfaction of the investigator
4.1.5 Patient has the capacity to provide written, informed consent for themselves

4.2. *Exclusion Criteria*

4.2.1 Participants with an active implanted electrical and/or neurostimulator device (e.g., cardiac pacemaker, cochlear implant).
4.2.2 Participants with congestive heart failure (CHF), severe cardiac or cerebrovascular disease.
4.2.3 Participants with uncontrolled epilepsy.
4.2.4 Pregnant, trying to get pregnant or breastfeeding female participants
4.2.5 Subjects participating in any other interventional clinical study.
4.2.6 Participants with other significant pain, medical or psychological problems that in the opinion of the investigator may confound the study assessments
4.2.7 Participants who have previous experience with the device
4.2.8 Patients with cranial deformities, prior cranial surgeries with violation of the calvarium, or shunt placement
4.2.9 Patients receiving concurrent nerve blocks or trigger point injections within the same visit

5. Methods:

5.1. Study design: Single-center, randomized, single-blind, sham-controlled crossover trial



5.2. Pretreatment phase
Informed consent in English will be obtained prior to enrollment into the study.

5.3. Treatment Phase
Upon receipt of informed consent, the patient will enter phase 1 of the study. This phase is used to determine baseline experience with the PREEMPT protocol and will involve obtaining pre-, intra-, and post-procedural pain intensity levels based on a standard visual analog scale. Subjects will then be contacted the following day to inquire about the presence of post-procedural headache. Following their initial treatment of BoNT-A, subjects will then be randomized to receive either remote electrical neuromodulation with Nerivio ® or stimulation with a sham device for their next BoNT-A treatment and enter phase 2. During phase 2, patients will again receive BoNT-A treatment via PREEMPT protocol at week 12 +/- 7 days (buffer period to accommodate rescheduling) and will also be treated with either Nerivio ® or receive stimulation with a sham device supplied by **Theranica Bio-electronics, Ltd**. Patients will have the device applied 20 minutes prior to starting the Botox procedure with an estimated total time of wearing the device around 40 to 45 minutes. Again, patients will be surveyed regarding their pre-, intra-, and post-procedural pain intensity and will be contacted on the following day re: post-procedural headache. Finally, patients will receive their final treatment of BoNT-A at week 24 +/- 7 days and will receive concurrent treatment with the alternative stimulation setting (either Nerivio ® treatment stimulation or sham stimulation). Pre-, intra-, and post-procedural pain levels and post-procedural headache will be recorded in an identical fashion.

5.4. Conclusion of study
The study ends 24 weeks after consent was obtained (excluding potential buffer time to accommodate rescheduling).

6. Data Collection and Monitoring

6.1. Clinical Assessments
Patients will have received a focused neurological exam at their prior clinic visit and will be surveyed regarding their pre-procedural, intra-procedural, and post-procedural pain, before, during, and after receipt of onabotulinumtoxinA with PREEMPT protocol. Per routine clinical practice, patients will be monitored for 5 minutes post-procedure to ensure lack of acute adverse effects to the procedure.

6.2. Post-procedural headache
Subjects will be contacted on the day following each administration of onabotulinumtoxinA to inquire about the presence of post-procedural headache, defined as a headache that lasts for 4 hours or more and is at least moderate in severity or during which abortive medications are used to treat the patient's head pain.

6.3. Patient History
Patient history will be collected to ensure accurate diagnosis of chronic migraines as well as to document currently prescribed abortive and prophylactic migraine medications. Patient medical history and device history will also be reviewed to ensure no contraindications to device administration.

6.4. Lab Work
None required

7. Outcome Measures

7.1. Primary Outcome Measure
The primary outcome is the reduction in pain intensity measured via Visual Analog Scale (VAS) among patients at the baseline or sham treatment compared to treatment with remote electrical neuromodulation using Nerivio ®.

7.2. Secondary Outcome Measures

7.2.1. Subjects will be contacted on the day following each administration of onabotulinumtoxinA to inquire about the presence of post-procedural headache, defined as a headache that lasts for 4 hours or more and is at least moderate in severity or during which abortive medications are used to treat the patient's head pain.

7.2.5. Any adverse events.

7.3. Statistical Analysis

Subjects will be randomized to treatment vs sham treatment groups utilizing the REDCap. Study data will be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic – Arizona. REDCap (Research Electronic Data Capture) is a secure, web-based

software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (**Harris, 2009; Harris 2019**).

7.3.1 Sample Size Consideration

Primary endpoint: Pain level change from pre-treatment/pre-sham, intra-treatment/intra-sham, and post-treatment/post-sham

A two-sided t-test achieves 80% to infer that the mean difference (between treatment and sham) is not 0 when the total sample size of a 2x2 cross-over design is 80 with an equal number in each sequence (n=40/sequence) when the actual effect size is 0.45 (standardized difference, medium effect size) and the significance level is 0.05.

7.3.2 Statistical Analysis Plan

Summary statistics will be used to describe the patient population's demographics and clinical characteristics. Patients' pain level change and post-procedure headache after each treatment/sham as well as patients' any adverse events will be summarized in descriptive statistics.

Linear mixed model will be used to analyze the primary outcome for 2 by 2 cross-over study design. Treatment group will be the primary predictor in the model while sequence and period will be adjusted in the model.

Generalized linear mixed model will be used to analyze the effect of treatment on the secondary endpoint presence of post-procedural headache. Similarly, treatment group will be used as the primary predictor while sequence and period will be adjusted in the model.

7.3.3 Interim Analysis Plan

Interim analyses: One interim analysis will be conducted after 50% of patients have completed the 24 weeks study period. The interim analysis will include the below stopping rule for efficacy and futility based on Lan-DeMets spending function with O'Brien-Fleming boundaries. Occurrence of adverse events will also be evaluated at the interim analysis.

Accrual	Total Number	Efficacy boundary (Z scale)	Alpha spent	Futility boundary (Z scale)	Beta spent
50%	40	+/- 2.96	0.003	+/- 0.35	0.04
100%	80	+/- 1.95	0.05	+/- 1.95	0.2

8. Potential Risks

8.1. Breach of confidentiality

There is minimal risk associated with the collection and recording of patient medical record numbers to permit review of the patient's medical record.

8.3 Remote Electrical Neuromodulation with Nerivio ®

Nerivo® is a wearable, remote electrical neuromodulation (REN) device controlled by smartphone application that has been cleared for the acute treatment of migraine in adults and adolescents. Thus, the device is non-invasive and non-pharmaceutical. The device is contraindicated in patients with congestive heart failure, severe cardiac or cerebrovascular disease, or poorly controlled epilepsy and should not be used in patients with active implantable disease such as vagus nerve stimulator (VNS), cardiac pacemaker, deep brain stimulator, or cochlear implant due to theoretical ability to disrupt regular function of the device. It should only be applied to healthy skin that is free if cuts, abrasions, burns, infection, or malignancy. It should not be used near metallic implants. Potential adverse reactions include skin rash or redness under the electrodes of the device.

Patients' skin will be examined for integrity prior to placement of the device. Patients who develop skin rash or redness in response to the study or sham device will be excluded from further investigation.

There is no known risk of Nerivio ® interfering with onabotulinumtoxinA efficacy or administration.

Nerivio ® User Manual will be included in supplemental information separate from this protocol.

8.2. OnabotulinumtoxinA administration

OnabotulinumtoxinA is a product of Allergan Pharmaceuticals (BOTOX ®, Abbvie, North Chicago, IL). Botulinum toxin is a neurotoxin produced the bacterium *Clostridium botulinum.* The mechanism of action of botulinum toxin is the inhibition of acetylcholine release at the neuromuscular junction by binding to SNARE (SNAP Receptor) proteins at the synaptic bouton. The pharmacologic mechanism of botulinum toxin prevents the build-up of intracellular sodium ions and subsequent generation of the endplate potential required for calcium channel activation that induces muscle contraction. Botulinum toxin is potentially fatal when absorbed systemically, typically via infection with *Clostridium botulinum* spores (i.e., botulism) or exposure to large amounts of foodborne toxin.

While the mechanism of action of botulinum toxin through inhibition of acetylcholine release at the neuromuscular junction is a sufficient explanation for its effects at reducing spasticity, it is a matter of debate how local, intramuscular injection of the toxin reduces headache frequency and intensity in patients with chronic migraine. Proposed mechanisms involve local uptake and inhibition of proteins known to be involved in migraine pathophysiology such as calcitonin gene-related peptide (**Burstein, 2020**). While further research is required to elucidate its mechanism, onabotulinumtoxinA has been found to be effective at reducing headache burden when applied via the PREEMPT protocol, which involves the injection of 5U into 31 injection sites (total 155U) with the option for additional injections (up to 40U) based on a follow-the-pain strategy and must be administered every 10 to 12 weeks to maintain effect (**Aurora, 2010; Diener, 2010**). In usual clinical practice, patients will receive between 150 and 200U based on vial size made available

by the pharmaceutical company with most patients receiving between 155 and 200U every 10 to 12 weeks.

The risks involved with local onabotulinumtoxinA for the treatment of chronic migraine include temporary increased neck pain, headache, bruising, bleeding, and infection at the injection site. There is a low risk of brow ptosis following administration of onabotulinumtoxinA to the forehead that is temporary. Patients are also informed that there is a Boxed Warning applied to onabotulinumtoxinA regarding the Distant Spread of Toxin Effect that can be life-threatening and involve symptoms similar to systemic absorption of the toxin, namely swallowing and breathing difficulties. Generally, the risk of life-threatening adverse effect is exceedingly rare and is highest in patients receiving the toxin for treatment of spasticity (higher unit amount injected) and in children (BOTOX full prescribing information).

8.3 Steps Taken to Mitigate Risk
Studies are conducted under the supervision of the investigating physicians who are trained and experienced in performing research in human subjects.

Inclusion and exclusion criteria, monitoring, and the clinical protocol are designed to ensure that risks are minimal. Subjects are informed that participation is voluntary, and they may refuse to participate and may withdraw from the study at any time without penalty.

With regard to confidentiality: (1) all subjects will be assigned a study ID number, (2) the link to identifiers will be deleted at the end of the study, (3) data will be stored in REDcap. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves, (4) study data will not be entered in subjects' medical records.

9. Management of Intercurrent Events

9.1. Adverse Experiences
The investigator will closely monitor subjects for evidence of adverse events. All adverse events will be reported and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required.

9.2. Premature Discontinuation
If a subject withdraws from the study, the subject will be replaced to provide the required number of subjects. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study. Data collected from patients who withdraw will be kept for analysis however they will not be included in the primary or secondary outcome measures.

10. Data and Safety Monitoring Plan

Studies conducted in the Department of Neurology follow the Mayo Clinic Institutional Review Board Policies and Procedures. All individuals working on the study are required to read and be familiar with and compliant with the IRB Policies and Procedures. The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of onabotulinumtoxinA for the treatment of chronic migraine. Based on the small size and relatively low risk nature of the protocol, the investigating physicians are involved in the monitoring plan. These individuals will review the

annual summary of adverse events. In addition, they will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

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Supplemental Material – ICHD-3 Criteria for episodic and chronic migraine

1.1 Migraine without aura

Previously used terms:

Common migraine; hemicrania simplex.

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B-D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)[2;3]
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without aura but have had fewer than five attacks should be coded 1.5.1 Probable migraine without aura.
2. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated).

1.2 Migraine with aura

Previously used terms:

Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine.

Description:

Recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes[1]
4. at least one aura symptom is unilateral[2]
5. at least one aura symptom is positive[3]
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
3. Scintillations and pins and needles are positive symptoms of aura.

1.3 Chronic migraine

Description:

Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like[1]) on ≥15 days/month for >3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days/month for >3 months, fulfilling any of the following[2]:
    1. criteria C and D for 1.1 *Migraine without aura*
    2. criteria B and C for 1.2 *Migraine with aura*
    3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis[3;4;5].

Notes:

1. The reason for singling out 1.3 *Chronic migraine* from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).
2. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least one month.
3. Because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*, this diagnosis excludes the diagnosis of 2. *Tension-type headache* or its types.
4. 4.10 *New daily persistent headache* may have features suggestive of 1.3 *Chronic migraine*. The latter disorder evolves over time from 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*; therefore, when these criteria A-C are fulfilled by headache that, unambiguously, is daily and unremitting from <24 hours after its first onset, code as 4.10 *New daily persistent headache*. When the manner of onset is not remembered or is otherwise uncertain, code as 1.3 *Chronic migraine*.
5. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of 8.2 *Medication-*

overuse headache may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic, and should be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded.

Supplemental Material – MIDAS

The Migraine Disability Assessment Test

The **MIDAS** (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS

Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months. Please take the completed form to your healthcare professional.

_____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?

_____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

_____ 4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

_____ Total (Questions 1-5)

What your Physician will need to know about your headache:

_____ A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

_____ B. On a scale of 0 - 10, on average how painful were these headaches? (where 0=no pain at all, and 10= pain as bad as it can be.)

Scoring: After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B).

MIDAS Grade	Definition	MIDAS Score
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

If Your MIDAS Score is 6 or more, please discuss this with your doctor.