IC PaIN Trial: Interstitial Cystitis Pain Improvement with Naltrexone; The effect of low-dose naltrexone on symptoms and pain of patients with interstitial cystitis/painful bladder syndrome: a randomized placebo-controlled prospective trial.

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Background and Significance

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating condition characterized by urinary urgency, frequency, nocturia, and pain, without evidence of urinary tract infection or other identifiable causes (1, 2, 6). This debilitating disorder gravely impacts affected patients' quality of life, and about 2.7-6.5% of US women have bladder symptoms consistent with IC/PBS. (1). IC/PBS is a diagnosis of exclusion, and more invasive testing, such as cystoscopy should only be considered when the diagnosis is not straightforward, as the only consistent cystoscopic finding that leads to the diagnosis of IC/BPS is the appearance of inflammatory lesions or ulcerations, termed Hunner's ulcers; these are only seen in about 15% of patients diagnosed with IC/PBS(7). Glomerulations (pinpoint petechial hemorrhages) may also be seen, but can also be present in healthy patients (17).

IC/PBS often coexists with other chronic pain syndromes, such as irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia (5). Studies suggest there may be a common pathogenic mechanism, such as abnormalities in autonomic function and in visceral nociception (3, 4). The exact etiology of IC/BPS is unknown, but several hypotheses have been proposed. These include dysfunction of the superficial layer of the extracellular matrix of the glycosaminoglycan (GAG) layer, downregulation of tight junction proteins, increased urothelial permeability, mast cell activation, neurogenic inflammation, and psychosomatic factors (13)

Treatment of IC/PBS remains challenging as the etiology of the disorder remains unclear, symptoms vary across patients, and there are few high-quality trials evaluating the efficacy and safety of treatment options. As such, many treatments exist (7), and they are generally limited to symptom relief (6). In 2011, the American Urologic Association proposed a six-stage treatment algorithm (8). First-line therapies include conservative behavioral interventions such as a bladder diet and timed voiding or bladder drills.

Second line treatments include pelvic floor physical therapy, oral medications and intravesicle instillations (8). Several oral medications including amitriptyline (Elavil), hydroxyzine, cimetidine and sildenadfil have been used in the treatment (18, 21).However, only one oral medication is FDA approved for the treatment of IC/BPS: pentosan polysulfate sodium (Elmiron). This medication takes months (from three to nine months) to help relieve symptoms. In placebo-controlled trials in patients with moderate or severe IC pantosan polysulfate sodium, the improvement in symptoms was 28% for those with moderate IC and 32% for those with severe IC. The placebo effect seen in these trials was 13% for moderate IC and 16% for severe. Adverse effects are relatively minor and include nausea, diarrhea, and headaches; more concerning effects like reversible alopecia, rectal hemorrhage, and elevated liver enzymes have been observed, but are rare (14).

Amitriptyline (Elavil) is a tricyclic antidepressant used off-label to treat IC/BPS, and appears to be more effective at higher doses, but use at these doses is limited by bothersome and dangerous adverse effects. Studies examining the efficacy of amitriptyline are conflicting; one randomized trial found a greater than 30% decrease in symptom score when compared to placebo, at doses of 25mg-100mg (18). Another study failed to find improvement in symptoms using 10-75mg, but sub analysis demonstrated significant improvement in symptoms at doses greater than 50mg (19). Adverse effects include anticholinergic effects (dry mouth and urinary retention), sedation, weight gain, orthostatic hypotension, and cardiac conduction issues (21), as well as increase the risk of suicidal ideology in some patients (15, 16).

Antihistamines are also used to mitigate symptoms and treat IC/PBS; patients are recommended to take them at bedtime as they can be sedating, and in doing so, can help with nocturia. Antihistamines are also helpful in treating IC/PBS patients who have other allergic disorders, as one of the proposed disease mechanisms for bladder symptoms is hypersensitivity. Hydroxyzine is the most commonly used antihistamine for the treatment of IC/PBS, with typical doses of 25-50mg. The adverse effects include sedation and dizziness (21). The only randomized clinical trial of hydroxyzine did not find significantly higher symptom improvement when compared to placebo. (20)

Cimetidine and sildenadfil have also been used in the treatment. Cimetidine, an H2 antagonost at doses of 200mg three times a day or 300 to 400mg twice a day was found to have benefit over placebo in treating symptoms. Sildenafil, a phosphodiesterase-5 enzyme inhibitor, at doses of 25mg also improved IC symptom and problem scores. (21).

Intravesical instillations include dimethyl sulfoxide, heparin or lidocaine. Intravesical therapy involves need for catheterization with risks of urinary tract infection, dysuria, urethral irritation, and increased bladder pain. These are usually administered once a week for several weeks, take several weeks to improvements symptoms,and sometimes require maintenance installations (21).

Third line treatment involves cystoscopy with low pressure hydrodistension. If Hunner's ulcers are present, fulguration with either laser or electrocautery and/or injection with a steroid can be performed (21). Neurostimulation is fourth line treatment. Fifth line therapies include the oral administration of cyclosporine and intradetrusor botulinum toxin A. Lastly, patients with refractory IC/BPS may undergo urinary diversion. However, patients need extensive counseling that they may have persistent pain even with a cystectomy (8). The large number of treatments supports that at present no one treatment is effective in managing symptoms of patients with IC/BPS (7).

Naltrexone and its active metabolite 6-betanaltrexol are reversible competitive antagonist of the classic opioid receptors (mu-, kappa- and delta), and naltrexone also binds to opioid growth factor receptor (OGFr)(22, 23, 24, 25). First synthesized in 1963, naltrexone was approved by the FDA in 1984 for the treatment opioid addiction in doses of 50mg to 100mg daily (23), and in 1994 it was approved for the treatment of alcohol abuse disorder (22). The use of naltrexone at doses lower than 5mg daily or up to 1/10 of the regular dose used for treatment of opioid dependence is termed low-dose naltrexone (LDN) (23, 24). LDN was initially used in the 1990s in patients with acquired immune deficiency syndrome, as LDN appeared to have an immune-modulating effect. Since then, LDN has been used as an off-label treatment for pain and inflammatory conditions seen in several autoimmune diseases including multiple sclerosis, Crohn's disease and fibromyalgia. (25)

In low doses, naltrexone acts as a neuroprotective glial modulator by inhibiting activation of microglia, which are central nervous system immune cells, activated by various stressors. Upon activation, they produce inflammatory and excitatory molecules, resulting in a pro-inflammatory cascade, leading to neurotoxicity. Naltrexone specifically binds as an antagonist to Toll-like receptor 4 (TRL4). TLR4 has downstream cellular signaling leading to pro-inflammatory cytokines including interlukin-1, tumor necrosis factor-alpha, interferon- beta, excitatory amino

acids, substance P, and nitiric oxide, resulting in neuroinflammation, (23, 24, 25, 29, 31). TLR4 is expressed in the lower urinary tract of both humans and mice (36). LDN also plays a role in modulating the neuroimmune axis by its action on maturation of dendritic cells and in mitochondrial apoptosis (23).

LDN also upregulates opioid signaling by intermittent blockade of opioid receptors for 4-6 hours, creating a rebound effect, increasing endogenous opioids (22) and upregulates opioid signaling, by increasing the production of opioid receptors. (25) One of the endogenous opioids increased, beta-endorphins, is known to have anti-inflammatory properties (23, 24). The increased production of endogenous opioids may also inhibit the proliferation of B and T lymphocytes, and modulate the immune system (23, 25). Furthermore, upregulated endorphins may produce neuropsychological benefits (29).

Some adverse effects have been reported with the use of LDN. Vivid dreams, nightmares and insomnia are possible side effects, which can be mitigated by changing drug administration from bedtime to morning (23), and do improve with longer duration of taking LDN (34). There is also a reduction in pain relief from narcotics for at least six to 24 hours after taking low-dose naltrexone. In addition, low-dose naltrexone should not be used in patients who are currently receiving opioid analgesics. Naltrexone is designed to suppress cravings for opioid and alcohol use. Individuals with moderate to severe alcohol use disorder who take naltrexone may experience withdrawal symptoms if they stop drinking than can be potentially fatal due to the development of seizures. Individuals who use opioid pain medication and take naltrexone will not have the same pain relief, and may take more medication to overcome this, resulting in a potentially fatal overdose.

Patients taking thyroid replacement may require a lower amount of thyroid medication and should have thyroid function tests performed regularly. Elevation of liver enzymes is a potential risk with naltrexone treatment, but is not felt to be common with low-dose therapy. Other potential side effects may include but are not limited to gastrointestinal disturbances, such as stomach cramps and diarrhea (24, 26, 35), agitation, anxiety, flu-like symptoms, and headaches. One case report reported increased yawning, dry mouth, and thirst (35). The effect of naltrexone on the menstrual system has had mixed results, with some studies reporting no differences (51, 52), while one study noted an increase in pulsatile luteinizing hormone and prolactin secretion (53). No studies with low-dose naltrexone have explored changes in the menstrual cycle.

Low-dose naltrexone should be compounded with short-acting fillers, and calcium carbonate should be avoided. LDN should be stopped at a minimum of 24 hours prior to the time narcotics may be needed for pain relief for a scheduled surgical procedure (24, 26). Absolute contraindications include pregnancy and opioid dependence. (23)

<u>Summaries of studies conducted to date</u>

There have been no studies investigating the efficacy of using LDN in the treatment of IC/PBS to date. Studies have shown benefit in helping to relieve pain in patients with fibromyalgia(38, 42), complex regional pain syndrome (40) and chronic low-back pain (38). These conditions are commonly associated with IC/PBS. Studies with LDN have also demonstrated improvement in disease activity in autoimmune conditions like inflammatory bowel disease and multiple sclerosis(22, 24, 25, 29, 30, 31, 32, 33). There is also evidence that LDN may enhance emotional

well-being (25, 34), life-satisfaction (34), and may be beneficial in some dermatologic conditions (29, 41).

A pilot study of eight women who participated in a 10 week, single-blind, crossover study of the immune effects of LDN in women with fibromyalgia noted improvement in fibromyalgia associated pain, along with reduction in known inflammatory plasma marks that was significant from baseline. Of these eight women, two experienced adverse effects from pre-existing conditions (32). In an open-label study of 42 patients with irritable bowel syndrome who took 0.5mg LDN for four weeks, overall symptom relief was seen in 76% of the patients, and there was an increase in pain-free days. Two adverse events possibly related to LDN were observed: stomatitis and mild allergic dermatitis (46).

A pilot study with forty patients with primary progressive multiple sclerosis was performed to assess the safety and tolerability of six months of LDN. Five of the forty patients left the study due to one episode of enuresis, worsening neurologic complaints, increased bilirubin, urinary tract infection leading to renal failure, and opioid use during the study (45). Overall, the medication was well tolerated.

A double-blind, placebo-controlled, crossover study of 31 women with fibromyalgia were treated with LDN for twelve weeks and placebo for four weeks. There was a significant reduction in pain score between the LDN and placebo. Reported adverse effects were of vivid dreams (37%) and headache, and these were more significant in the LDN group (42)

A pilot study was done to examine the effectiveness of LDN in reducing the symptoms of fibromyalgia. Overall symptom severity was significantly reduced in the drug condition, as contrasted to baseline and placebo conditions. In the entire group of participants, LDN reduced fibromyalgia symptoms by 30.2% over placebo. Specific symptoms, including average pain, highest pain, fatigue, and stress, were also significantly impacted by the drug. The observed effects were accompanied by a very low incidence of side effects, suggesting LDN may be an effective and well-tolerated treatment option for individuals with fibromyalgia. (44)

There have been several studies using LDN in patients with multiple sclerosis. One study sought to evaluate the efficacy of 4.5mg nightly naltrexone on the quality of life of multiple sclerosis (MS) patients. In this single-center, double-blinded, placebo-controlled, crossover study, the efficacy of 8 weeks of treatment with 4.5mg nightly naltrexone was evaluated on self-reported quality of life of MS patients. LDN was well tolerated, and serious adverse events did not occur. LDN was associated with significant improvement on mental health quality of life measures (42). Another randomized-controlled trial desires to study the effect of LDN on the Quality of Life (QoL) of patients with relapsing-remitting and secondary progressive multiple sclerosis. While this study did not find therapeutic efficacy with LDN, the authors reported it was a safe therapeutic option. (43)

LDN has demonstrated amelioration of symptoms in conditions associated with interstitial/painful bladder syndrome. The proposed mechanism of action of LDN in animal studies suggests that neuroinflammation is reduced, opioid signaling is upregulated thus increasing the sensitivity of signaling, and endogenous opioids are increased, including beta-endorphins, which have anti-inflammatory properties and may produce neuropsychological benefits. IC/PBS is a poorly understood syndrome, characterized by pain and likely

inflammation with several treatment modalities that are either not effective, time consuming or have adverse risks associated with them.

Hypothesis: Our hypothesis is that low-dose naltrexone will have greater than 30% reduction in symptoms as defined by the Interstitial Cystitis Symptom Index in patients diagnosed with interstitial cystitis from baseline when compared to placebo. The 30% reduction in pain is a standard outcome measure in the pain literature (48, 49, 50). This improvement has been seen in prior studies where LDN was used to treat pain syndromes (44).

Objectives

The **primary objectives** of this prospective, randomized placebo-controlled study is to determine whether there is a significant decrease in IC symptoms and pain when treating interstitial cystitis/painful bladder syndrome with low-dose naltrexone. The **secondary objectives** of this study are to investigate if LDN has an impact on reducing the number of patient voids during the day, and at night, determine if there is an improvement in problems associated with IC, determine if there is a reduction in pelvic pain and urgency/frequency symptoms, determine if there is a reduction in pelvic pain and urgency/frequency bother, determine if there is an effect on quality of life in patients taking LDN, determine how well patients are able to tolerate low-dose naltrexone, and what adverse effects are experienced by patients taking low-dose naltrexone.

Specific aims

1. Determine if low-dose naltrexone is effective in treating IC symptoms
2. Determine if low-dose naltrexone is effective in treating IC pain
3. Determine if low-dose naltrexone is effective in reducing IC associated problems
4. Determine if there is an impact on reducing the number of patient voids during the day
5. Determine if there is an impact on reducing the number of patient voids at night
6. Determine if there is an effect on quality of life in patients taking LDN
7. Identify how well LDN is tolerated
8. Identify adverse reactions associated with LDN
9. Determine if taking LDN decreases adjuvant pain medication use

Outcome measures

1. The primary outcome measures will include
    a. The effect of LDN in decreasing symptoms associated with IC/PBS when treating with low-dose naltrexone as scored by the Interstitial Cystitis Symptom Index as compared to placebo.
    b. The effect of LDN in decreasing pain associated with IC/PBS when treating with low-dose naltrexone as scored by visual analog scale as compared with placebo.
2. The secondary outcome measures will include:
    a. The decrease in IC/PBS associated problems when treating interstitial cystitis/painful bladder syndrome with low-dose naltrexone as scored by the Interstitial Cystitis Problem Index
    b. The change in number of patient voids during the day when comparing LDN against placebo as determined from 24 hour bladder diary performed by patient prior to initiating treatment, and at the conclusion of 6 weeks of treatment.

c. The change in number of patient voids during at night when comparing LDN against placebo as determined from 24 hour bladder diary performed by patient prior to initiating treatment, and at the conclusion of 6 weeks of treatment.
d. The decrease is pelvic pain and urgency/frequency symptoms
e. The decrease in pelvic pain and urgency/frequency bother
f. Patient perceived changes in quality of life as measured by the medical outcomes study short form 36 (SF-36)
g. The percentage of patients complaining of adverse effects from LDN including vivid dreams, nightmares, insomnia, GI disturbances such as stomach cramps or diarrhea, agitation, anxiety, flu-like symptoms and headaches. A check list of these symptoms will be provided at the follow up visit.
h. Patient tolerability of LDN using a tolerability survey, as well as instructing the patient to return any remaining medication at the end of the 6 week study period.
i. The decrease in use of pain medications while using LDN as determined by a pain medication diary

Study Design

This will be a randomized double-blinded placebo-controlled prospective trial performed by the Center for Pelvic Health at the NorthShore University HealthSystem to determine the effect of using low-dose naltrexone on symptoms of patients with interstitial cystitis/painful bladder syndrome. Patients meeting diagnostic criteria for IC/PBS by AUA guidelines will be eligible to participate. A patient must then meet all applicable inclusion and exclusion criteria.

Primary endpoints

1. Effect of LDN in decreasing symptoms associated with IC/PBS
2. Decrease in pain symptoms associated with IC/PBS

Secondary endpoints

1. Decrease in IC/PBS associated problems
2. Decrease in number of patient voids during the day
3. Decrease in number of patient voids at night
4. The decrease is pelvic pain and urgency/frequency symptoms
5. The decrease in pelvic pain and urgency/frequency bother
6. Changes in quality of life
7. Patient tolerability of LDN
8. Adverse effects/reactions of LDN
9. Decrease adjuvant pain medication use while taking LDN

Number and Definition of Arms

There will be two study arms

1. Study medication arm: The first arm will receive LDN one 2mg capsule at night for two weeks, followed by two 2mg capsules (total of 4mg) for the remaining four weeks of the study.
2. Placebo arm: The second arm will receive the placebo for six weeks, and will take 1 capsule at night for the first 2 weeks, and then two capsules of the placebo at night for the remaining 4 weeks.

Blinding
This study will include a placebo. Study participants and providers will be blinded to which treatment they are receiving (placebo or LDN). Keefer's Compounding Pharmacy will create a placebo and compound the study medication into a 2 mg dose capsule. The NorthShore pharmacy will then place 70 capsules of placebo or study medication in moisture tight, light-resistant prescription bottles with appropriate labeling. When a participant enrolls, the pharmacy will provide the prescription bottle with the correct pills (either placebo or study medication) for the research personnel to pick up from the NorthShore pharmacy and give to the participant. This will ensure the trial remains double-blinded.

Randomization
The randomization will be done by statistician prior to initiation of the study, and will be kept with the pharmacy. Once a participant is enrolled, a call will be made to the pharmacy who will supply the correct medication, either the LDN or placebo, to maintain blinding.

Indication and patient population
LDN has demonstrated amelioration of symptoms in conditions associated with interstitial/painful bladder syndrome. The proposed mechanism of action of LDN in animal studies suggests that neuroinflammation is reduced, opioid signaling is upregulated thus increasing the sensitivity of signaling, and endogenous opioids are increased, including beta-endorphins, which have anti-inflammatory properties and may produce neuropsychological benefits. IC/PBS is a poorly understood syndrome, characterized by pain and likely inflammation with several treatment modalities that are either not effective, time consuming or have adverse risks associated with them.

Sample Size:
Using a randomized double-blinded design, we estimate that a sample size of 22 patients in each group (total N=44) will achieve an 80% statistical power to detect a minimum 30% reduction in pain symptoms for LDN over placebo group when using an alpha of 0.05.

Duration and Number of Sites
Enrollment will begin following approval by the IRB in the spring of 2020, and patient participation will last for six weeks. Patients diagnosed with IC/PBS by urogynecology providers at the Center for Pelvic Health in the NorthShore University HealthSystem will be eligible to participate.

Study Population
Patients diagnosed with IC/PBS by one of the urogynecology providers at the Center for Pelvic Health in the NorhShore University HealthSystem by diagnostic criteria for IC/PBS by AUA guidelines will be eligible to participate. A patient must then meet all applicable inclusion and exclusion criteria.

Inclusion criteria
1. Patients aged eighteen and older
2. Meet criteria for IC/PBS as defined by the American Urology Association as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms or more than six weeks duration, in the absence of infection or other identifiable causes" (8)

3. Newly diagnosed and treatment naïve for IC/PBS or previously diagnosed with IC/PBS, but who have no received treatment in the past four weeks. Patient who use anti-inflammatory medication on an as needed basis in the four weeks prior to the study will be included.
4. Have had a cystoscopy in the last 6 months prior to study entry to rule out confounding conditions
5. English speaking
6. Working telephone number
7. Able to attend research visits

Exclusion criteria:

1. Patients under the age of 18
2. Patients with known liver disease, including total bilirubin >1.2, AST> 32, ALT> 54 within the last six months or with enrollment screening testing
3. Patients with known kidney disease
4. Patients who have thyroid disease and who are taking thyroid replacement medications
5. Patients with known neurologic disease affecting bladder function
6. Patients with known bladder or urethral cancer
7. Patients with bladder, urethral, or ureteral calculi
8. Patients who have had a positive urine culture or a clinical UTI in the past 6 weeks
9. Patients who are currently pregnant or breast feeding (15)
10. Patients who are actively using opioid analgesics
11. Patients with moderate-severe alcohol use disorder
12. Patients who are actively using sleep aids
13. Patients who are regularly using anti-inflammatory medications, such as daily Celebrex for arthritis. Those who use an anti-inflammatory medication on an as needed basis may use the medication prior to enrollment in the study.
14. Patients who have had a known adverse reaction to naltrexone
15. Patients who are acutely ill
16. Patients who are diagnosed with a significant psychological comorbidity that would interfere with study participation (32)
17. Patients who have had a bladder instillation or had oral medical treatment for IC/PBS in the past four weeks.
18. Patients diagnosed with other chronic pelvic pain syndromes, such as endometriosis
19. Patients who are unable to swallow pills/capsules
20. Patients who have had previous treatment with low-dose naltrexone
21. Patients who have previously scheduled surgeries or procedure during the study time period that would require analgesia.
22. Patients who are sexually active and of childbearing potential who are unwilling to use an established and reliable form of contraception for the duration of the study.
23. Patients who are unwilling to have a serum blood test to assess serum transaminases and serum bilirubin.

Withdrawal criteria:

Patients can self-withdrawal at any time from this study, and they will be informed that doing so will have no impact on their medical care within the practice. Patients who become pregnant, experience serious adverse effects, or are deemed unable to continue the study for by study personnel will be withdrawn by study personnel. In the

event of withdrawal from the study, the participant will be asked to return any unused study medication.

Human Subject Protection

Rationale for Subject Selection

Patients meeting criteria by the American Urology Association definition of IC/PBS are the ideal study population to investigate a novel therapy for IC/PBS.

Evaluation of benefits, risks and discomforts

Patients enrolled in this study may benefit from this novel treatment for IC/PBS as they may find faster symptomatic relief in comparison to traditional treatment modalities, which may take weeks or months to have benefit. In addition, patients in both the medication and the placebo group will receive first-line behavioral therapy for IC/PBS that include a bladder diet and bladder drills. Some adverse effects have been reported with the use of LDN, the most common of which include vivid dreams, nightmares, and insomnia. Other potential side effects include but are not limited to gastrointestinal disturbances, such as diarrhea and stomach cramps, agitation, anxiety, flu-like symptoms, increased yawning, dry mouth, increased thirst, and headaches. Naltrexone is designed to suppress cravings for opioid and alcohol use. Individuals with moderate to severe alcohol use disorder who take naltrexone may experience withdrawal symptoms if they stop drinking than can be potentially fatal due to the development of seizures. Individuals who use opioid pain medication and take naltrexone will not have the same pain relief, and may take more medication to overcome this, resulting in a potentially fatal overdose. Patients should not experience any discomfort in taking the medication. There is an added burden of an additional visit to enroll in the study, having two blood draws, two 24-hour bladder diaries, as well as completing questionnaires. An additional benefit is that more attention and better care is given to patients enrolled in studies.

Reproductive risk

The reproductive risks of low-dose naltrexone are unknown. All study participants who are sexually active and of childbearing potential will be required to undergo a urine pregnancy test at the start of the study, and to use an established form of contraception, such as oral contraceptives, intrauterine device, implants, patches, vaginal rings and/or barrier device for the duration of the study. Study participants will be instructed to discontinue study medication in the event that they become pregnant, and to notify research personnel, so they can be removed from participation in the study.

Premenopausal study participants will be advised to keep a menstrual cycle chart to monitor any deviation from their regular cycle, which will be provided to them. They will be informed that in the event of any menstrual irregularity, they should inform study personnel, and they should be thoroughly evaluated in our office, including a pregnancy test.

In addition, study participants will be advised not to breastfeed while participating in the study. The use of low-dose naltrexone in breastfeeding has not been studied.

The study consent form states the following, and will be reviewed with all potential study participants:

"You should not become pregnant while on this study. It is not known whether the study drugs will affect an unborn baby, a pregnant person, or impact sperm. You should use effective birth control methods if you become pregnant and you wish to be in this study. If you become pregnant during this study, you should notify the study doctor right away. If you become pregnant you will have to stop participation in the study. Birth control may not stop pregnancy. Only totally stopping sexual intercourse can guarantee that pregnancy will not happen. If you think your birth control has failed, you should not rely on home pregnancy tests. Instead, you need to call your study doctor right away to arrange for medical pregnancy tests.

You should discontinue all study medications should you become pregnant. Additionally, you should not be breastfeeding an infant/toddler while in this study"

COVID-19 Risk
COVID-19 poses a real risk to the safety of study participants and research personnel. This study protocol was written prior to the start of the pandemic. As such, a step-by-step start up plan was created in March 2021 to minimize the risk of exposure to the virus by study participants and research personnel. Please see the attached document for specifics of the protocol.

Consent and assent process and documents
To qualify, patients must first be diagnosed with IC/PBS by one of the urogynecology providers at the Center for Pelvic Health in the NorhShore University HealthSystem. As this patient population is difficult to identify based on chief complaint, potential study participants will be recruited after diagnosis of IC/PBS.

Patients will be introduced to the study in a few different ways. The provider may mention the study and supply the consent form; the provider may mention the study, or if study personnel is available and the patient's schedule allows, study personnel will meet with the potential participant in person. At that time, they will be asked about inclusion and exclusion criteria and be given a consent form, if they are interested. For patients not seen by study personnel at the time of their appointment, they will be contacted by phone by research personnel. Any patient declining participation will be noted, so as not to contact them about this study again.

Potential participants will be encouraged to read the consent form thoroughly and to discuss the study with family, a primary care physician, other physicians, and/or friends. If they desire to participate, they will make an appointment to return to the Center for Pelvic Health of the NorthShore University HealthSystem to sign the consent form, to complete intake forms, to have their blood drawn, and to receive the study medication.

Compensation
Study participants will receive $50 gift card upon completion of the study if they finish all study questionnaires, blood work, vital sign assessments, and the two bladder diaries. This will be given to them in person at their follow up appointment or mailed to them once all materials are completed. In the event that study participants are unable to complete the study, they will receive prorated compensation of $20 in the form of a gift card.

Schedule of visits/assessments

Screening/eligibility determination
Patients must first receive a clinical diagnosis of IC/PBS by one of the urogynecology providers at the Center for Pelvic Health in the NorhShore University HealthSystem. As this patient population is difficult to identify based on chief complaint, potential study participants will be recruited after diagnosis of IC/PBS. Patients interested in participating will be screened by research personnel, either in person, or over the telephone. Only patients meeting all relevant inclusion criteria, and those who do not meet the exclusion criteria will be able to participate. These individuals will be given the consent form, either in person or through the mail.

Consent
Consent will be obtained in clinic by research personnel, after study participants have had ample time to discuss the study with family, a primary care physician, other physicians, and/or friends. They will make an appointment with research personnel at a convenient time for the study participant.

Enrollment
After signing the consent form, participants will be given a study identification number (ID). This ID will not be linked to their medical record. There will be a master sheet kept in a locked filing cabinet at the Center for Pelvic Health at the Skokie Ambulatory Care Center. Only those study personnel on the R8.1 delegation log will be able to access this master sheet. The participant's name and study ID will also be typed into a spreadsheet and stored on the Collaboration Portal, and access will only be given to Nani Moss.

Baseline Evaluation
Study participants will be asked to answer demographic information including:

1. Age
2. BMI
3. Menopausal status
    a. If premenopausal, type of contraception
4. Tobacco use
5. Marijuana use
6. Pain medication use in the last month
7. Prior medical and surgical history, including medications and allergies
8. Length of time they have been experiencing symptoms of IC/PBS
9. Specific symptoms they are experiencing

Along with the following validated questionnaires:

1. Interstitial Cystitis Symptom Index
2. Interstitial Cystitis Problem Index
3. Pelvic pain and urgency/frequency patient symptom scale (PUF)
4. Visual Analog Scale
5. Medical Outcomes Study Short Form 36 (SF-36)
    a. This will be scored prior to the participant leaving the office. In the event that they have low scores in areas assessing "role limitations due to emotional problems," (questions 17, 18, 19) "energy/fatigue" (23, 27, 29, 31) or "emotional well being" (24, 25, 26, 28, 30), participants will be offered a referral to discuss any mental health concerns, if they desire.

At the enrollment appointment, vital signs will be obtained, including blood pressure. If participants are premenopausal, they will be asked to undergo a urine pregnancy test. Patients will be given a lab requisition form for a hepatic panel at the time of enrollment for a blood draw to evaluate serum transaminases and bilirubin. Once participants have their blood draw, they will be given and instructed to take one capsule nightly for two weeks, then increase their dosage to two capsules at night for four weeks. They will be given a log where they can record the date and time they take the medication, along with space for any additional notes they wish to share. Prior to starting the study medication, patients will be asked to complete a 24-hour bladder diary. They will also be instructed not to start the study medication until their blood work results with normal liver function. Participants will be called with the results of their blood work.

Treatment Schedule
Participants will be given a prescription bottle with 70 capsules. For the first two weeks, participants will take 1 capsule at night. After two weeks, they will take two capsules at night. Participants will be given a log to record taking the medication.

All patients will receive information about a bladder diet and bladder drills to assure patients are receiving treatment known to be beneficial in IC/PBS.

Follow-up Schedule
If serum transaminases and bilirubin are elevated at the baseline blood test, study participants will be notified of their results, withdrawn from the study, and encouraged to follow up with their primary care provider.

After two weeks, participants will be contacted by research personnel to check to see that they completed the bladder diary, to make sure they are taking the medication, and to ask about any adverse effects from the study medication. If adverse effects are noted, study personnel will attempt to trouble shoot. For example, the most commonly reported adverse effect in previous trials is vivid dreams. If study participants experience this, they will be encouraged to try taking the medication in the morning. If study participants have not completed the 24 bladder diary, they will be encouraged to do so as soon as possible.

Participants will also be encouraged to call prior to this two week check in telephone call with any questions or concerns that arise.

At the completion of the six weeks, patients will return to the office for:

1. A provider appointment to discuss additional therapeutic options for treatment of IC/PBS
2. Vital sign assessment including blood pressure
    a. If blood pressure is elevated from baseline, will recommend patients repeat a blood pressure with the primary care provider; if they do not have a primary care provider, we will have them obtain a blood pressure check in 1 week.
3. Blood draw for study exit hepatic panel
    a. Study participants will be called with the results of their post-study blood test results
4. Complete study questionnaires
    a. Interstitial Cystitis Symptom Index

   b. Interstitial Cystitis Problem Index
   c. Pelvic pain and urgency/frequency patient symptom scale (PUF)
   d. Visual Analog Scale
   e. Medical Outcomes Study Short Form 36 (SF-36)
      i. This will be scored prior to the participant leaving the office. In the event that they have low scores in areas assessing "role limitations due to emotional problems," (questions 17, 18, 19) "energy/fatigue" (23, 27, 29, 31) or "emotional wellbeing" (24, 25, 26, 28, 30), participants will be offered a referral to discuss any mental health concerns, if they desire.
   f. Study completion and tolerability survey
5. Return unused study medication
6. Provide two completed 24-hour bladder diaries
   a. One performed prior to starting the medication
   b. One performed at completion of the study last day
   c. Participants will be given instructions about completing this on the last day of taking study medication, or the day after completion of all study.

Ethical and Regulatory considerations
Regulatory document collection:
Patients will fill out the above mentioned forms prior to starting the study, then again at the conclusion of the study. Documents will be kept in a locked filling cabinet and only those individuals listed on the RI 8.1 delegation log will be able to access it. In addition, the information will be typed into spreadsheets and stored on the Collaboration Portal.

IRB review
IRB approval of the revised protocol including the comments and recommendation from the FDA will be submitted for review prior to initiation of enrollment.

Informed consent administration:
Potential study participants will be given the consent form to participate in this study prior to being asked to formally enroll by signing the consent form to allow for ample time to read the consent form and to discuss the study with family, other physicians and friends, if they so choose.

Study procedures
Patients who have been newly diagnosed with IC/PBS or those who have not received treatment in the past four weeks, who are interested in participating in the study and who meet inclusion, and who do not meet exclusion criteria will be given a consent form in the clinic or sent one by mail. Potential participants will be encouraged to discuss the study with family, a primary care physician, other physicians, and/or friends.

Once patients decide they would like to participate, they will make an appointment to return to the Center for Pelvic Health of the NorthShore University HealthSystem and meet with research personnel for:

1. Consent
2. Vital sign assessment including blood pressure
3. Completion of intake forms

4. Randomization
5. Blood collection
6. Urine pregnancy test if premenopausal
7. Distribution of study medication.
8. All patients will receive information about a bladder diet and bladder drills to assure patients are receiving treatment known to be beneficial in IC/PBS.

Prior to starting the study medication, patients will be asked to complete a 24-hour bladder diary.

The study medications will be listed in epic as "naltrexone/placebo" to inform other providers that the patient may be taking low-dose naltrexone as part of a research study. The study medication and placebo will be free of charge to patients, placing no additional financial burden on the patient or insurance company. The blood collection and hepatic panel will also be performed free of charge for study participants.

Participants will also be encouraged to contact research personnel with any questions or concerns at any point during the research study. If serum transaminases and bilirubin are elevated at the baseline blood test, study participants will be notified of their results, withdrawn from the study, and encouraged to follow up with their primary care provider.

Participants will be instructed to take one capsule nightly for two weeks, then increase their dosage to two capsules at night for four weeks. They will be given a log where they can record the date and time they take the medication.

After two weeks, participants will be contacted by research personnel by phone to check to see that they completed the 24-hour bladder diary, to make sure they are taking the medication, and to ask about any adverse effects from the study medication. If adverse effects are noted, study personnel will attempt to trouble shoot. For example, the most commonly reported adverse effect is vivid dreams. If study participants experience this, they will be encouraged to try taking the medication in the morning. If study participants have not completed the 24 bladder diary, they will be encouraged to do so as soon as possible.

At the completion of the six weeks, patients will return to the office for:

1. A provider appointment to discuss additional therapeutic options for treatment of IC/PBS
2. Vital sign assessment including blood pressure
3. Blood collection for study exit hepatic panel
4. Complete study questionnaires
    a. Interstitial Cystitis Symptom Index
    b. Interstitial Cystitis Problem Index
    c. Pelvic pain and urgency/frequency patient symptom scale (PUF)
    d. Visual Analog Scale
    e. Medical Outcomes Study Short Form 36 (SF-36)
    f. Study completion and tolerability survey
5. Return unused study medication
6. Provide two completed 24-hour bladder diaries
    a. One performed prior to starting the medication

   b. One performed at completion of the study last day
      i. Participants will be given instructions about completing this on the last day of taking study medication, or the day after completion of all study
7. This concludes their participation in this research study

Study drug and comparator
Drug shipment/receipt: The medication will be compounded by Keefer's pharmacy into 2mg capsules. The medication will be shipped to the Skokie inpatient pharmacy.
Drug packaging: Keefer's pharmacy will be asked to supply 1,540 capsules of the study medication and placebo, which is enough for twenty-two study participants. Seventy capsules of medication and identical placebo will be placed into separate but identical moisture tight and light-resistant amber vials by the NorthShore pharmacy with specific lot numbers and expiration dates as determined by Keefer's pharmacy.

Drug storage: The medication will be stored at the NorthShore Skokie inpatient pharmacy in tight, light-resistant containers. The Beyond-Use-Date (BUD) for this nonaqueous formulation of low-dose naltrexone HCl capsules will be labeled as six months.

Drug preparation: The LDN study medication and placebo will be compounded and prepared by Keefer's pharmacy.

Drug dispensing and accountability: The medication will be dispensed by the Skokie NorthShore pharmacy to the research personnel to provide to the participant. Participants will return their pill vial, including any unused medication at the time of their six-week follow up visit. Any residual medication will be documented, and the medication returned to the pharmacy for disposal by onsite destruction.

Drug administration: the patients will take their appropriate randomized medication for a total of six weeks. The first two weeks, patients will take one capsule at night, and for the last four weeks, they will take two capsules at night.

Contraindications/concomitant medications: Absolute contraindications to taking LDN include pregnancy, moderate-severe alcohol use disorder, and opioid dependence.
In the case reports and small randomized trials, LDN does not appear to interfere with other medications patients were taking at the time of the study.

Breaking the blind: In the event of an adverse event, a phone call can be made to the NorthShore Skokie inpatient pharmacy to determine if they are taking the study medication or placebo. If this should occur, the phone call should be followed up with written documentation in the form of an email with notification of the break in the blind.

Drug destruction: Study participants will be requested to return the pill vials to clinic. Any residual medication will be documented, and the medication returned to the pharmacy for disposal by onsite destruction.

Medication compliance assessment: Study participants will be requested to return the pill vials to clinic. Any residual medication will be documented, and the medication returned to the

pharmacy for disposal by onsite destruction. Participants will also be asked to keep a log of when they take their medication.

Safety Assessment

Adverse Experiences (AEs): Study participants will be asked to document any adverse experiences or events they experience while participating in the study. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used for adverse event reporting. The CTCAE describes an adverse event as "any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure**."**

Documentation of AEs: All AEs experienced by study participants will be documented in the collaboration portal.

Coding of AEs: AEs will be given a grade according to the CTCAE version 5.0

Serious Adverse Events

Definition: Serious AEs will be given a grade according to the CTCAE version 5.0
Reporting: Serious AEs will be documented in writing

Expected AEs/toxicities: To date, there are no reports of interactions between LDN and other medications. The sample size of these studies is small, and there are likely a large number of interactions that have yet to be tested (39). Other trials have reported vivid dreams (34), nausea, epigastric pain, mood alteration, mild irritability, headache, and joint pain. (43)

Unplanned visits: Study participants will be encouraged to contact research personnel with any questions or concerns they have about the medication or the study. If study personnel determine the patient needs a clinic visit, the patient will be seen by a provider, and that visit will be documented in Epic as a medical visit. The visit will also be included in the patient's research documentation.

Subject Completion and Early Withdrawal

Procedures for completion

Upon completion of the six-week study period, participants will have an appointment with their physician to discuss additional treatment options for IC/PBS. At that visit, study participants will complete study forms and submit two 24-hour bladder diaries, and have a blood sample collected. They will receive $50 in compensation. In the event that study participants are unable to complete the study, they will receive a prorated compensation of $20 in the form of a gift card.

Procedures for early withdrawals:

Patients will be free to withdrawal for any reason or if deemed necessary by research staff or any other medical provider.

Reasons for withdrawals:

Research personnel and medical providers may withdrawal participants at their discretion. Possible reasons for research staff to withdrawal study participants include elevated serum

transaminases and bilirubin, inability to make scheduled appointments, moving out of the area, inability to properly take study medication as seen by returning a large number of capsules. If study participants are withdrawn, the reason for their withdrawal will be documented.

Data collection method
Data will be collected by paper questionnaires. These hard copies will be kept in a locked filing cabinet at the Center for Pelvic Health of the NorthShore University HealthSystem at the Skokie Ambulatory Care Center. Only study personnel in the delegation log will have access to this filling cabinet. The data will be entered into an electronic format in the collaboration portal. Patient privacy will be maintained by keeping a master list of patient and study identification number, which will be in the locked filing cabinet. No patient identifiers will be kept in the data collection spreadsheet.

Study Monitoring/Audits:
Once a month, study data protocol will be reviewed by research personnel to ensure proper documentation of study participants and address any issues or concerns that have arisen.

Data Analysis
Efficacy analyses: The data will be analyzed on the basis of intention-to-treat (ITT) principle. Two-way repeated measures analysis of variance (ANOVA) will be used to compare the efficacy between experimental and placebo group. We will conduct mixed-effects logistic regression model (for binary outcome) and linear mixed model (for continuous outcome) with patient-specific random intercept and treatment, time, and treatment-time interaction to examine the differences between two treatment groups. Baseline demographics and clinical characteristics will be entered as time-invariant covariates if baseline group differences are observed. Statistical analyses will be using SAS 9.4 (SAS Institute Inc., Cary, NC), and p-value<0.05 will be considered statistically significant.

Safety analyses: This will be based on the incidence and type of AEs. Safety variables will be summarized for all patients and compared between two treatment groups using t-tests (parametric) or Mann-Whitney U test (nonparametric) for categorical variables and Chi-square or Fisher's exact test for continuous variables.

Patient tolerability to the study medication: A tolerability survey will be administered at the follow up visit. The survey will include frequency of skipping a dose or discontinuation of medication due to pill size or required frequency of taking the medication. Percentage of patients who discontinue the study medications will be compared between both groups using a one sample t-test.

Interim analyses: The data will be reviewed after the enrollment of half study participants to evaluate for serious adverse events. In addition, as participants will receive a 2 week phone call by research personnel, and will be encouraged to reach out with any issues or concerns, research personnel will be aware of adverse events on a continual basis. At the time a patient notifies research personnel of an adverse event, the research team will discuss the event and whether it is safe to continue the study.

Confidentiality
Definition and Purpose

A confidentiality agreement (CDA) is a legal agreement between at least two parties which outlines information the parties wish to share with one another for certain evaluation purposes, but wish to restrict from wider use and dissemination. These agreements can also be referred by different titles including Confidential Non-Disclosure Agreements (NDAs) or Secrecy Agreements. In these agreements, the parties agree not to disclose the proprietary, non-public information covered by the agreement. CDAs are commonly executed when two parties are considering pursing a relationship together and need to understand the other's processes, methods, or technology solely for the purpose of evaluating the potential for a future relationship. CDAs are also valuable to protect the ability to patent an invention, something that can be compromised if a disclosure of the invention becomes public knowledge

During this research, protected health information (PHI) will be collected, PHI will only be used for study purposes, which may include access to past, present, and future medical records, including information housed in the electronic medical record, information about research procedures including research office visits, medical tests, procedures, interviews and questionnaires by research personnel. Non-research staff within NorthShore who need the information to perform their jobs, such as treatment and billing personnel may review this material. Other individuals who may have access to PHI include the NorthShore IRB board, NorthShore research quality improvement program, federal and state agencies, and public health and safety authorities. PHI will only be shared when necessary, and those individuals will be asked to protect the privacy of study participants.

Potential benefits, risks, or adverse effects:
Patients enrolled in this study may benefit from this novel treatment for IC/PBS as they may find faster symptomatic relief in comparison to traditional treatment modalities, which may take weeks or months to have benefit. In addition, patients in both the medication and the placebo group will receive first-line behavioral therapy for IC/PBS that include a bladder diet and bladder drills. Some adverse effects have been reported with the use of LDN, the most common of which include vivid dreams, nightmares, and insomnia. Other potential side effects include but are not limited to gastrointestinal disturbances, such as diarrhea and stomach cramps, agitation, anxiety, flu-like symptoms, increased yawning, dry mouth, increased thirst, and headaches. Contraindications to the use of LDN include pregnancy, moderate-severe alcohol use and opioid dependence. Patients should not experience any discomfort in taking the medication. There is an added burden of an additional visit, collecting two 24-hour bladder diaries, as well as completing questionnaires. An additional benefit is that more attention and better care is given to patients enrolled in studies.

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Appendices

1. Informed consent form
2. Interstitial Cystitis Symptom and Problem Index
3. Visual Analog Scale
4. Bladder Diary
    a. Pretreatment
    b. Post treatment
5. Medication log
6. Pelvic pain and urgency/frequency patient symptom scale (PUF)
7. Medical Outcomes Study Short Form 36 (SF-36)
8. Demographic questionnaire
9. Study completion questionnaire
10. Patient tolerability survey
11. Study timeline for patients
12. Bladder diet
13. Bladder drills
14. Phone scrip for interest in study (pre-screened patients)
15. Phone script for 2 week check in