Low-dose Naltrexone for Bladder Pain Syndrome: A Randomized Placebo-controlled Prospective Pilot Trial

Study Protocol and Statistical Analysis Plan

NCT04450316

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Low-dose naltrexone (LDN) for Bladder Pain Syndrome (BPS)

Enrollment Goals: N=40, 1:1 randomization

Start Date: TBD pending IRB approval

Purpose: An RCT of 40 patients diagnosed with bladder pain syndrome (BPS) to test the efficacy of low-dose naltrexone (LDN) in reducing pain.

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Research Coordinator: [redacted]

Lab Manager: [redacted], PhD

Primary Feasibility Endpoint: Study completion in the groups to which patients are randomized.

Primary Efficacy Endpoint: The proportion of subjects in the LDN and placebo groups that are responders with greater than 20% reductions in 7-day average of worst daily Numeric Rating Scale of Pain scores after 8 weeks of treatment. (Will compare pre-intervention to week 8)

Education and Training:
All research staff team members will perform the responsibilities as outlined by the delegation of authority log. Human Subjects Training and HIPAA training will occur as required by Stanford Policy. Additionally, all team members will receive a copy of this document, the Lab Policy Manual, and will be trained directly by the Principal Investigators (PIs) on the purpose of the study and their responsibilities. Research staff will be trained on Informed Consent, Phone Screening, and Case Report Form Completion by the research manager, who will monitor appropriate conduct and form completion on an ongoing basis, in collaboration with the PIs and study monitor/regulatory manager. Research team meetings will occur regularly to ensure ongoing understanding by study staff and to address any concerns.

Facilities: Patients will be screened by phone. The physicians and research managers will be able to work at established offices to complete the screening and follow-up apart from normal clinic follow-up.

Sufficient Time: The recruitment and follow-up will likely take 8 hours per week on average spread among the research staff. Each of the physicians have dedicated academic time which they will use to complete the research and the research manager, Corrinne Jung, has time as part of her allocated schedule to assist.

Access to the target population: The urology clinic and Pelvic Health Center at Stanford sees 10-15 patients with chronic bladder pain syndrome each week. Therefore, for a goal patient

population of 40 patients, it will take approximately 12 weeks to accrue patients assuming 1/3 of patients meet criteria and are interested in the study. We expect that most patients would be motivated to participate in the study as patients are keen to try new treatments as the established treatments are not effective enough. This is a single-site study and all patients will be recruited from Stanford.

Access to resources if needed as a consequence of the research: We do not anticipate that additional resources would be needed. We will ensure that patients on placebo can crossover to the treatment group at the conclusion of the study. Patients who benefited by LDN will be referred back to their provider with a study letter if they wish to continue treatment.

1) Purpose:

Bladder pain syndrome (BPS) is a constellation of symptoms associated with the urinary bladder in the absence of an identifiable cause. The American Urologic Association has a tiered recommendation for treatment options for BPS, but unfortunately, only 50% of patients experience acceptable relief[1]. Our investigators have anecdotally noticed that patients with BPS who were prescribed low-dose naltrexone (LDN) for other indications noted a marked improvement in their bladder symptoms[2]. The purpose of the study is to study the possible effect of low-dose naltrexone for pain relief in patients with BPS.

2) Study Procedures

Recruitment:

Patients will be referred from the Stanford Urology Clinic, Stanford Gynecology Clinic, Pelvic Health Center or Pain Management Center. Clinic staff will tell patients about the study and ask for permission for the research team to contact the patients. In some cases, the study team may conduct a chart review to identify eligible patients and will then reach out and ask for permission to discuss the research.

Screening:

Screening will take place over the phone via an IRB-approved phone screen script. Patients meeting initial eligibility criteria will be enrolled via Stanford REDCap e-consent.

Inclusion Criteria:

- Men and women with non-Hunner and Hunner lesion disease
- Meeting AUA definition of BPS: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder associated with lower urinary tract symptoms of greater than 6 weeks duration in the absence of infection or other identifiable cause.
- Age over 18
- Stable treatment for 1 month
- Urinary frequency 8 or higher while awake. Nocturia 2 or higher. BPIC-SS 19
- Agreement to not take opioids through the duration of the trial

Exclusion:

- Substance Use Disorder Diagnosis including Opioid Use Disorder Diagnosis
- Known allergy to naltrexone or naloxone
- Participation in another clinical trial
- Current or planned pregnancy, or breastfeeding
- Any intravesical instillation in last 8 weeks
- If on Elmiron, stable dose for last 3 months
- If on amitriptyline, stable dose for last 3 months
- Any botox within last 6 months
- Treatment for Hunners in the last 6 months
- Any new Interstim settings within last 3 months
- Any new pelvic floor physical therapy in last 12 weeks
- Any change in or new OTC meds over last 2 months.
- Any pain interventions in the preceding 6 weeks (epidural steroid injection, sympathetic block, peripheral nerve block, lumbar medial branch blocks)
- Opioids chronically for IC/BPS in the past and have been off for >1 year
- Recent short-term (within one week of enrollment) opioid use for flairs

Consent:

Consent will be obtained by a member of the research team knowledgeable about the study and able to answer the patient's questions. As much time as is necessary will be devoted to the consent discussion. Participants may speak with us over the phone at a later date if they wish to read the consent form further on their own. Participants will be given as much time as necessary to fully consider participation. It will be made clear to the participants that they are under no obligation to participate and their standard of care will not be affected. Participants will be given ample opportunity to discuss the consent form and ask questions.

Consent will be sent in email form using REDCap. Participants should be alerted that the research coordinator will read through the consent form with them, taking a maximum of 20 minutes to complete the process. The participant should only sign the form once all his/her questions have been answered.

There is a 7-day baseline assessment period followed by active treatment for 8 weeks. At completion of primary outcome assessment anyone on placebo could go on LDN and remain in an observational study with LDN treatment.

Study Procedures

After completion of informed consent, participants will be sent baseline assessments to be completed prior to starting the 7-day diary of assessments to determine subsequent trial eligibility. These assessments will include demographics, participant contact information, body pain diagram, brief pain inventory, Neuro-QoL SF, and PROMIS measures administered via CAT including:

- Pain Behavior
- Physical Function

- Sleep Disturbance
- Pain Interference
- Fatigue
- Anxiety
- Depression

The 7-day diary of assessments will include the numerical rating scale of pain, daytime voiding diary, nocturia diary, BPIC-SS, O'Leary Sant symptom and problem indices, and Global response assessment scale.

At the start of week 8 of treatment, participants will complete the same 7-day assessments of pain including the numerical rating scale of pain, daytime voiding diary, nocturia diary, BPIC-SS, O'Leary Sant symptom and problem indices, and Global response assessment scale.

Participants will complete a blinding assessment during the first 3-7 days and at the end of week 8 along with the same baseline assessments listed above including the body pain diagram, brief pain inventory, and PROMIS measures.

Randomization
Participants will be randomized on a 1:1 ratio to either LDN or placebo. The randomization sequence will be logged by the study coordinator in a REDCap randomization log blinded to other research staff and clinical team and outcome assessors.

Medication Schedule
One capsule will be saved for the purposes of confirming randomization if needed. The remaining 56 tablets will be delivered via mail labeled with the Subject ID. Each capsule will contain either 4.5mg LDN or placebo. Each patient will take 1 capsule per day for a total of 8 weeks consumed 1 hour prior to bedtime.

Adverse Event Calls
Patients will be contacted biweekly regarding adverse events and to assess average pain score over the last 24 hours.

Completion Call
After completion of week 8, participants will receive an unblinding consultation with the study coordinator completing randomization. Those randomized to placebo will have the option of continuing in an 8-week observational study of LDN at no cost. They will continue to receive adverse event calls and complete the same assessments starting at week 8 for the 7-day diary and additional baseline assessments listed above. Participants who were randomized to LDN will be referred back to their provider with a study letter if they wish to continue treatment.

Patient Withdrawn or Study Completion

If a patient is withdrawn from the study, lost to follow-up, or when a patient reaches the study endpoint, the study coordinator will document study completion by filling out the "Study Stop Point" instrument electronically in REDCap.

Patient Privacy

Patients will be identified with 2 identifiers when answering the telephone. Only HIPAA-compliant messages will be left for the patients. The research staff will ask the patient if the time is appropriate for a discussion of confidential information at the start of each phone call.

Data Management

Data will be maintained on appropriate case report forms when assessments are obtained via phone or will be entered directly into a REDCap database by the patient. First entry into the REDCap database will occur during the phone screening to assess study eligibility. Binders will be stored in locked cabinets or drawers.

Screening will be maintained through the Online Screening Form project in REDCap. The following information will be recorded: the patient name, the date the patient was spoken with, the researcher conducting the screening, the screening result (Screen Success, Screen Failure, and Evaluation in Progress). Enrolled patients will be maintained in the main project in REDCap. The Online Screening Form project will be deleted after enrollment for the project is complete. In the event that a larger study is undertaken with IRB approval, the Online Screening data will be maintained until that study finishes accruing.

All original case report forms will be stored in binder(s), behind consent forms printed after completion of REDCap e-consent.

Trial Safety

Potential Risks

LDN

At 4.5mg, side-effects are expected to be less than the standard oral dose of 50mg. Clinical anecdotal evidence suggests virtually no side-effects at this dosage. An exception is rare sleep disturbances. Naltrexone at 50mg daily is reported to produce side-effects in in the treatment of opioid use disorder including nausea, headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, and somnolence. Patients will be instructed to avoid the use of opioid medications during the course of the study.

Risk of Telephone Contact

The primary risk of telephone contact involves breach of confidentiality. All research personnel are trained in confidentiality procedures and adequate protections will be in place to minimize this risk. All research personnel must be HIPAA trained. Personnel enrolling participants must complete CITI training, Group 1 and 8 or Group 7.

Adverse Event Reporting

ADVERSE EVENTS (AE) will be monitored and recorded during the Intervention Protocol at each biweekly phone call. All adverse events will be recorded on an Adverse Event Case Report Form. The PIs will be immediately alerted to the occurrence of adverse events and will review the data regularly. Adverse events will be reported in aggregate to the IRB annually.
Known, minor adverse effects will be assessed for and tracked during biweekly calls. Known and unknown major adverse events will be documented, and reported to a study physician for follow-up.

SERIOUS ADVERSE EVENTS (SAE) is defined according to the FDA as any adverse experience that result in any of the following outcomes:

- Life-threatening
- Death
- Hospitalization/prolongation of hospitalization
- Congenital anomaly
- Persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

AN UNANTICIPATED PROBLEM (UP) is defined as unexpected (not in the consent form or package insert, or unexpected in its severity or frequency), harmful, and related (probably caused by the research treatment). Unanticipated Problems will be reported to the IRB within 10 days.

A MAJOR PROTOCOL DEVIATION OR VIOLATION includes any procedure that differs from the IRB approved protocol that was intended to eliminate an immediate hazard to the participant, was harmful, or is possible serious or continued non-compliance by a study staff member. Serious adverse events, unanticipated problems, and major protocol deviations will be communicated by the study staff to the PI and regulatory manager immediately.
All minor protocol deviations (those that do not meet the definition of a major deviation and do not affect the interpretation or outcome of the study) will be reported to the IRB annually.

Trial Monitoring

Adverse Events, Serious Adverse Events, Unanticipated Problems, and Protocol Deviations will be monitored on a continual basis and reported per information in the Adverse Events section.

Patient Adherence will be monitored as described in the relevant section.

The PIs will hold regular staff meetings to assess study team member understanding of responsibilities as per the Education section.

Additional ongoing monitoring will occur as detailed below. Results will be recorded on a Monitoring CRF. The PI will review and sign-off on the results and any suggested resolutions.

Case Report Form Completion

The first 10 patients will have case report forms and consent forms reviewed for accuracy and completion immediately after enrollment and entry into the follow-up period. After the first ten

patients, case report forms and consent forms will be evaluated for completeness every 3-6 months, whichever is sooner. A monitoring results report will be sent to the entire study team and results will be discussed at the subsequent study team meeting. Ongoing issues with data completion will be addressed with the individual team member and re-training may occur as necessary.

Consent Form Completion

Consent forms will be evaluated for completeness of all signatures, required initials, and dates. Any missing signatures will be obtained by mailing the patient a copy of the consent form and requesting the signature with the current date. Any missing study team signatures will be obtained and dated with the current date. Patients with missing signatures who are unable, or unwilling, to provide missing signature will be withdrawn from the study and data will not be used.

Electronic Data Verification

Electronic data is entered via the Stanford REDCap system. Patients enter responses directly into the electronic system. Case Report Forms are entered into REDCap by study staff.

Verification will occur via visual inspection. Discrepancies will be noted, original source data checked, and the correct value entered. All verified data will be noted with the reviewer's initials and date. Corrections will be noted with the date, initials, and reason for correction. Consistent errors will prompt a more comprehensive review of the data at the PIs discretion.

Evaluation of Efficacy

Primary Feasibility Outcome: Study completion in the groups to which patients are randomized.

Primary Efficacy Outcome: The proportion of subjects in the LDN and placebo groups that are responders with greater than 20% reductions in 7-day average of worst daily Numeric Rating Scale of Pain scores after 8 weeks of treatment. (Will compare pre-intervention to week 8)

Secondary Efficacy Outcomes:
Change in pain interference as measured by BPI, PROMIS depression, frequency, nocturia, BPIC-SS score, O'Leary Sant symptom and problem indices scores, and Global response assessment scale score.

Statistical Analysis

SAS Enterprise Guide will be used for all analysis. We plan a formal analysis of factors leading to failure to complete the study based on baseline variables obtained at the time of consent. Patients will be dichotomized according to the primary feasibility outcome: study completion in the group to which they were randomized. We will examine the differences in baseline variables between groups using the t-test for continuous variables and chi-square test for categorical variables. Logistic regression will be used to identify factors associated with failure to complete the study.

No interim analysis will be conducted. For efficacy, we plan an intention to treat analysis of all patients randomized for the primary efficacy outcome. Per-protocol analysis will include randomized subjects who completed 50% of diary entries during the primary endpoint period (weeks 1-8). Subjects are considered treatment failures with early protocol termination. Baseline demographics will be assessed via t-tests for continuous variables and chi-square tests for categorical variables. Covariates demonstrating significant differences between groups will be adjusted in the final multivariate model. SAS will be used for all analyses.

Sample Size

This is intended to be a pilot study. Pending results of the study, a study with 80% power assuming a 57% response rate in the LDN group vs. 30% response rate in the placebo group for the pain endpoint would require 104 patients.

1. Bosch PC. A Randomized, Double-blind, Placebo-controlled Trial of Certolizumab Pegol in Women with Refractory Interstitial Cystitis/Bladder Pain Syndrome. *Eur Urol.* 2018;74:623-630.

2. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clinical rheumatology.* 2014;33:451-459.