Version

1.1

IRB PROTOCOL

EH18-128: Examining the role of improved NSAID management in treating dysmenorrhea NCT03697720, May 31 2018

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Examining the role of improved NSAID management in treating dysmenorrhea

Gynecology Research Lab GyRL

Chapter 1

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Overview:

Many of the women experience severe menstrual pain, yet undermanage their pain level by not taking a sufficient amount of NSAIDs. Notably, biochemical analyses demonstrate that the administration of naproxen prior to the initiation of the COX-2 cascade results in nearly complete suppression of prostaglandin synthesis; attempting to block synthesis afterwards only leads to a gradual and incomplete suppression.[1] The single, but underpowered trial, comparing menstrual pain relief between prophylactic versus response use to pain with ibuprofen did not find a difference.[2] It is possible that differences in prophylactic use of naproxen and ibuprofen could be due to different preferential binding to COX-1 and COX-2 receptors. Aside from this trial, clinical investigators have not sufficiently investigated prophylactic use of NSAIDs prior to the onset of menses. Although an educational trial regarding prophylaxis did demonstrate increased patient knowledge, reduction of menstrual pain was not evaluated.[3] Therefore, in the present study we will establish whether prophylactic and adequate dosages of Naproxen are capable of reducing menstrual pain more than response use. Secondly, we will establish whether reduction of menstrual pain with optimized naproxen use can reduce bladder pain via cross-organ sensitization or central sensitization. We hypothesize that cross-organ sensitization (**COS**) is the mechanism by which dysmenorrhea may lead to some forms of chronic pelvic pain. Uterine inflammation during menstruation likely contributes to chronic pelvic pain (CPP) by triggering neurogenic inflammation in adjacent organs.[4] This COS has been demonstrated with experimental injury and infection in animal models.[5,6] Our prior findings discussed above[7,8] motivate our present central hypothesis: *dysmenorrhea produces CPP via repetitive COS episodes*.

In our ongoing study looking at the relationship between dysmenorrhea, COS and CPP (EH13-094), we planned to determine whether oral contraceptive pills (OCPs), by alleviating menstrual pain could reverse the development of COS. However, our interim analyses of participants in this study identify that many are unwilling to initiate OCPs due to the perceived side effects and fear of hormones. Other interventions to reduce the development of COS also plausibly exist, notably NSAIDs. Therefore, we propose to re-enroll many of the participants from EH13-094 who gave permission for future contact. We will utilize their baseline assessment visit data in order to establish whether naproxen can improve menstrual and bladder outcomes. After consent, prior data will be linked with the current study. We will also open this study to new participants who will be asked to perform a baseline visit (bladder test, pressure tests, EEG, questionnaires and blood draw). Participants will be invited to an open label (non-randomized) prospective trial of naproxen. After six to eight months of diary data, urine monitoring, and blood samples, a repeat visit (bladder test, pressure tests, EEG, questionnaires, and blood draw) will be conducted. The majority of the testing details below have been previously approved for the ongoing study EH13-094.

Additionally, we will investigate whether mechanisms involved in pain sensitivity predict responses to effectiveness of NSAID treatment for menstrual or bladder pain. Several studies identify that women with menstrual pain have central sensory processing abnormalities akin to what is observed in women with chronic pelvic pain states.[9–11] Focused investigation into gynecological risk factors for bladder pain syndrome is of particularly high value, as it more commonly affects women [12], and current treatments, such as pentosan polysulfate,[13] amitriptyline, [14] or cystoscopic hydrodistension[15] are only modestly effective. The limited efficacy of these treatments reflects the multifactorial mechanisms underlying BPS, particularly in later stages, which may include cross-organ sensitization, central nervous system sensitization, mucosal inflammation, and neuropsychological factors.[16] One underlying hypothesis for this finding is that repetitive episodes of

dysmenorrhea promote cross-organ or central sensitization. This is supported by clinical observations[17] and experimentally in animal models of provoked uterine inflammation.[6] Mechanisms involved in central pain modulation can be evaluated with conditioned pain modulation and pressure pain testing[10,18] and both will be used in this proposal. Additionally, we will look at neural mechanisms using audio and visual tasks[19] with EEG. We will determine whether baseline mechanisms are correlated with menstrual and bladder outcomes. The within subject design also allows us to determine if changes in mechanisms (baseline vs repeat visit) are associated with better outcomes.

Study participants

Inclusion Criteria:

Reproductive-age women (age 18-45) with dysmenorrhea will be recruited. Cases will have: a) average menstrual pain ≥ 5/10 (0=no pain and 10=the worst imaginable pain) on at least one day during menses or during withdrawal uterine bleeding from cyclic OCs without painkillers, b) menstrual pain in the region between the umbilicus and the perineum, above the level of the inguinal ligament, and c) indication the participant has attempted to resolve pain by medical means (including NSAIDs and/or OCPs). In the circumstance that a participant originally assigned to the dysmenorrhea group does not reach a pain of 5 on any days on the daily diary, this will be handled on a case-by-case basis particularly if they used a continuous around-the-clock, effective pain treatment regimen. Participants who endorse bladder symptoms (subclinical urgency, frequency, bladder pain) on the phone screen or bladder symptoms as reported in EH13-094 will be preferentially recruited (at least 50% of enrolled participants); those who do not endorse bladder symptoms may be determined ineligible. They must not have a formal urological diagnosis such as overactive bladder or painful bladder syndrome.

Exclusion criteria:

Includes: a) presence of active pelvic or abdominal malignancies (primary or metastatic), b) absence of regular menses (including current pregnancy, recent pregnancy, or active breast feeding), c) active genitourinary infection in the last four weeks, d) unable to read or comprehend the informed consent in English, e) unwilling to complete study procedures, and f) presence of hypertension or risk for developing hypertension, g) unwillingness to take naproxen and/or placebo, h) or contradictions to taking naproxen (allergies, kidney disease, anemia, alcoholism, cardiovascular disease, stomach or intestinal ulcer or abnormal liver function). Participants with a history of epilepsy will not complete the visual unpleasantness task.

Recruitment:

Participants will primarily be recruited based on prior participation in the parent study (EH13-094), which has currently more than 100 potential participants. Additional recruitment may occur from NorthShore's clinical sites in the Chicago-area and from the community through advertising in: NorthShore University HealthSystem's outpatient clinics; web-based advertising; posters and flyers in local businesses (coffee shops, athletic clubs) and on college campuses; referrals

from local gynecologists; and the Illinois Women's Health Registry based at Northwestern University's Feinberg School of Medicine. All flyers and ads will be IRB approved. We will use IRB approved ads from our Recruitment Registry (EH16-117) that informs participants about any of our open studies in our lab. Participants may call our research hotline directly, respond to our online pre-screen, or after they indicate interest and give permission, their doctor will send us their contact information and a research coordinator will call the patient to formally assess eligibility using a phone screen. At the end of the phone screen, participants will be asked if we have permission to put their phone screen and contact information into our recruitment registry (EH16-117).

Phone Screen

All callers will complete a phone screen to assess eligibility before being scheduled for a screen visit. At the end of the phone screen, all callers will be asked if we have their permission to keep their phone screen information and contact them for future studies. Participants who indicate yes will be added to our recruitment registry (EH16-117) study upon study closeout. Eligible callers will be scheduled for a screen visit. We may attempt to match groups for age and demographics. Thus, in some cases, eligibility on the phone screen may vary based on the study's current need for individuals with certain demographics for each group. We may also require dysmenorrhea participants to endorse bladder symptoms on the phone screen in order for them to be eligible to come in for a screen visit. During the phone screen, we will discuss when their last period occurred and when they anticipate their next period to schedule the study visits. Participants will be instructed not to donate blood before the study visit to avoid excessive blood draw. Participants will receive directions from well-known medical educational web sites (such as https://www.mayoclinic.org/diseases-conditions/menstrual-cramps/ , https://www.webmd.com/women/menstrual-cramps). Our trial is in consensus with expert recommended medical guidelines that are suggested on these web sites.

Study Visits

We will perform 3-4 study visits: a screen visit, a baseline study visit, a blood draw study visit, and a follow-up study visit. Participants that have participated in EH13-094 in the last 12 months will not need to participate in the baseline study visit as the data was collected during the EH13-094 assessment visit.

Consent

Informed consent will be obtained by a trained research assistant at the screen visit before any questionnaires or study procedures are completed.

Questionnaires

At the screen, baseline and follow-up visit (either in person or over the web using a REDCAP, secure interface) participants will complete the following questionnaires: a) complete medical, surgical, and gynecological history, and b) a psychosocial assessment using short-form PROMIS instruments (pain behavior, pain interference, fatigue, sleep, anxiety, depression, physical function, satisfaction with participation in social roles, and 10 item global health scale).[20] Participants will also complete the following pain rating questionnaires (the Interstitial Cystitis Problem and Symptom Indices, the Pain Catastrophizing Scale, Revised Short-form McGill Pain Inventory[72] and MIDAS headache questionnaire.)[67] These scales have been linked to pain intensity and quality of life

in CPP sufferers, and catastrophizing (rumination, magnification, and feelings of helplessness about pain) is a well-validated intervention target for many cognitive-behavioral approaches for chronic pain.[21–24] Validated, CPP-specific assessment tools will be used to characterize IBS (Rome III criteria)[25] and bladder pain symptoms (Genitourinary Pain Index).[26] Subjects will also complete the Female Sexual Function Index (FSFI)[68] and Brief Symptom Inventory (BSI)- based questionnaire containing 6 somatization questions selected from the BSI-18[69] plus a vision question, and the Complex Medical Symptoms Inventory (CMSI)-General, Fibromyalgia Symptoms, Fatigue, and Vulvodynia sections.[70,71]

Rapid Bladder Test

At the screen visit, all participants will be asked to undergo a "rapid bladder test." Participants will be asked to rate their bladder pain on a 0-100 VAS scale when they reach "first urge." If a participant arrives to the visit already at first urge, we will have them rate their pain and if not $\geq$ 10 we will wait 15 minutes past first urge and have them rate their pain again. This is because the participant may not have been focusing on the feeling of their bladder. Participants not already at first urge will be encouraged to drink water (at least 20 oz) during the screening visit until they reach first urge at which point a pain rating will be attained. After they reach first urge, they can go to the bathroom and leave their urine sample.

Pelvic Floor Exam:

The baseline and follow-up visit includes internal vaginal pressure-pain threshold testing, which is similar in nature to the pelvic floor portion of a gynecological exam. Thus, for participants who have never had a gynecological exam, a study nurse or study doctor may complete a simple exam of the pelvic floor at the screen to promote understanding of the internal vaginal pressure-pain threshold testing that will be completed at the baseline and follow-up visit. This ensures that the integrity of our data is not biased by unfamiliar experience. Participants will be asked whether they have ever had a gynecological exam on the phone screen and a simple exam of the pelvic floor for those that say they have never had an exam will be scheduled into their screen.

Creatinine Test:

A creatinine test will be conducted to check for kidney function for all participants. This will be done via blood draw at the screen visit.

Menstrual Diaries:

All participants will be asked to complete daily diaries for a full menstrual cycle to assess their baseline scores.

Baseline Visit:

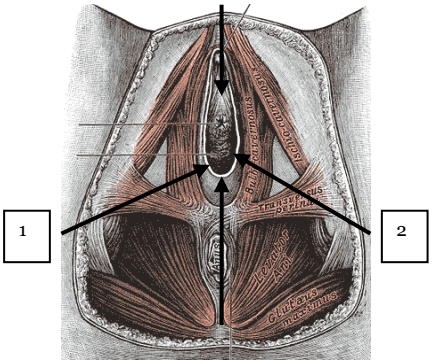
A baseline visit will be performed for all participants that have not conducted an assessment visit for EH13-094 in the last 12 months: **[Note all of these assessments are the same as the assessments approved in EH13-094**]. The baseline visit will be scheduled to occur during the luteal phase (15 to 25 days after the start of the prior menstrual cycle). Participants will be asked to confirm that menstrual pain or bleeding has not started during the baseline visit.
Food: Baseline Visits are very long so we will offer snacks to the participants (e.g., teddy grahams and fruit roll-ups).

Instrumentation: During the baseline visit, EMG and EKG electrodes, and respiratory rate monitors will be applied and information will be recorded throughout the visit. EMG leads will be placed on the lower abdomen during the bladder testing to measure muscular recruitment. The abdominal EMG leads will be moved to the knees once the bladder pain test is completed. The EKG leads and respiratory belt are placed to measure autonomic activity. The autonomic activity will be recorded to verify nociceptive experience. During each testing session, participants will also have their blood pressure and pulse taken.

Bladder pain test: All participants will first undergo bladder pain testing described in our validation study[7]. Subjects will be provided directions for the bladder study. The bladder study involves voiding and obtaining baseline measurements of bladder volume with a 3D ultrasound abdominal transducer (GE Voluson 750, Wauwatosa, WI). After hydration with 20 oz of water, participants are instructed to report when they reach standard levels of bladder urgency: first sensation, first urge, and maximum tolerance and volumetric measurements of the bladder will be made. At each of these time points and every 15 minutes, 0-100 VAS measurements of pain and urgency are recorded. After scanning at maximum tolerance, subjects will urinate in a graded toilet hat to allow for measurement and saving a urinary specimen. Samples will be banked for analyses. If the participant gives permission in the consent form, urine samples will continue to be stored after the study is completed for possible future analyses by our lab on women's health conditions. If the participant does not give permission in the consent form for analyses beyond the current study, their sample will be destroyed upon study completion.

View of introitus in lithotomy position with relative position of pelvic floor exam points (exam finger inserts **into** introitus at these sites) (Lewis, 1918)

Cutaway of pelvis showing index finger examining left iliococcygeus site (#5) (adapted from (Peters, et al., 2007))



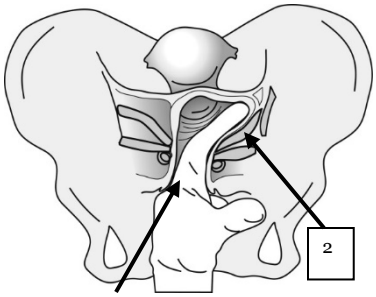


Diagram 3:
All points are examined 3 cm proximal to the vaginal introitus
#1: right iliococcygeus - located medial to the length of the tendinous arch
#2: left iliococcygeus
#3: 12 o'clock position, anterior vaginal wall (adjacent to the bladder)
#4: 6 o'clock position, posterior vaginal wall (adjacent to the rectum)

Pressure Pain Threshold Test: Participants will undergo body and pelvic floor pressure pain threshold testing following the same validated protocols in our published studies[27,28] using digital external and internal vaginal pressure algometers. The body algometer (for example models see www.paintest.com) is a commonly used hand-held device in pain research that measures the

amount of pressure applied to a 1 cm^2 circular rubber tip. The vaginal algometer consists of 2.5 cm^2 circular force sensitive resistor, which fits over the pad of the examiner's index finger under an exam glove (Detailed documentation was provided in a separate earlier supplement to the IRB). Prior to evaluation, subjects will report their baseline pain on a NRS 0-10 scale and will be asked to identify any painful body sites.

To evaluate bodily pain pressure thresholds, we will assess three external measurement sites corresponding to American College of Rheumatology fibromyalgia tender point sites: the right trapezius, the right medial knee fat pad, and the right greater trochanter.[29] One additional site will be a sham tender point, the middle of the forehead. A digital algometer (described above) will be used to conduct the external site measurements using a ramp rate of 0.5 $kg/cm^2/s$. Trials of the shoulder, hip, and knee may be terminated by examiner at 7.0 kg/cm^2 and trials of the forehead may be terminated at 4.0 kg/cm^2 in the case that the subject does not reach pressure pain threshold before then. Subjects will report level of pain at the time they pressed the button on a NRS 0-10 scale immediately after testing each individual site. After a two minute break, the sites will be retested again.

Next, we will use the vaginal algometer (described above), The four pelvic sites will be accessed by intravaginal exam, with all measurements conducted using the right index finger (Diagram 3) and a ramp rate of 0.5 $kg/cm^2/s$. Internal trials may be terminated by examiner at 3.0 kg/cm^2. A trained clinician will perform all pressure-pain tests. Subjects will report the pain at the time they pressed the button on a NRS scale immediately after testing each individual site. After a two minute break, the sites will be retested again. In order to compare within-subject results from the baseline and follow-up visits and in order to standardize timing of post-testing time scores (collected every 5 minutes as described below), the order of testing sites will not be counterbalanced. Subjects will be allowed to rest for another 5 minutes, and subject will be queried on the level of NRS pain at each site again (shoulder, hip, knee, forehead, global vagina). Subjects will be queried every 5 minutes until pain returns to baseline levels or up to 30 minutes (the time of resolution in minutes will also be recorded).

Conditioned Pain Modulation (CPM) : CPM testing involves repeating pressure pain threshold testing in the presence of a heterotopic stimulus (in this case cold water). The testing stimulus will be a mechanical pressure on the left medial knee fat pad. As in the first task, pressure will be applied (0.5 $kg/cm^2/s$ ramp) until the participant achieves pressure pain threshold. Baseline pressure pain thresholds of the testing stimulus on the left knee and left shoulder will be determined. After waiting approximately 2 minutes, the conditioning stimulus will be applied by instructing the subject to insert their right hand up to their wrist into a bucket of water maintained between 0-6° C. After 10 s of immersion, subjects will be asked to rate their level of hand pain on a NRS 0-10 scale. After 20s of immersion, the pressure pain threshold will be re-applied using a 0.5 $kg/cm^2/s$ ramp rate at the knee and the participant will be asked to rate their knee pain at the time they reached threshold (i.e. pressed the button) on a NRS 0-10 scale. After testing (~20s of immersion), subjects will immediately remove their hand and the pressure pain threshold will be determined at the shoulder. After waiting 5- and 10-minutes after water immersion, the testing stimuli will be re-applied. This paradigm combines a method for measuring CPM used by Dr. Clauw[30] and methods for accurately measuring participation of descending inhibition by Dr. Hellman.[31] CPM will be measured by the standardized differences in pain threshold, EMG activity and autonomic responses before and after heterotopic stimulation. This strategy will provide the most reliable measurement of descending inhibition.[31,32]

Temporal Summation (TS): Participants will be instrumented to undergo tests of spinal pain modulation. Temporal summation will be tested using an algometer on the right medial knee fat pad.

We will repeatedly apply an amount of pressure (0.5 kg/cm2/s ramp rate; ITI = 5-15 seconds) equal to the average of the participant's two pressure pain thresholds assessed during the first task. After each press, the participant will be asked to rate their pain on a NRS 0-10 scale. The pressure will be applied ten times or until the participant rates their pain as a 6, whichever comes first.

EEG Testing: Subjects will be instrumented with a standard EEG cap. Encephalography (EEG) recordings will be obtained using a standard montage and equipment. A trained research assistant or nurse will place the EEG cap and electrodes. All participants will undergo a resting state EEG task in order to analyze brain activity patterns associated with pain behavior. Participants will be asked to focus on a fixation cross on a computer monitor with their eyes open and sitting with their eyes closed for one minute each. In total, the task is expected to take 10 minutes. All participants will complete a handedness questionnaire,[33] consisting of a series of questions asking which hand they use for different activities, in REDCap, which will help us interpret our EEG results.

Sensory Amplification Tests: To evaluate whether sensitivity extends to other modalities we will use a software application that measures self-reported unpleasantness to increasingly loud and bright stimuli (safe and well below thresholds that could cause auditory or visual damage).

Auditory stimuli will be provided by waveforms generated by a PC and transmitted through headphones calibrated by an audio monitor[34] . Each stimulus will be a two-tone combination of 1200 and 1350 Hz. Sounds will ranged in 5 dB steps from 35 to 90 dB SPL (A-weighted). After receiving instructions, the subject will be presented with a series of sounds, in random order of intensity. After each 2 s stimulus, the participant will be asked to rate its unpleasantness from 0 ("not at all unpleasant") to 20 ("the most unpleasant sound imaginable").

Visual stimuli will be displayed on a computer monitor capable of providing up to 300 lux. In this 3 min task, two visual stimuli will be presented in an alternating block design. The control stimulus is a fixed crosshair centered in the middle of a solid background; the experimental stimulus will be a flashing (12.5 Hz) blue/yellow checkerboard presented at varying levels of brightness (luminance) in both an ascending and random manner. Each subject will be presented with 6 test patterns alternated with 6 blanks patterns. Subjects will use a 0 ("not at all unpleasant") to 20 ("the most unpleasant pattern imaginable") numerical descriptor scale to rate the unpleasantness of each visual stimulus and the entire task.

The visual task may be annoying or elicit a headache or nausea in sensitive individuals. Participants may stop at any time. The sensory testing will take in total about 20 minutes and will be performed while the participant is connected to EEG.

Additional quality controls: We may need to repeat a task, modify electrode positions, reconfigure equipment, or adjust features in the environment to evaluate the quality of our data acquisition scheme. For example, if a PPT measurement was not obtained or an electrode does not stay put, we may ask the subject to allow us to repeat additional measurements. All embedded quality controls with permission from the subject will be documented in the subject record.

Hormone Measurements**:** We will ascertain that subjects have not had more than 100 ml of blood drawn over the past 24 hours or 200 ml over the past 30 days. After completion of the pressure/pain testing, a trained nurse, physician, or phlebotomist will draw up to 60 mL of blood into vacutainers. Separation of serum and plasma will be performed using centrifugation and samples will be aliquoted and banked appropriately to allow for hormone measurements and analyses. To control for the potential influence of reproductive hormones on pain sensitivity, and test our hypothesis about the role of hormonal influences on neurophysiological pain assessments, we will measure serum samples for E2, P4 and testosterone using methods that do not cross-react to contraceptives (some participants may be taking contraceptives) from the UVA or Emory Assay core.[35] If the participant gives permission in the consent form, blood samples may also be analyzed for genetics. If the participant gives permission in the consent form, blood samples will continue to

be stored after the study is completed for possible future analyses by our lab on women's health conditions. If the participant does not give permission in the consent form for analyses beyond the current study, their sample will be destroyed upon study completion.

Naproxen:

Participants will be instructed on usage of prophylactic and recommended dosage of naproxen. Participants will be instructed to take one Naproxen (500 mg) pill in the morning and one again 12 hours later the first day before their anticipated first day of menses. The research coordinators will help interpret the menstrual pain calendars for the participants to predict their next menstrual cycle. Participants will continue to take a pill twice daily for the first 3 days of their menstrual period. If participants still have menstrual pain the following day, they will be instructed to continue taking 2 pills a day until their pain stops. Any unrelieved pain can be treated with acetaminophen (according to directions listed on the package). Participants will continue taking pills before and during their period for 6-8 months until the follow up visit is performed. In the event that a participant has been taking Naproxen for 3 consecutive days and has been asymptomatic (i.e., not started their menses) we will have them stop taking the study medication. The research staff will instruct them to start taking it again as soon as they start their period.

The dosage does not exceed the maximal daily recommended over the counter dose for Naproxen (1500 mg first day, 1000 mg subsequent days).

Between visit measurements:

Diaries: On each day of menstrual bleeding and/or pain, participants will complete a daily diary. The daily diary will be completed using REDCap and asks them to rate their menstrual, bladder, and bowel pain (using a numeric rating scale where 0-no pain, 10-worst pain imaginable), describe any bleeding, and what time the study medication wastaken. They will be asked to record any other pain reliever/medication they tried that day (heat pads, muscle relaxers, herbal teas, etc) in the notes section. They will be instructed to not take any additional painkillers except acetaminophen during their menses or while taking the study medication. Outside of their menses, they can treat their pain however they normally would (flu, headache). To protect confidentiality, subjects will not enter identifying information and only use their assigned subject ID #.
Urine: Participants will be told that urine samples will allow us to verify they are taking the study medication as directed. Participants will be asked to freeze urine collected from the evening of day 2 of their menses for each cycle. 6 storage vials will be provided. The urine samples will allow us to verify if participants are taking the provided pills.
Blood: Participants will be instructed to arrive at Evanston Hospital for a scheduled blood draw1.5-3 hours after ingesting naproxen pills. This will allow us to verify naproxen is sufficiently absorbed to provide therapeutic effects. Only one naproxen absorption blood draw will be performed per participant. Participants will be allowed to choose the most convenient period day for testing, but cannot come on the first day.

Follow up visit:

Six to eight months later, participants will be invited to return for a follow-up visit. Participants will perform the same measurements obtained in the original baseline visit. In the event participants are unable to return for a complete baseline visit, participants will receive a prorated stipend for partial

completion of items (including questionnaires). Participants will bring in any unused study medication to this visit.

Power Analysis/Data Analysis:

The primary outcomes are menstrual pain and bladder pain. Menstrual pain will be evaluated by comparing diary data and questionnaire data from baseline to 6-8 months after treatment. We estimated the needed sample size with a power analysis. Historically, the effects of NSAIDS are known to have a large effect size (dz>.7). A power analysis (α=.05,1-β=.80) suggests that to detect a more moderate effect of dz=.7 sample size of 20 would be needed. To account for a ~20-30% drop out rate, we will recruit 30 participants.

An additional primary outcome is bladder pain as measured by the experimental bladder pain test and the GUPI questionnaire. We estimated the needed sample size with a power analysis. The effects of oral contraceptives on bladder pain had enormous effect size (dz=2.9). Unfortunately, too few participants were willing to take oral contraceptives. A power analysis (α=.05,1-β=.80) suggests that to detect a more moderate effect of dz=1 sample size of 10 would be needed. We will attempt to attain a sample size of n=20 to allow detection of and even lower effect size dz=0.7 (per the primary outcome for menstrual pain).

Secondary outcomes include predicting NSAID effectiveness via the investigated mechanisms. We predict impaired conditioned pain modulation and reduced pain pressure thresholds will predict NSAID effectiveness for dysmenorrhea. With n=20, we can detect relationships between treatment response and conditioned pain modulation or pain pressure threshold testing with a correlation coefficient (Pearson's r) exceeding 0.38.

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