Mass General Brigham

ClinicalTrials.gov Protocol (Including Statistical Analysis Plan) Coversheet

Study Title: Non-Steroidal Anti-Inflammatory Drug (NSAID) Response and Central Sensitization of Pain in Women With Dysmenorrhea

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Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Laura A. Payne, PhD
Project Title:	Non-Steroidal Anti-Inflammatory Drug (NSAID) Response and Central Sensitization of Pain in Women with Dysmenorrhea
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1. Background and Significance

Insufficient pain relief with NSAIDs is a common cause of suffering in women with dysmenorrhea:
Dysmenorrhea (pain during menstruation) is the most common gynecological complaint in girls and women (1) and has a major impact on quality of life and productivity (2). Moderate to severe menstrual pain affects approximately 25% of reproductive-age women, and is even more prevalent in military women (31.2% – 36%) (3,4). Although non-steroidal anti-inflammatory drugs (NSAIDs) are the most effective nonhormonal treatment for most pain conditions including dysmenorrhea, NSAIDs fail to provide adequate menstrual pain relief in as much as 18% of women (5,6). Although dysmenorrhea may be secondary in nature (due to causes such as endometriosis, fibroids, etc.), anatomical factors are often unrelated to NSAID resistance (5). NSAID resistance may be partially explained by poor drug absorption (7), but it is also hypothesized that NSAIDs' inability to treat some pain conditions effectively is due to central sensitization of pain. Indeed, osteoarthritis patients with impaired central sensitization (as measured with conditioned pain modulation; CPM) have less effective pain relief from NSAIDS than patients with less central sensitization (8,9). Additional work in an animal model of osteoarthritis suggests central sensitization is associated with NSAID resistance (10). However, additional studies are needed to determine the role of central sensitization in NSAID non-response, particularly in women with dysmenorrhea (5,11,12). It is possible that NSAID resistance may be a specific and measurable biomarker for central sensitization of pain in women dysmenorrhea that would help elucidate women at risk for chronic pain.

Central sensitization of pain in dysmenorrhea:
"Central sensitization" of pain refers to long-lasting sensory amplification and impaired pain modulation as a result of alterations in neural processing of pain signals (13). Sensory amplification involves widespread increased excitability of sensory inputs and cortical amplification and can be evaluated with laboratory methods (14,15). Impairments in pain modulation are caused by reductions in descending inhibition of pain pathways, and these deficits have been demonstrated with CPM tasks (13,15-17). Although the exact mechanisms underlying central sensitization and associated deficits in descending pain modulation are not completely understood, the experience of repeated noxious stimuli (i.e., pain) is directly involved in the genesis of central sensitization, at least for some individuals (17). In this sense, dysmenorrhea can put women at risk for central pain sensitization as, by definition, the condition

involves the repeated experience of pain, often over the entirety of a woman's reproductive lifespan, particularly for women who are unable to find adequate pain relief for menstrual pain. The amplification of pain in central sensitization has been directly linked to the emergence of chronic pain. Data from the past several decades have consistently shown that women with dysmenorrhea have increased pain sensitivity (18) and impaired pain modulation, across behavioral (19) and neural (20) measures (also see Payne et al.) (19). Yet, the identification of specific biomarkers within the population of dysmenorrhea is the next challenge for our field. Despite research emerging over the last decade, we still know little about the factors contributing to the transition from recurrent menstrual pain to central nervous system impairments in pain processing.

Dysmenorrhea and chronic pain:

An extensive body of evidence now clearly demonstrates that menstrual pain is a risk factor for future chronic pain (21-24). Although almost all women with chronic pain previously had menstrual pain (25) only subset of women with dysmenorrhea will go on to develop chronic pain. Thus, it is important to identify a sub-phenotype of women with dysmenorrhea at increased risk. Chen and colleagues (26) identified three symptom-based phenotypes of women with menstrual pain characterized by: 1) mild, localized pain in the abdomen, 2) severe, localized pain, or 3) multiple severe symptoms at a number of body sites. Pain in more body sites is a common indicator of central sensitization and is associated with likelihood of having overlapping chronic pain condition (11,27). In a follow-up study with another large sample, women with phenotypes of either severe, localized pain or multiple severe symptoms reported greater perceived ineffectiveness of NSAIDs compared to women with the mild, localized pain phenotype (28). In support of this data, Hellman (29) has identified a subtype of dysmenorrhea with bladder sensitivity (termed DYSB) with impaired pain modulation that predict early symptoms of chronic pelvic pain. Preliminary two-year follow-up data from these participants suggests this DYSB group has acute risk for developing chronic pelvic pain; over 40% of DYSB participants met diagnostic criteria for either bladder pain syndrome or irritable bowel syndrome in one year. At two years' follow-up of n=119 women, they found a significant number of DYSB women with continued and worsening pelvic pain. Although retrospective questionnaires suggest this cohort may have less effective pain relief with NSAIDS, a prospective study is needed (30). Thus, data suggest that the experience of menstrual pain is not consistent across women, and women who experience the most severe pain and symptoms are not able to achieve effective pain relief.

The repeated experience of pain, coupled with inability to achieve pain relief, has the potential to establish a vulnerability to chronic pain, possibly through the mechanisms of central sensitization. Identification of biomarkers related to central sensitization in dysmenorrhea is the critical next step to determining who is at risk for chronic pain and tailoring effective treatments. NSAID non-response is a particularly important mechanism to identify, as individualized treatment approaches would focus on pain management through the use of other interventions, which could include hormonal treatments, cognitive behavioral therapy for menstrual pain (31). or brain-based interventions such as transcranial direct current stimulation (32).

Preliminary data:

Data from co-Investigator Dr. Hellman's lab (7) showed that, while on their menses, dysmenorrheic participants (n=23) answered self-report questionnaires about their menstrual pain, including a numerical rating scale (NRS) to assess their current level of menstrual pain. Following baseline assessments, participants received naproxen and reassessed menstrual pain 90 minutes later. Afterward, blood was collected to quantify naproxen, the metabolite Odesmethylnaproxen (ODN), and

inflammatory molecules (PGF2α, PGE2, lipoxin A4 [LXA4], leukotriene E4 [LTE4]) using HPLC-MS. Serum concentrations for naproxen, ODN, and inflammatory molecules were reliably measured across a range of standards (r2 > 0.99) and were stable with their storage paradigm for up to 2 years. Naproxen effectiveness, reported as a percent change in pain rating before and after taking naproxen, varied across dysmenorrheic participants. Naproxen effectiveness was negatively correlated to serum naproxen ($r = -0.49$, $p = 0.019$) and ODN ($r = -0.45$, $p = 0.032$) concentrations. They were also able to establish that their threshold for detecting PGFα, PGE2, LXA4, LTE4 is 1 pg/mL – sufficient for the proposed analyses. Notably, whereas PGF2α and PGE2 are thought to be inhibited by naproxen, LXA4 and LTE4 are not.

To better understand the factors for NSAID-responsive and NSAID-resistant menstrual pain, Hellman and colleagues generated a latent model of the DYS and DYSB cohort (33). Structural equation modeling was used to demonstrate that whether NSAID resistance was associated with nociplastic pain using the generalized sensory sensitivity questionnaire (GSS). For comparison, we also analyzed non-nociplastic components (termed SPACE and composed of unrefreshing Sleep, Pain, Affective disturbances, Cognitive issues, and reduced Energy) (27). The GSS construct was associated with NSAID-responsive menstrual pain (n =178). However, the SPACE construct was significantly associated with NSAID-resistant menstrual pain. Thus, NSAID responsive and resistant menstrual pain may involve different mechanisms. Notably GSS was also significantly correlated with other forms of non-menstrual pelvic pain, suggesting that this same nociplastic mechanism may underlie risk for the development of other pelvic pains.

Our research team also recently conducted a survey-based study of approximately 1,200 women nationwide and, for those who reported having menstrual pain, inquired about whether they take medication (such as NSAIDs) and, if so, how well the medication works. Response choices were “not at all,” “somewhat,” “moderately well,” “very well,” and “works completely.” We collapsed women with responses indicating the medication works “not at all” or “somewhat” into the “non-responder” category and women with responses of “moderately well,” “very well,” or “works completely” into the “responder” category. Of the 512 women who answered this question, 182 were non-responders and 330 were responders. Compared to responders, on a 0 (none) to 10 (worst possible) scale, medication non-responders reported significantly higher levels of and greater interference from menstrual pain (7.40 v. 6.19; 7.01 v. 5.71, respectively; $ps < .01$), more severe menstrual symptoms on a menstrual symptom questionnaire (70.4 v. 56.6; $p < .01$), greater non-menstrual bodily pain (5.5 v. 4.2; $p < .01$; 0-10 scale), and endorsed more bodily pain locations over the past month (7.74 v. 6.16; $p < .05$) (unpublished data). These data further support the notion that women who are not able to find menstrual pain relief from medication may represent a pain phenotype with greater indices of central sensitization of pain.

Although one of our previous studies did not find impairment in CPM in adolescents with dysmenorrhea, evidence of heightened pain sensitivity was still demonstrated in this population (18). These findings suggest the possibility that subgroups of girls with impaired descending modulation were not identified, particularly because participants were recruited and enrolled only based on self-reported menstrual pain ratings. As described early, phenotypic biomarkers are critical to identifying those who may show impaired pain modulation and have an increased risk for chronic pain.

2. Specific Aims and Objectives

The main objective for the proposed proof-of-concept clinical trial is to evaluate the relationship of NSAID response and standardized laboratory measures of central sensitization of pain in adult women with chronic, moderate-to-severe dysmenorrhea. This objective will be achieved through the following specific aims:

Aim 1. To test Hypothesis 1, we will evaluate the relationship of NSAID response to demographic (age), menstrual cycle characteristics (self-reported average menstrual pain, age at menarche, lifetime duration of menstrual pain), and urinary NSAID/metabolite concentration in adult women with dysmenorrhea.

Aim 2. To test Hypothesis 2, we will characterize the relationship between NSAID response and laboratory measures of central sensitization in women with dysmenorrhea, after controlling for demographics, menstrual cycle characteristics, placebo response, and urinary NSAID/metabolite concentration.

Based on existing literature and findings from both Dr. Payne's and Dr. Hellman's laboratories, we hypothesize:

1. NSAID response in adult women with dysmenorrhea is predictable by menstrual characteristics and pharmacological factors. (Hypothesis 1)
2. NSAID response will predict measures of central sensitization of pain, such that NSAID non-response will be associated with increased measures of central sensitization, after accounting for confounding factors. (Hypothesis 2)

3. General Description of Study Design

The study is a randomized crossover "form and function" drug study of an approved and marketed over-the-counter drug product. The study is investigating the relationship between drug absorption (as assessed by amounts of Naproxen and metabolites found in urine) and symptom relief in women with moderate-to-severe menstrual pain.

4. Subject Selection

Recruitment:
Advertisements and Flyers: Study advertisements/flyers will be posted on online forums (e.g., Craigslist, Yahoo groups, etc.), on social media, at general internal medicine clinics, on MGB's Rally for Research website, and at community centers (e.g., libraries, etc.) within the greater Boston area.

Community Recruitment: Recruitment will also occur at local community groups/events, such as PTA meetings, social/community group meetings, community fairs/events, etc. Initial contact will be made within the group setting by a research associate; interested individuals can either take a flyer and contact the research team or can give the research team member their contact information if they prefer to be contacted by the research team.

Previous Studies: Participants will be recruited from those who had expressed interest in or participated in a previous study (MGB IRB numbers 2019P001729 and 2021P002543) and who gave permission to be contacted for future research opportunities. These potential participants will be contacted using the phone/email scripts attached to this application.

Study Participants:
Participants will include 70 pre-menopausal adult women (ages 18 – 50) with moderate-to-severe average menstrual pain, rated at least 6/10 on a 0 (no pain) to 10 (worst pain possible) NRS (34) consistently for at least the previous 6 months.

Inclusion and exclusion criteria were determined to both maximize the generalizability of the findings by including the most diverse sample possible, while minimizing the possibility of including participants that are not representative of the population being studied. Through these criteria, we are attempting to exclude women who have started menopause, as well as those with self-reported or established chronic pain conditions, as a large body of research already demonstrates enhanced central sensitization in these populations (13,17).

Inclusion Criteria:
1) Female aged 18-50 years
2) Menstrual pain rated at least 6/10 on a 0 (no pain) to 10 (worst pain possible) NRS for all menstrual cycles in the previous 6 months
3) Regular menstrual cycles over the past year (at least 9 in the previous 12 months)
4) Self-reported menstrual cycle averaging 22-35 days
5) Access to a smartphone and email, and willing/able to receive text messages
6) Able to read and understand English
7) Ability and willingness to provide written informed consent

Exclusion Criteria:
1) Use of oral contraceptives or any exogenous hormones in the previous 3 months prior to participation
2) Variable levels of menstrual pain in the previous 6 months
3) Self-reported symptoms consistent with a chronic pain condition (e.g., pain in any body area lasting longer than 3 months) or previous diagnosis of a chronic pain condition
4) Currently pregnant or breastfeeding
5) History of pelvic inflammatory disease or sexually transmitted disease
6) Acute illness or injury that would potentially impact pain task performance (e.g., fever, flu symptoms) or that affect sensitivity of the extremities (e.g., Reynaud's disease)
7) Allergy to naproxen or having a health condition that contradicts use of naproxen or affects naproxen metabolism (e.g., kidney disease)
8) History of uncontrolled high blood pressure or uncontrolled anemia (due to possible complications from NSAID use).

Additional considerations for military personnel, etc.:

- Detainees and prisoners of war will not be recruited for this study.
- Military personnel will not be targeted for recruitment. It is possible that an active duty or veteran military member may see the study advertised via the methods described in this application, but it would not involve their superiors/supervisors. Thus there will be no possibility of superiors influencing subordinates to participate in the study.

- No participants will participate in the study while they are on military duty. Any participants recruited from the community who happen to be servicemembers will participate in the study on their own time.
- No recruitment events will occur that specifically target military personnel, nor that advertise specifically to military personnel or take place on military property or at military events. The study team acknowledges that were this to happen, the IRB would need to appoint an ombudsman who is not associated with the research team, and that the ombudsman would need to be present at recruitment events targeting military personnel in order to ensure voluntariness of participation.
- Potential participants who lack capacity to make a decision about consent to participate (for any reason, including age, condition, or other reason) will not be recruited for this study.

5. Subject Enrollment

Screening:
Potential participants will complete 4 preliminary eligibility questions built into the Rally website. [All advertisements direct potential participants to the Rally site to express interest. If a participant reaches out via other means (e.g., direct email to study staff), they will be administered these 4 questions over the phone.]

Participants who meet initial eligibility based on the Rally screening questions will then undergo a brief telephone screen to provide the participant with more information about the study and ensure study inclusion criteria are met. Verbal consent to screen will be obtained after the potential participant is given the study description but prior to administration of the full eligibility questions.

Eligibility will be determined by a trained research team member during administration of the telephone screen. If participants endorse a positive history of any of the eligibility items on the phone screen, the research team member will present this information to the PI and/or Co-I's for their determination.

Following the telephone screening, eligible participants whose cycle-related eligibility window (i.e., days 8-14 of the current menstrual cycle) is upcoming will be scheduled for the consent/laboratory session. Participants who are past the 8-14 day window in their current cycle will be told about text messaging procedures and that the research team will reach out to schedule their in-person visit once their period has started and the visit window is determined.

Consent:
Eligible subjects will be sent .pdf copies of the consent form by e-mail and told that they will be given time to review them. The consent process will not occur until the in-person intake visit, so the length of time subjects are given to decide whether they wish to participate in the study varies. However, there will always be at least one day in between screening and their appointment so there is ample time for them to contact us (via email, work phone numbers, etc.) if they have any questions or no longer wish to participate in the study.

The REDCap eConsent module will be used to obtain consent from all participants during the in-person visit. The consent process will be conducted in a private room. Senior Research Project Manager Ms. Laura Seidman will initiate a Zoom videoconference with PI Dr. Payne using the lab's laptop and Dr. Payne's MGB Zoom account. Dr. Payne will conduct the consent process with participants over Zoom

and will guide them through the REDCap eConsent module, which will also be opened on the lab laptop. Ms. Seidman will be available to assist with any technical difficulties.

Potential participants who are seen as part of one of the investigators' clinics will be informed that the research study is voluntary, does not influence their care in any way, and is not being done to improve their condition. After initial contact, all recruitment, screening, and corresponding will be done by the research team (as opposed to the physician/clinical staff) to help the participant distinguish their research participation from their clinical care.

After the enrollment visit, participants will be randomly assigned by the McLean Research Pharmacy to one of two groups: NSAID first or placebo first. This will ensure that study participants and study staff are blind to what participants will take at each cycle.

6. Study Procedures

Consent/Laboratory Visit:
The first visit will be scheduled during the mid- to late-follicular phase of the menstrual cycle (Days 8-14, with Day 1 being the first day of menstruation), based on participants' self-report of their most recent menstruation. If they are more than 14 days since the first day of their last menstrual period, they will wait until the next menstrual cycle begins and scheduled for a time between Days 8-14. First, participants will provide written informed consent, as described above. Then participants will complete questionnaires and laboratory pain tasks, as described below. Participants will also complete a urine drug and pregnancy test.

Laboratory pain testing:
At the laboratory session, enrolled participants will then undergo a series of laboratory pain tasks to assess central sensitization. These tasks are well-validated and extensively used in other studies of pelvic pain (e.g., 35-37). All laboratory pain tasks will be administered by trained female members of the research team.

Generalized mechanical sensitivity (MAST task):
First, pressure pain sensitivity will be assessed using the Multimodal Automated Sensory Testing (MAST) system (36-39), which includes a computer-controlled handheld device that administers pressure to the thumbnail via a rubber probe. Participants hold the MAST device like a joystick and the probe administers pressure in the center of the thumbnail bed. The MAST procedure is conducted in two parts: 1) familiarization procedure and 2) ascending test procedure. The familiarization procedure is conducted on the left thumb and consists of a series ascending pressures beginning at 0.50 kg/cm^2 and increasing in 0.50 kg/cm^2 increments. Each pressure is delivered for 5 seconds. After the pressure is released, the participant will be prompted to rate the pain evoked by the preceding pressure using the 0-100 NRS. The familiarization procedure is stopped at the first occurrence of one of the following three situations: the participant indicates a pain rating greater than or equal to 50/100, when the maximum pressure of 10 kg/cm^2 is reached, or when the participant indicates that she no longer wishes to continue. The ascending test procedure is then conducted on the right thumb. The pressure sequence is the same as during the familiarization procedure; the ascending test procedure is stopped when the participant indicates a pain rating greater than or equal to 70/100, when the maximum pressure of 10 kg/cm^2 is reached, or when the participant indicates that she no longer wishes to continue. The MAST device has

been used in a number of studies assessing pelvic pain in adult women (36-37, 40-42). A major innovative advantage of the MAST device is that it is fully automated thereby eliminating tester bias effects and increasing reproducibility – a major limitation with almost all prior studies that use quantitative sensory testing (QST) (38).

Conditioned Pain Modulation (CPM):
We will also use the MAST device to measure conditioned pain modulation (CPM) (43), a measure of central sensitization. CPM tests the magnitude of descending pain inhibition, which is considered to be a critical mechanism involved in the chronification of pain. CPM is measured by evaluating changes in pain sensitivity in response to conditioning stimulus. Numerous animal studies have demonstrated that changes in descending modulation are critical for the development of chronic pain (44,45). The value of using CPM to measure descending inhibition has been demonstrated by its ability to predict the development of chronic postsurgical pain and effectiveness of duloxetine for diabetic neuropathy (46,47).

Trapezius, MAST p50, MAST p70 ("T/p50/p70") stimuli unit:
This unit of stimuli consists of three discrete stimuli, each rated by the participant on the 0-100 NRS after the stimulus has been administered. First, pressure is applied to the right trapezius for 5 seconds using a handheld pressure algometer with a 1 cm^2 flat rubber probe. Pressure will be increased at a rate of 0.5kg^2/sec until the destination of 4kg/cm^2 is reached. Second, pressure is applied for 5 seconds to the right thumbnail using the MAST device at p50 (i.e., the amount of pressure at the first instance of a pain rating of at least 50/100 during the above MAST task, individually-tailored to each participant). Third, pressure is applied as described in #2 except at p70 (same as above but at a rating of at least 70/100). This stimuli unit will first be administered immediately following the MAST task. It will then be administered two additional times as outlined below.

After the first T/p50/p70 stimuli unit is completed, participants will immerse their left hand up to approximately 2 inches above the wrist into a commercial cold pressor unit. Water will be maintained at 5 degrees C and will be circulated to avoid localized warming around the hand. Fifteen and thirty seconds after hand immersion, participants will rate the amount of pain they feel in their hand due to the cold water. Immediately following the 30-sec rating, while the participant's hand is still in the water, one T/p50/p70 stimuli unit will be administered. After 60 seconds total hand immersion time has elapsed, participants will be instructed to remove their hand from the water. Additional hand pain ratings will be given as the hand is being removed from the water and every 30 seconds for the following two minutes. Participants will be instructed to try to keep their hand in the water for the duration of the task but that they are free to remove their hand at any time if they are unable to keep it in the water. Water of 5 degrees C has been used in our own and others' work and is appropriate as a brief conditioning stimulus in a CPM task (18, 48, 52).

Two minutes after the hand is removed from the cold water, a final T/p50/p70 stimuli unit will be administered.

Temporal Summation (TS):
Next, temporal summation will be assessed using two fixed intensity pointed skin probes at 256mN and 512mN (49). The temporal summation task is conducted in two parts: 1) familiarization procedure and 2) test procedure. The familiarization procedure is conducted with the 256mN probe while the participant is seated in a chair. Familiarization is conducted on the left forearm and includes a single application of

pressure lasting 0.5 sec, following which the participant rates the pain intensity on a 0-100 NRS. Then a series of 10 sequential pressures is applied at a rate of 1 Hz. Following the final application in the series, the participant rates the pain level for the entire series (i.e., temporal summation/"wind-up"). The temporal summation test procedure is identical to the familiarization procedure except that it is conducted with the participant lying in a supine position, is conducted on the right forearm and suprapubic sites, and is conducted first with the 256mN probe and then again with the 512mN probe. Three series are conducted on each site with at least 10 seconds separating each series. One additional series of 10 pressures is then conducted on each site during which the participant rates the first, fifth, and tenth pressures individually on the 0-100 NRS. This task has been used in a number of previous studies (e.g., 49-51).

Bladder Pain Task (BPT):
Lastly, visceral pain will be assessed using a provoked bladder pain task (53-55). Participants are first instructed to use the restroom and empty their bladder. Then participants will be instructed to drink 20 ounces of water within 5 minutes. Bladder pain and urgency are rated on a visual analog scale (VAS) (i.e., slider)at four different occurrences: first sensation (when the participants first feels able to urinate), first urge/desire (described as when the participant would ask for a rest stop if in the car), maximum tolerance (when the participant is no longer able to hold more urine), and after voiding following task completion. Participants are also asked every 15 minutes to rate pain and urgency on the VAS. At maximum tolerance, participants are asked to use the VAS to rate four pain descriptors (i.e., sharp, pressing, dull, and prickling). Elapsed time to each threshold is also recorded. If a participant does not reach her maximum tolerance by 45 and 60 minutes, she will be asked to drink an additional ten ounces of water at each time point. After reaching maximum tolerance, the participant will be asked to use the restroom and will use a toilet hat to collect the urine, which will be measured to quantitatively assess bladder fulness. BPT is capped at 2 hours.

Dr. Payne has extensive experience administering various types of QST laboratory pain protocols (18, 56-58).

NSAID/placebo cycles:
Following the laboratory visit, participants will be randomly assigned to receive either 550 mg sodium naproxen or pill placebo for the upcoming menstrual cycle. 550 mg naproxen sodium is the highest FDA approved starting dosage and is equivalent to 500 mg naproxen (59); the sodium formulation quickens absorption (60). Although typical use in the USA is 440 mg because of over-the-counter availability, 550 mg is the most commonly-studied dosage and associated with more pain relief and less missed school days when compared to other NSAIDs (61-63). At the onset of at least moderate pain after bleeding has started (at least 6/10 on the 0-10 NRS) (34), participants will rate their menstrual pain level immediately before taking the NSAID/placebo (pre-pain rating) and again 4 hours later (post-pain rating). The post-pain rating will be subtracted from the pre-pain rating to determine the response measure (for each the NSAID cycle and the placebo cycle). Participants will also collect a urine sample at home immediately after the post-pain rating and place it in the freezer.

Participants will complete REDCap surveys sent by text message. The post-pain rating surveys will be triggered by the completion of the pre-pain rating survey, and timestamps will be checked to ensure compliance to the protocol. Identical procedures will be employed for the next menstrual cycle, with participants taking either sodium naproxen or pill placebo – whichever had not been taken at the previous cycle – and calculating the response measure as described above. Overall NSAID response will

be calculated by subtracting the placebo cycle response measure from the NSAID cycle response measure. This will result in a single measure indicative of the degree of NSAID response, while controlling for placebo effects.

Participants will return both urine samples to McLean after the second cycle. Concentrations of naproxen, PGF2α and PGE will be performed with HPLC-MS at the University of Illinois core facility similar to Hellman's prior study (7). We will adjust for urinary concentration by both volume and creatinine as recommended (64). Primary analyses will focus urinary NSAID concentration at 4 hours as a covariate, but the additional measurements (metabolites, PGF2α, and PGE) will allow for further exploration of biological mechanisms of NSAID resistance.

Remuneration:
Participants will be compensated $75 for completion of the laboratory pain session, $50 for the first cycle test, and $100 for the second cycle test. For participants without reliable transportation or access to public transit, we will reimburse up to $50 for rideshare costs for the in-person study visit. Payment will be via check or Advarra payment card, whichever the participant prefers.

Measures:

Consent/Lab Visit:
1. Demographics and menstrual history: assesses demographic variables, characteristics of the menstrual cycle (e.g., average cycle length, duration of bleeding, and average menstrual pain) and menstrual/pelvic health history (e.g., history of endometriosis, adenomyosis, fibroids, etc.). This measure will be completed at the consent/laboratory visit.
2. Two-Item Conjoint Screen (TICS): a brief 2-item measure assessing potential overuse of alcohol and other substances (70).
3. Pain Catastrophizing: measured using the Pain Catastrophizing Scale (PCS) (65), a 13-item scale that asks participants to indicate the degree to which they have different thoughts when experiencing pain. The PCS includes three subscales: rumination, magnification, and helplessness.
4. Menstrual Sensitivity Index (MSI): 8 items modified from the Visceral Sensitivity Index (66-68) to assess menstrual symptom-specific anxiety (71).
5. Situational Catastrophizing Questionnaire (SitCatQ): A 6-item measure to assess participants' catastrophic thinking during the laboratory pain tasks (69) will be administered following each of the four pain tasks (i.e., MAST, CPM, TS, and BPT).
6. Central Sensitization Inventory (CSI) Part A: A 25-item measure assessing the extent to which participants experience signs and symptoms of central sensitization (e.g., somatic symptoms, sensory sensitivity, cognitive difficulties, etc.) (72).
7. PROMIS-57 v2.1 adult profile: A profile measure of health including subscales for physical functioning, anxiety, depression, fatigue, sleep disturbance, social roles and activities, and pain interference (73-80).
8. Chronic Overlapping Pain Conditions (COPC) Screener: Assesses symptoms related to the diagnoses of a number of pain conditions that have been identified as often co-occurring in the population and more frequently in women than in men (81; e.g., fibromyalgia, temporomandibular disorder, chronic low back pain, etc.) (82).

During NSAID response cycles:

1. Pre-pain rating questionnaire: one question assessing level of menstrual pain at that moment on the 0-10 NRS.
2. Post-pain rating questionnaire: will consist of the same pain rating as above, plus a few questions asking about any possible side-effects or adverse events that were experienced in the four hours since taking the drug/placebo.
3. Two items assessing timing of urine sample collection and freezing [administered only on the day evening of the day when medication was taken].
4. Daily safety/adverse events monitoring questions for duration of bleeding.

Interview:
At the completion of the final NSAID/placebo cycle, all participants will undergo an open-ended, qualitative interview designed to assess their reactions to the study, explore the social, emotional, and cognitive aspects of their pain experience, identify successes and obstacles to pain relief. These interviews will be conducted using MGB-approved video conferencing platforms (i.e., enterprise Zoom, MS Teams) and will be audio and video recorded. Interviews will be transcribed either by members of the research team or by a transcription company. In the event that a transcription company is used, we will only send the audio files, not video files.

Data and specimen sharing:
De-identified urine sample specimens will be sent to Dr. Hellman's site for processing at the University of Chicago laboratory.

Data collected as part of this study will be sent to Dr. Kevin Hellman, PhD, the PI of the subaward site, NorthShore University HealthSystem. Dr. Hellman is a Research Scientist at NorthShore University HealthSystem, and Research Associate Professor in the Department of Obstetrics and Gynecology at the University of Chicago Prizker School of Medicine. Data may also be sent to Dr. Frank Tu, MD, MPH. Dr. Tu is the Gynecology Division Director in the Department of Obstetrics and Gynecology, NorthShore University HealthSystem, and Clinical Associate Professor at the Pritzker School of Medicine, University of Chicago.

Data shared with Drs. Hellman and Tu will include cleaned, coded, and processed data from the self-report questionnaires and laboratory pain sessions. Data will be coded and the code key will remain with the McLean research team; no identifiable information will be sent to collaborators. Data will be sent using MGB-approved file transfer methods (i.e., LabArchives, MGB enterprise Dropbox, and MGB-affiliated email addresses).

Return of Research Results:
No research results will be returned to participants.

7. Risks and Discomforts

Side effects of NSAIDs:
Participants using NSAIDs as part of study participation may experience side effects, including: upset stomach, nausea, heartburn, headache, drowsiness, dizziness, and increased blood pressure. It is possible that there may also be other side effects as a result of taking the drug product.

Other Risks:
During the study, participants may be uncomfortable answering certain questions about their levels of stress, etc., in response to questions asked by the research staff and by questionnaires. However, these discomforts are not more likely than the individuals would experience in daily life, and participants do not have to answer any question they do not wish to answer. Participants may also feel uncomfortable while collecting the urine samples.

Although unlikely, un-approved access to the research records may occur or there may be a breach in confidentiality.

During the laboratory pain tasks, participants may experience brief physical discomfort. Pain tasks pose only minimal risk. The discomfort caused by the tasks is unlikely to exceed levels of discomfort or fearfulness that subjects experience naturally when unexpectedly encountering mild pain stimuli in their own environment and stops quickly when the task is ended.

Minimization of Risks:
Several measures will be taken to minimize risks/discomforts. All participants will be carefully screened to minimize possible risks caused by the NSAID drug product.

Trained research staff will be present at all times during the laboratory pain tasks to talk with participants and assist them if they are experiencing difficulty. Because Dr. Payne and her lab staff have been conducting lab pain studies for over ten years, we have considerable experience recognizing and supporting stressed participants. We have developed ways of carrying out laboratory pain research to minimize threat, and to make it an interesting and pleasantly novel experience. Furthermore, participants will be told that they do not have to answer any question that they do not wish to answer, that they may stop at any time, and that they can elect not to take part in any aspect of the study that is bothersome to them. Also, the experimenter will discontinue the study if distress is observed in the subject whether or not the subject expresses distress.

The pain tasks are under participants' control since they may stop the tasks at any time. Dr. Payne's completed K23 study and in-progress R01 study have successfully completed over 400 laboratory testing sessions using similar protocols with no adverse events.

During study sessions on the McLean campus, a physician from the Massachusetts General Hospital-Internal Medicine Associates, Belmont (MGH-IMAB) clinic on the McLean campus will be available for consultation should any medical emergency arise. The MGH-IMAB service is staffed 24 hours per day/7 days per week with a physician who is board certified in internal medicine

Discomfort caused by urine sample collection will be minimized by providing extensive training and support while participants are collecting the samples at home.

Instructions for study participation will include taking NSAID/placebo pills with food to reduce any short-term gastrointestinal distress. In case of severe side effect or reaction, participants will be instructed to assess their symptoms as they would when taking other over-the-counter medication and to go to urgent care, the emergency department, or call 911 depending on level of severity. Participants will also be instructed to notify the study team immediately if they end up pursuing any of those treatment options.

8. Benefits

Benefits to participating individuals:
Participants may experience menstrual pain relief from either the Naproxen or the placebo pill after taking it.

Benefits to Society:
Recent research on menstrual pain have focused on better understanding 1) why women have menstrual pain and associated symptoms, 2) the factors that contribute to limited relief from existing interventions, and 3) which biomarkers of menstrual pain indicate increased vulnerability to chronic pain. This study will directly address these questions by examining a non-invasive, identifiable biomarker (response to non-steroidal anti-inflammatory drugs; NSAIDs) that could be associated with mechanisms involved in the transition from recurrent to chronic pain. In the long-term, the findings from this study have the potential to directly affect patient care, as women who are unable to achieve adequate relief from NSAIDs may be encouraged to seek other evidence-based treatments (e.g., cognitive-behavioral therapy, different types of medication, transcranial direct current stimulation, etc.) designed to address central sensitization of pain, with the goals of alleviating women's suffering and preventing alterations in pain processing that may lead to chronic pain.

9. Statistical Analysis

Power analysis:
A power analysis was performed for Aim 2 using Monte Carlo simulations. The covariates and NSAID response are simulated using empirical distributions derived from prior publication and clinical observations. The response variables were simulated based on the hypothesized effect sizes (medium, Cohen's d = 0.5) and the simulated covariates. The linear regression models in Aim 2 were then applied to the simulated data. This simulation was repeated for 1,000 times and the power is estimated as the proportion of simulations in which all three p-values of NSAID response for the measures of central sensitization are significant after Bonferroni correction. The simulations reveal a sample size of 45 achieves greater than 80% power of detecting all three associations simultaneously. Recruiting and enrolling 70 participants will allow us to achieve sufficient power even if over 30% of individuals dropout of the study.

Aim 1.
The relationship of the two response cycles (NSAID and placebo) to the covariates of interest will be evaluated separately. For each response, a linear regression model will be used in the analysis with the response as the outcome and age, three menstrual cycle characteristics, and urinary NSAID/metabolite concentration as covariates. The continuous covariates will be standardized before the regression analysis. Transformation of the outcomes will be conducted if their distributions deviate substantially from a normal distribution. Regression diagnostics will be used to detect potential outliers and multi-collinearity, based on which outlier removal and dimension reduction of covariates through principal component analysis will be performed. The resulting p-values of covariates from the two models will be adjusted for multiple comparisons with Bonferroni correction. Significant associations will be determined if the corresponding adjusted p-values are smaller than 0.05. The list of significant

covariates for NSAID response will be compared to the list for placebo response for their clinical implications.

Aim 2.
Three linear regression models will be used to characterize the relationship between NSAID response and laboratory measures of central sensitization (CPM and TS), each of which will serve as the outcome variable of a regression model. The covariates in all three models will be age, menstrual cycle characteristics, placebo response, and urinary NSAID/metabolite concentration. Similar pre-processing and regression diagnostics will be performed as in Aim 1. The p-values of NSAID response for all three central sensitization measures will be adjusted for multiple comparisons with Bonferroni correction.

10. Monitoring and Quality Assurance

The PI, Dr. Payne, will be responsible for maintaining quality control over the data collection process and for securing its confidentiality. The PI will oversee the process of data collection and ensure that the data obtained from the online self-report questionnaires and urine samples are reviewed for completeness and accuracy. Reviewed data will be secured in locked file cabinets in the project offices or on restricted secure servers with password access only.

Adverse event monitoring:
During the study, potential threats to the safety and well-being of participants will be carefully monitored. Every day of each menstrual period (bleeding days), participants will complete a measure assessing whether or not they have experienced the symptoms listed above as risks (i.e., upset stomach, nausea, heartburn, headache, drowsiness, dizziness, increased blood pressure, and symptoms of allergic reaction (i.e., swelling, rash, shortness of breath, etc.)). Participants will also be able to report any other symptoms not otherwise included on the list. If any symptoms are reported, a research team member will contact the participant for more information, which will be presented to the PI, Co-Is, and study physician, Dr. Olivera Bogunovic. Based on the gathered information, the research team will determine the severity, expectedness, and relatedness of the effect, and whether or not it represents a change from the participant's baseline. The research team will then use Mass General Brigham IRB's guidance and policies to determine whether or not the event meets reporting criteria, and if so, which reporting timeline applies (e.g., 5 business days vs. at continuing review). The study team will follow all Mass General Brigham guidance and policies for recording and reporting unanticipated problems and adverse events. Given that the proposed project is a low risk intervention, we anticipate these occurrences to be unlikely, but we will implement this plan in case of such occurrence.

Monitoring process:
Study performance and safety monitoring will be conducted by the safety committee, made up of the PI and co-Investigators. This committee will receive biannual summaries containing information on each item in the list, presented in a blinded manner. A trained research associate will be in charge of preparing reports for the committee. In the case of safety concerns, requests by the committee for un-blinded information will be made to Dr. Payne who will provide the necessary information. Documentation of the reviews will be kept in a secure electronic file. The following performance and safety characteristics will be reported to the safety biannually.

Performance Summary:

1. Recruitment rates, including number of subjects who are approached, screened, percent eligible, reasons for non-eligibility, and study timepoint completion rates
2. Demographics of screened and enrolled participants
3. Percent of participants evaluated at each study point and reasons for losses to follow-up

Safety Summary:

1. Any reports of adverse events (Aes) or serious adverse events (SAEs) and summary of actions taken
2. Unexpected risks and unexpected benefits
3. Any other unrelated, possibly related, and related adverse events by subject

No stopping rules or defined rules for withdrawing participants from the study have been established. This study not being conducted under an IND/IDE and does not have an industry-sponsored protocol for adverse event reporting. We will follow the NIH/DOD and MGB guidelines for adverse event reporting for Aes that occur while participants are completing study procedures and/or events that participants report occurring as a result of study procedures.

Because this is this is a low-risk study, there will be no external independent DSMB. Dr. Payne and the Co-Investigators will form the internal DSMB, as outlined above. Research Project Manager, Ms. Laura Seidman, BS, CCRP, will be the primary study staff member monitoring and assuring the validity and integrity of the data and adherence to the IRB-approved protocol. Ms. Seidman will consult with PI Dr. Payne as needed. Ms. Seidman will review all data collected within 2-3 days of collection and will run the weekly lab meetings during which data will be discussed.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens

☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
☒ Additional privacy and/or confidentiality protections

Per updated MGB policy about email encryption with research participants ("Requests to Receive Unencrypted Email," 5/6/21), all study-related email communication falls into the low-risk category described in sections I1A and B and will therefore be sent without encryption.

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