Endogenous Modulation and Central Sensitization in New Daily Persistent Headache in Children

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Boston Children's Hospital

CHeRP IRB Additional Protocol Information:

TITLE: Endogenous Modulation and Central Sensitization in New Daily Persistent Headache (NDPH) in Children

A. Specific Aims/Objectives

Primary Aims

Aim 1.1: Psychophysical Characterization of NDPH: To define differences in altered modulatory systems using offset analgesia as well as detailed clinical descriptors as part of a clinical evaluation and chart review in well characterized NDPH pediatric patients in the symptomatic and recovered state.

- *We hypothesize that there will be significant differences and psychophysical parameters of offset analgesia between the symptomatic and recovered state. Specifically, there will be less pain inhibition as measured by the OA paradigm in the symptomatic patients.*

Aim 1.2: Treatment Effects in NDPH: To define the effects of naltrexone on patients with NDPH using offset analgesia.

- *We hypothesize that there will be significant differences in offset analgesia in the pre vs. post treatment groups.*

Aim 1.3: Comparing Offset Analgesia in NDPH patients to Healthy Controls: To determine whether the offset analgesia in patients with NDPH is impaired when compared to the OA responses of healthy controls included in IRB protocol (P00025596).

- *We hypothesize that OA in patients with NDPH will be significantly impaired compared to the healthy controls.*

Secondary Aims

Aim 2.1: Laboratory Markers of Disease Persistence: To define the potential of pain-related inflammatory markers in predicting disease persistence. Specifically, a cytokine panel consisting of Interleukin 1 Beta, Interleukin 6, Interleukin 8, and Tumor Necrosis Factor will be collected for evaluation.

- *We hypothesize that Inflammatory Markers will also define differences in responders vs. non-responders.*

Aim 2.2: Brain Markers of Disease Resilience: To evaluate brain markers of disease state through an evaluation of resting state endogenous modulatory systems (viz., cingulate -> PAG connectivity).

- *We hypothesize that specific functional brain connectivity will define significant differences in modulatory systems (viz., Anterior Cingulate -> PAG Connectivity) in responders vs. non-responders.*

Aim 2.3: Brain Markers of NDPH Compared to Healthy Controls: To compare the fMRI imaging and brain markers of patients with NDPH to healthy controls.

Future Directions

Genetic Analysis: To identify genetic variants associated with NDPH recovery vs. persistence, a single-nucleotide polymorphism (SNP) microarray will be designed based on known variants associated with chronic pain. Saliva samples will be collected during the first study visit, then de-identified and stored for candidate gene association studies at a later time. All HIPAA identifiers will be removed from the samples prior to analysis, and genetic data will be identified only by anonymous study ID. Individual results will not be returned to subjects/families.

B. Background and Significance

New daily persistent headache (NDPH) is a primary headache disorder with a reported prevalence of 3.5% in adolescents (Lipton et al., 2011). NDPH is characterized by the daily and unremitting headache pain patients experience with a distinct onset (IHS, 2013). Patients with NDPH have compromised academic performance, school absence, anxiety, depressed mood, sleep impairment, family disruption, and high health care costs (Baron & Rothner, 2010; Evans & Seifert, 2011; Rabner et al., 2017). Despite the known significant impairment associated with NDPH, the process by which some patients with NDPH recover within months while others do not is unknown. With the goal of enhancing the clinical definition of NDPH, we will describe differences between patients with NDPH who recover within a few months and those who do not.

Additionally, little is known about which medications effectively manage and treat NDPH (Rozen, 2014). One proposed medication that may benefit children and adolescents with NDPH is low-dose naltrexone. Naltrexone is an anti-inflammatory agent, similar to the opioid antagonist naloxone (Younger, Parkitny, & McLain, 2014). Naltrexone is an effective treatment for opioid addiction (Younger et al., 2014), however, it was recently discovered that when taken in low doses (1/10 of the typical dose) naltrexone is capable of reducing the severity of chronic pain symptoms (Younger, Noor, McCue, & Mackey, 2013). By acting on glial cells in the nervous system as well as other receptors in the brain, naltrexone is capable of exerting analgesic effects (Younger, Parkitny, & McLain, 2014). With this analgesic property, it has been speculated that low-dose naltrexone may be an effective treatment for the management of several chronic pain conditions, including headache.

Low-dose naltrexone has the ability to mitigate pain symptoms in individuals with chronic pain. The effects of low-dose naltrexone on individuals with fibromyalgia have been extensively studied. In a pilot study conducted by Younger and Mackey (2009), when taken in low doses, naltrexone reduced self-reported daily pain and fatigue in patients with fibromyalgia. In an attempt to replicate these findings, Younger and colleagues (2013) again examined the effects of low-dose naltrexone in the treatment of fibromyalgia. Their study showed that, after a twelve-week period, women with fibromyalgia who were treated with naltrexone reported a reduction in pain in comparison to those who were treated with placebo (Younger, et al. 2013).

Chopra and Cooper (2013) present two case studies in which low-dose naltrexone was used to treat Complex Regional Pain Syndrome (CRPS). Treating CRPS with naltrexone mitigated the

symptoms in a 48-year-old male and eliminated the symptoms in a 12-year-old female, with notably no side effects from taking low-dose naltrexone in either case (Chopra and Cooper, 2013). Low-dose naltrexone has also been used to treat pain associated with Crohn's disease with promising outcomes (Smith et al., 2007). Per self-report diary over a three month period, low-dose naltrexone was found to greatly decrease symptoms associated with the disease and increase quality of life in a sample of patients 18-years and older (Smith, et al., 2007). Although more research must be conducted to evaluate long-term effects of using low-dose naltrexone, prior studies show that there are little short-term consequences associated with using this drug as a form of treatment for chronic pain symptoms. We aim to assess the efficacy and safety of low-dose naltrexone in the treatment of patients with NDPH.

C. Preliminary Studies

This will be a new project with no ongoing research in patients with NDPH. Use of OA and fMRI imaging are currently investigated in other patient populations at BCH, including in healthy control populations and will be used to compare with the NDPH sample from this protocol (OA data - P00025596; fMRI data - P00019376).

D. Design and Methods

(1) Study Design

The sample size will include 150 participants, consisting of 100 patients with NDPH and 50 healthy controls (non-headache patients) visiting the Pediatric Headache Program, ages 10-17 years old. Eligible patients will be identified from a review of medical records for patients returning to the Pediatric Headache Program for follow-up care. Age and gender matched healthy controls will be recruited from the greater Boston area, including siblings of patients, children from local schools, children previously enrolled in other BCH studies as healthy controls, and per advertising per wall brochures, Craig's list, and per the MBTA in Boston.

The design is both cross-sectional and longitudinal as different participants will participate in the study for different amounts of time. Healthy controls will participate in only one visit while patients with NDPH will participate in two or three visits. The study contains three components: study visits and evaluations, a naltrexone trial, and an imaging component. All participants will undergo the initial evaluation, with NDPH participants participating in one to two other evaluations. Study visits include a physical and neurological evaluation, a blood draw, and an evaluation utilizing offset analgesia. Participants with NDPH will begin a trial of low-dose naltrexone at Visit 3. The trial will last for three-months and conclude at Visit 4. Select participants with NDPH will also complete the imaging component consisting of an fMRI brain scan. See "Study Timeline" section for complete details on each task and when they will occur.

Of note, it was particularly challenging to recruit healthy controls for this study, particularly due to the COVID-19 pandemic. Because healthy control data is such a valuable part of this study in order to better understand how the NDPH population differs from typical adolescents, healthy control OA data from P00025596 and healthy control fMRI data from P00019376 will be used to compare with the NDPH sample data.

(2) Patient Selection and Inclusion/Exclusion Criteria

Eligibility criteria include: 1) Patients meeting clinical ICHD-3-Beta classification for NDPH; 2) Age 10-17 years, all sexes, races, and ethnicities; 3) English speaking; 4) Able to wean off headache prophylactic medication 2 weeks prior to start of Naltrexone trial (patient

will still be able to use abortive medication throughout the duration of the study); on stable psychotropic medication for mild anxiety and/or mood disturbance for 2 weeks.

Exclusion criteria include: 1) Children and adolescents with significant chronic medical illness: CNS (secondary headache disorder other than mild TBI); Cardiac, Pulmonary other than stable asthma, Metabolic, Renal, Hepatic; 2) Significant psychiatric disorder, such as major depression, somatization disorder, and psychosis; 3) Pregnancy; 4) Intellectual delay or cognitive limitations precluding completion of questionnaires or following instructions.

(3) Description of Study Treatments or Exposures/Predictors

- Low-dose naltrexone: Participants with persistent NDPH will once daily take 4.5mg of naltrexone orally for three months.
  - Naltrexone is an anti-inflammatory agent, similar to the opioid antagonist naloxone. Naltrexone is an effective treatment for opioid addiction (Younger et al., 2014), however, it was recently discovered that when taken in low doses (1/10 of the typical dose) naltrexone is capable of reducing the severity of chronic pain symptoms (Younger et al., 2013). A similar drug, methylnaltrexone, has indications for use in children with opioid induced constipation.

(4) Definition of Primary and Secondary Outcomes/Endpoints

Primary Outcomes

1. A change in pain intensity scores and headache frequency- The NRS, numerical rating scale will be used, with a pain score between 0 to 10, with 0 being no pain and 10 being worst pain imaginable, for NDPH patients, chronic and recovered, completing 3 months of naltrexone, as compared to a cohort of patients with NDPH on standard treatment.
2. A difference in response (self-reported pain intensity-NRS) regarding heat pain between NDPH patients, chronic and recovered, and controls using the OA paradigm.
3. A difference in laboratory testing, including inflammatory markers, in patients with NDPH, chronic and recovered, and controls, indicating a difference in modulatory tone.
4. A difference in default network connectivity in NDPH patients, chronic and recovered, and controls.

Secondary Outcomes

1. A change in functional disability scores - The functional disability inventory (FDI) will be used to assess differences in disability pre- and post-naltrexone treatment, as well as between recovered and persistent patients.
2. A change in self-perceived pain sensitivity - The Pain Sensitivity Questionnaire (PSQ) will be used to assess differences in pain sensitivity pre- and post-naltrexone treatment, as well as between recovered and persistent patients.

(5) Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

<u>Offset Analgesia</u>:

Offset analgesia will be examined by applying a 3-tempeature paradigm described previously validated in adults volunteers, using individualized test temperatures to ensure that children are not exposed to greater than moderate heat pain, defined as a rating of 50mm out of 100mm on an electronic visual analog scale (eVAS). Testing will be completed using the

Medoc TSA-2001 device (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel). The thermal sensory analyzer operates by a microcomputer-driven 3 cm x 3 cm (9 cm^2) Peltier contact thermode. The entire thermode- stimulating surface is placed in contact with the skin on the volar surface of the non-dominant forearm and secured by a Velcro band without stretch. The thermode baseline temperature is kept at 32^0C (room temperature) and stimulation temperature has a potential range of 0–50^0C for safety reasons. A preset computer-controlled temperature paradigm is programed to deliver a specific temperature patterns. During all tests, patients will rate heat pain intensity continuously in real time using the linear, electronic visual analogue scale (eVAS). Patients will use their dominant hand to operate sliding knob of the eVAS with the following two anchors on 0 to 100 mm line. The left endpoint designated as “no pain sensation” (0 mm) and the right endpoint as “most intense pain sensation imaginable” (100 mm). Patients will be instructed to move the slider in proportion to their pain intensity in real time during testing.

Testing Procedures

On the day of testing and after obtaining consents from a guardian and assent from the child, a single researcher will perform all sensory tests in a quiet room, temperature 20–23^0C, with the patient comfortably seated or reclined, and the non-dominant forearm skin site will be exposed to ambient temperature for 10–15 min before testing. Patients will not be permitted to view the QST computer screen. The volar forearm will be divided into three zones and the probe will be moved to a new zone for each test with 2-3 min breaks between tests to avoid adaptation and sensitization of the skin. Prior to testing, children will be exposed to 2-3 training stimuli of 42-44^0C for 5 seconds to familiarize themselves with the stimulus and electronic VAS. Then, patients will participate in a test to determine the individualized test temperature that will be used for dynamic, constant and control tests.

1. **Identification of the individualized test temperature**: First, individualized test temperatures for the offset analgesia paradigm will be determined. We will determine the lowest temperature that evokes moderate pain, defined as an eVAS score of 50mm on a scale of 0mm (no pain) to 100mm (most intense pain sensation imaginable). This is equivalent to a score of 5 on a scale of 0-10 on a numeric rating scale, i.e., 50% of maximal heat pain perceived by individual patients. Each temperature stimulus will be held for 5 seconds, and then return to room temperature for 30 seconds before the next temperature is applied. The first temperature stimulus will be set to 42^0C (a median threshold for heat pain detection temperature i.e., at 50th percentile for children ages 7-15 years). Then the temperature will be increased by 1^0C increments, every 30 seconds until the lowest temperature that evokes an eVAS of 50mm is achieved. The maximum temperature will be set to 49^0C. Thus, if a temperature of 49^0C does not evoke moderate pain (50 mm rating on a scale of 0-100 mm on the electronic VAS) in a patient or healthy control subject the test will be terminated to avoid potential skin burn and patient or subject will be excluded from this study procedure. With this method of testing, no patient or subject will be exposed to more than what they perceive as moderate pain. We previously found that the normal reference interval for heat pain threshold (the point at which mild pain is felt) for children ages 6-17 years is 39 – 46^0C (25th – 75th percentiles) and 35.6 – 50.0^0C (2.5th - 97.5th percentile), and thus we begin our assessment of test temperatures at the median threshold of 42^0C.

2. **Response to a *Dynamic Test* Stimulus**: A reduction in self-reported pain intensity when the test temperature is applied for 5 seconds, raised by 1^0C for 5 second, reduced by 1^0C, and held for 20 seconds. Pain is assessed throughout the test in real time using the computerized eVAS. This test will be completed three times.

3. **Response to a *Controlled Stimulus* on forearm skin**: A reduction in self-reported pain intensity when the test temperature is applied for 5 seconds, raised by 1^0C for 5 second, reduced to 32^0C, and held for 20 seconds. Pain is assessed throughout the test in real time using the computerized eVAS. This test will be completed three times.

4. **Response to a *Constant Test* stimulus on forearm skin**: A reduction in self-reported pain intensity when the test temperature is applied at a constant rate for 30 seconds. Pain is assessed throughout the test in real time using the computerized eVAS. This test will be completed three times.

Questionnaires:

1. Functional Disability – The Functional Disability Inventory (FDI; Claar & Walker, 2006) assesses children's self-reported difficulty in physical and psychosocial functioning due to their physical health. The measure consists of 15 items concerning perceptions of children's activity limitations during the past two weeks. Children rate these activities on a 5-point scale ranging from 0 ("No trouble") to 4 ("Impossible"), and total scores are computed by summing the items. Scores on the FDI range from 0 to 60, with higher scores indicating greater disability.

2. Pain Sensitivity – The Pain Sensitivity Questionnaire (PSQ; Ruscheweyh et al., 2012) is a 17-item measure where respondents answer how painful a daily life situation would be for them. Items are rated on a scale ranging from 0 ("not painful at all") to 10 ("worst pain imaginable"). 14 of the items ask about situations that the majority of healthy subjects would rate as painful (e.g., bump your elbow on the edge of a table; burn your tongue on a hot drink). Three items describe situations that are normally not rated as painful by healthy subjects (e.g., taking a warm shower). These items are interspersed between the "painful" items to serve as non-painful sensory reference for the subjects and are not included in the total score.

(6) Study Timeline (as applicable)

As the study timeline differs between participant groups, we have outlined the specific timeline for each group.

Participants who are healthy controls:

These participants will be in the research study for the initial visit only. The visit will last 2 hours and consist of the activities noted in the table below for "Visit 1: Initial Evaluation." Following consent, participants will be briefly evaluated by a physician or nurse practitioner as part of a routine neurological and physical exam. They will then be evaluated using offset analgesia. Next, they will be asked to collect a saliva sample and complete a few questionnaires on pain sensitivity and functional disability. Finally, participants will have blood drawn (no more than 15ml) from one arm. There are no follow up visits for healthy controls and they will receive their compensation for participating in the study before they leave the hospital.

Due to trouble in recruiting healthy controls, particularly as a result of the COVID-19 pandemic, we will use the OA healthy control data from IRB protocol P00025596 and fMRI healthy control data from IRB protocol P00019376 in order to compare the NDPH patients to healthy controls.

Participants with New Daily Persistent Headache:

Participants with NDPH will be in this research study for about 4-7 months. The table below details the full timeline of participants completing the entire study. It is important to note that of those 7 months, they will only take the drug, low-dose naltrexone, for 3 months.

The first visit will last 2 hours and consist of the activities noted in the table below for “Visit 1: Initial Evaluation.” Following consent, participants will be briefly evaluated by a physician or nurse practitioner as part of a routine neurological and physical exam. They will then be evaluated using offset analgesia. Next, they will be asked to collect a saliva sample and complete a few questionnaires on pain sensitivity and functional disability. Finally, participants will have blood drawn (no more than 15ml) from one arm.

The next visit will consist of a phone call lasting no more than 15-minutes that covers the activities noted in the table below for “Visit 2: 3 Month Post Initial Evaluation.” On this call, participants will discuss their current headache health with a member of the research team. Based on this conversation, participants will be categorized into two groups: “improved” or “persistent”. Both groups will return for the next visit one month later. “Improved patients” will continue their current care, however, “persistent” patients will wean off all daily/preventative medication for the next month prior to the third visit.

Participants with NDPH who are categorized as “Improved”:

The third visit will last 2 hours and consist of most of the activities noted in the table below for “Visit 3: 1 Month Post Phone Call.” The visit will start with a brief evaluation by a physician or nurse practitioner as part of a routine neurological and physical exam. Participants will then complete a few questionnaires on pain sensitivity and functional disability and again be evaluated using offset analgesia. Finally, they will have blood drawn (no more than 15ml) from one arm. This will conclude the visit for most participants. A portion of “improved” participants will randomly be selected to participate in the imaging component of the study on the same day as the third visit (timeline detailed in section “Imaging Component Participants”).

Participants with NDPH who are categorized as “Persistent”:

The third visit will last 2 hours and consist of most of the activities noted in the table below for “Visit 3: 1 Month Post Phone Call.” The visit will start with a brief evaluation by a physician or nurse practitioner as part of a routine neurological and physical exam. During this meeting, the physician or nurse practitioner will discuss the trial of low-dose naltrexone and instruct the participant on when to take it. They will then complete a few questionnaires on pain sensitivity and functional disability and again be evaluated using offset analgesia. Finally, they will have blood drawn (no more than 15ml) from one arm. This will conclude the visit for most participants. A portion of “improved” participants will randomly be selected to participate in the imaging component of the study on the same day as the third visit (see section “Imaging Component Participants”).

The fourth and final visit will last 2 hours and consist of the activities noted in the table below for “Visit 4: 3 Month Post Visit 3.” The visit will start with a brief evaluation by a physician or nurse practitioner as part of a routine neurological and physical exam. Participants will then complete a few questionnaires on pain sensitivity and functional disability and again be evaluated using offset analgesia. Finally, they will have blood drawn (no more than 15ml) from one arm. This will conclude the study for all participants.

Imaging Component Participants:

A selection of participants will randomly be selected to participate in the imagine component of the study on the same day as the third visit (referred to in the table below as “Visit 3: 1 Month Post Phone Call”). The imagine component will add an additional 45 minutes to the visit and consist of a routine, resting state fMRI brain scan. fMRI healthy control data from IRB protocol P00019376 will be used in order to compare the fMRI data for NDPH patients to healthy controls.

Study Visit Timeline (NDPH)	Visit 1: Initial Evaluation	Visit 2: 3 Month Post Initial Evaluation (Phone Call)	Visit 3: 1 Month Post Phone Call	Visit 4: 3 Month Post Visit 3
Consent /Assent	**X**			
Physical/Neurological Exam	**X**		**X**	**X**
Offset Analgesia	**X**		**X**	**X**
Saliva Sample	**X**			
Questionnaires	**X**		**X**	**X**
Blood Draw	**X**		**X**	**X**
Medication Changes		**X (Possible end of prophylactic/daily medication)**	**X (Start of Naltrexone)**	**X (End of Naltrexone)**
MRI (only for a portion of participants)			**X**	

E. Adverse Event Criteria and Reporting Procedures

There are potential adverse events associated with naltrexone. Some commonly reported side effects include anxiety, nervousness, trouble sleeping, headaches, abdominal cramping, diarrhea, gastrointestinal distress, nausea, irritability, loss of appetite, drowsiness, joint stiffness, and nasopharyngitis (common cold). Taking naltrexone while using high doses of opioids can cause serious injury, coma, or death. Patients will be advised of all of these adverse events in the consent form and again prior to receiving naltrexone during Visit 3. Patients will also be advised to report any adverse events to the research team and in the case of a serious reaction to call 911 and/or proceed to the emergency room.

It is important to note that these are the potential adverse events associated with naltrexone administered at its normal dosage, and not in a low-dose which will be taken in this study. Prior studies detailing the use of low-dose naltrexone have reported adverse events related to sleep (i.e., insomnia, more vivid dreams), nausea (Smith et al., 2007; Younger & Mackey, 2009; Younger et al., 2013) and in one study headaches (Younger et al., 2013). One case series reported no adverse events (Chopra & Cooper, 2013). If a participant reports an adverse event, the PI and the Data and Safety Monitoring Board (DSMB) will both be immediately notified. The PI will speak with the participant and, depending upon the severity of the adverse event and the participant's desire, discuss the continuation or termination of their participation in the study.

It is also possible that an abnormal finding may be found on an fMRI. If this occurs, Dr. LeBel (PI) will call or meet with the participant to discuss the findings and refer the family to the proper Boston Children's Hospital service if needed.

Additionally, due to the neurological/physical examination and the questionnaires administered, there is a possibility that a participant may become distressed. If this occurs, they will be given the option of stopping the study. Dr. LeBel (PI) and staff psychologist, Dr. Kaczynski (co-PI), will be available by page and phone for consultation regarding any participant that may be experiencing distress. Should additional mental health support be required, patients and families will be referred to the appropriate Boston Children's Hospital service. If there is any indication of risk for harm to self or others, a risk assessment will be conducted and a mental health clinician will decide on the best course of action to ensure the safety of the child or parent. To deal with potential discovery of

child abuse, the Child Protection Team at Children's Hospital will be consulted and a 51-A filed in accordance with that consultation.

F. Data Management Methods

All patients will be assigned a unique identifier that will not be linked to any patient identifying information. Data will initially be collected in case report forms and then entered into a secure REDCap database. Any research information collected during the study on paper forms will be stored in locked cabinets with access limited to the PI and research personnel associated with the study. All health information is protected by HIPAA (Health Insurance Portability and Accountability Act) and all health records are kept confidential. Patient's birthdate, name, and all other identifying information will be removed when analyzing and reporting the data. Any personal identifying information will be stored separately from other information the patient provides and no personal identifying information will be reported in any publications or presentations. Identifying information will be kept in a password protected and secure file with limited access by research personnel. Once data collection and compliance mandates are complete, identifying information will be destroyed.

Due to trouble in recruiting healthy controls, particularly as a result of the COVID-19 pandemic, we will use OA healthy control data from IRB protocol P00025596 and fMRI healthy control data from IRB protocol P00019376 in order to compare the NDPH patients to healthy controls. The PI's of those two protocols are also co-investigators of this protocol and will internally run the analyses from the two respective datasets, and only aggregated post-comparison results will be shared with the study team. No de-identified data will be shared or compared in any way between protocols.

G. Quality Control Method

Data quality control will be assured through automated and manual methods. The study database enhances data quality through required entry fields for critical data and automatic flags for missing or out of range data. Efforts will be made to minimize data entry error by the development of a user friendly database. All data entry will be double checked with source files. QST testing for OA will be monitored by Dr. Sethna, senior researcher in QST methodology. fMRI data will be monitored by Dr. Borsook, senior investigator in Pain Imaging.

H. Data Analysis Plan

We will analyze pain scores (NRS), FDI and PSQ scores as continuous variables. Differences of these parameters from baseline will be the outcomes variables. The differences in pain, FDI, and PSQ scores will first be tested for normality. Assuming normality, t-tests will be conducted to investigate the differences between the two randomized groups. If data does not appear to be normal, Wilcoxon Rank Sum Tests will be performed in contrast to t-tests. Descriptive statistics will be calculated in order to summarize socio-demographic characteristics of study participants. Frequency tables will be generated to describe gender, psychological and pain related comorbidities, history of injury including pain duration, previous treatment methods and interventions. Similarly, frequency tables will be generated to depict physical exam characteristics. Continuous characteristics such as age and BMI will be tested for normality using the Shapiro-Wilk test. Continuous characteristics will be summarized using mean and standard deviation if the distribution appears normal, or will be summarized using median and interquartile range if the distribution does not appear normal. We will evaluate baseline differences between those with persistent NDPH, with recovered NDPH and healthy controls across various outcome measures (pain intensity, headache frequency, FDI, PSQ) as well as OA and inflammatory markers, using chi-square and t-test for categorical and continuous variables, respectively. Additionally, differences in the same measures will also be assessed pre- and post-naltrexone treatment.

I. Statistical Power and Sample Considerations

In order to detect a moderate effect in the difference in pain scores pre- and post-naltrexone treatment, with an α of 0.05 and a β of 0.8, we will need a sample size of 50 subjects per group. With the consideration of NDPH subject dropout, we estimate a sample size of 160 subjects in total, 55 per NDPH group and 50 controls. We propose 3 years for completion, including imaging.

J. Study Organization

Not applicable as data will only be collected at the Pediatric Headache Program, located in the Waltham satellite location of Boston Children's Hospital. The PI (Alyssa LeBel, MD) is the director of the clinic and will provide oversight and guidance for all study participants and personnel.

K. References

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