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Effect of Low dose Naltrexone versus Naproxen Extended-release for Pain Relief in knee osteoarthritis, a Triple-blinded, Non-inferiority Phase II Randomized Controlled Trial (FREEDOM) - Study protocol

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Abstract:

Background and objectives: Osteoarthritis (OA) is a degenerative articular disease that affects approximately 240 million people worldwide, with knee OA accounting for 80% of this burden. One of the aims of pharmacological treatment in OA is to reduce pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective for pain relief in OA but have considerable renal, hepatic, cardiovascular, and gastrointestinal adverse effects, with the resultant increase in morbidity and mortality. Naltrexone is an orally activated opioid antagonist that has varied dose-dependent pharmacodynamic effects: Analgesic and anti-inflammatory effects are exhibited only at low dosage ranges of 0.5mg to 4.5mg (Low Dose Naltrexone LDN) while retaining a favorable adverse effect profile. This study aims to test the non-inferiority of LDN against Naproxen.

Methodology: This is a prospective phase II triple-blinded, two-arm, parallel-group, non-inferiority randomized controlled trial. The intervention group will receive low dose naltrexone 4.5 mg once daily, and the control group will receive extended-release naproxen 1000 mg once daily during the 12 week trial duration. Our sample size will be 118 patients recruited from a single Orthopedic referral center in the USA.

Discussion: The use of LDN for pain relief in osteoarthritis (OA) may be beneficial due to its favorable adverse effect profile. To the best of our knowledge, there is no published data on LDN use in OA even though preliminary evidence has documented its safety and tolerability in a variety of chronic pain conditions.

INTRODUCTION

Background

Osteoarthritis (OA) is a degenerative articular disease that affects approximately 240 million people worldwide. One of the most disabling conditions in the elderly is knee OA, accounting for 80% of this burden (Cross et al., 2014). The origin of pain in OA might be from the inflammation within joint structures like the synovium, menisci, ligament insertions, and subchondral bone with the periosteum also transmitting pain from nociceptors stimulated by physical, mechanical, and chemical stimuli via the pain-sensing afferent neurons (O'Neill & Felson, 2018).

Abbreviations

OA: Osteoarthritis
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
LDN: Low-dose Naltrexone
VAS: Visual Analogue Scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis index
SF-36: Short Form Health Survey
TLR-4: Toll-like receptor 4
IL: interleukin
TNF: tumor necrosis factor
ESR: Erythrocyte sedimentation rate
HTN: Hypertension
ACR: American College of Rheumatology
KL: Kellgren & Lawrence
KFT: Kidney function tests

Although anxiety, depression, and sociocultural factors can influence pain perception, significant evidence points towards central and peripheral nervous system sensitization as the source of pain in OA (Lluch et al., 2014; Neogi et al., 2016).

Non-steroidal-anti-inflammatory drugs (NSAIDs) are a common pharmacological option for pain relief in OA even though they have considerable renal, hepatic, cardiovascular, and gastrointestinal adverse effects that result in increased patient morbidity and mortality (Crofford, 2013). Naltrexone, a cyclopropyl derivative of oxymorphone similar in structure to naloxone and nalorphine (a morphine derivative), is an orally activated opioid antagonist that has pharmacodynamic effects that vary depending on the administered dose (Calabrese, 2013). Its desirable analgesic and anti-inflammatory effects are exhibited when administered at a low dosage of 0.5mg to 4.5mg (Low Dose Naltrexone).

Low-dose Naltrexone (LDN) exerts these effects through two distinct receptors; the mu-opioid receptors which mediate the endogenous analgesic process via β endorphins, and the Toll-Like receptor 4 (TLR4), which downregulates the signaling of pathways that affect multiple inflammatory cytokines including interleukin (IL) -1, Interferon β, nitric oxide, and tumor necrosis factor (TNF)-α, resulting in the anti-inflammatory effect of LDN (Okun et al., 2011).

The clinical utility of LDN has been studied in various chronic pain and inflammatory conditions such as Crohn's disease, Fibromyalgia, Multiple sclerosis, and Rheumatoid arthritis with good results (Parker et al., 2018). However, the effects of LDN in mild to moderate forms of OA are unknown. A paucity of previous trials evaluating the non-inferiority of LDN to standard therapy also raises the uncertainty of the use of LDN either as a primary agent or as an adjunct for the relief of the pain of OA (Katz et al., 2010). The principal advantages of LDN are that it is a generic medication that is inexpensive with fewer reported adverse effects when compared to the common NSAIDs used in chronic pain management (Patten et al., 2018).

Objectives

This study aims to test the non-inferiority of LDN against Naproxen, an NSAID that has been documented for use as an effective pain reliever in OA (van Walsem et al., 2015). The primary objective will be assessed using the Visual Analogue Scale (VAS) scored at baseline and the end of the 12th week. Secondary objectives will also be assessed with the VAS score at the 4th and 8th week and the WOMAC and SF-36 questionnaires will be used to assess the quality of life of study participants. The average consumption of acetaminophen for breakthrough pain will also be compared between groups.

METHODS

Study Design

This study is a phase II, two-arm, parallel-group, triple-blinded, non-inferiority randomized controlled trial. The intervention group will receive low dose naltrexone 4.5 mg once daily, and the control group will receive extended-release naproxen 1000 mg once daily during this 12-week trial.

Study Setting

We will conduct this trial in one Orthopedic referral center in the United States. Orthopedic Surgeons and Primary care physicians within the city will be contacted through letters requesting them to refer their patients to be screened for inclusion into the trial.

Eligibility Criteria

Participants aged 50 to 85 years who meet the inclusion and exclusion criteria for the study will be recruited. OA diagnosis would be based on the American College of Rheumatology (ACR) clinical diagnostic criteria for idiopathic knee OA. Other inclusion criteria will include ESR less than 40 mm/hour, rheumatoid factor less than 1:40; Kellgren and Lawrence radiographic classification of OA grade two or higher (Kellgren & Lawrence, 1957); and a VAS score of more than 40 mm at the baseline.

Participants should also be capable of understanding and agreeing with the informed consent.

At the time of entry into the trial, participants will also undergo a VAS test-retest evaluation every 30 minutes for 2 hours to assess the individual variability of VAS because of the subjective nature of VAS. Individual variability of not more than 4 mm on VAS test-retest scoring will be considered acceptable for being enrolled into the trial (Bijur et al., 2001).

Exclusion criteria include patients who have contraindications to the use of Naltrexone or Naproxen, such as ischemic heart disease, heart failure, uncontrolled HTN with systolic pressure (> 180 mmHg or < 90 mmHg), or a sitting diastolic pressure greater than 100 mmHg or less than 50 mmHg at initial screening, cerebrovascular disease, history of severe liver disease, kidney disease, or CrCl less than 30 ml/min. Patients will also be excluded if they are pregnant or lactating; have a history of allergy to either Naltrexone or Naproxen, have drug or alcohol abuse/dependence, and history of major depressive disorder refractory to medical treatment. Patients with secondary knee OA or knee surgery in the last 9 months (e.g., arthroscopy), who have an active peptic ulcer or a history of inflammatory bowel disease, who plan surgery during the study, or had intra-articular procedures to relieve pain within 3 months (corticosteroid and hyaluronic acid injections), or patients with active cancer or acute or chronic infections that may require antimicrobial therapy during the trial, or who have previously used LDN for more than eight weeks, or have coagulopathy or are on anticoagulants will also be excluded from the trial.

Interventions

The intervention group will receive naltrexone 4.5mg orally once daily and the control group will receive naproxen 1000mg orally once daily. The clinical trial unit will prepare medication packs containing 28 tablets, with these packs numbered according to the randomization list. Dispensing of naltrexone and naproxen will be on a 4-weekly basis, in medication packs of 28 tablets, until the 12 weeks are completed.

Naltrexone and NSAIDs have both been documented to cause dyspepsia. As a result, if a participant develops dyspepsia, treatment will be with a proton-pump-inhibitor, H2 receptor antagonist, or by reduction of the dose of the investigational drug to alternate daily dosing. Upper gastrointestinal endoscopy would be recommended where appropriate.

Randomization and Blinding

The randomization of participants will be accomplished using the blocked randomization technique with variable block sizes of 4 and 6 subjects to reduce predictability and also to maintain allocation concealment in groups. This randomization strategy will be achieved via an online randomization plan generator.

The randomization sequence will be generated by a research assistant who will be responsible for the participant's allocation alongside a pharmacist. The study is a triple-blinded trial in which health care providers, participants, and data analysts are blinded. To avoid bias, we will ensure that the medication to be taken by participants in both the intervention and control groups are delivered in similar presentation and packaging, with the tablets having the same color, size, shape, feel, taste and smell; both medications will be administered once daily. The assessments regarding the subjects' evaluation and the application of the VAS pain score will be conducted by healthcare providers. The data analysts will access the groups labeled with non-identifying terms - A (for group control) and B (for group intervention). The research assistant and pharmacist will be the only ones aware of the patient's randomization and allocation and will have the responsibility for distributing the medications to the patients. The research assistant will be the first contact in cases where emergency unblinding may be necessary especially if a participant has a medication-related adverse reaction.

In case of any major adverse effects, including but not limited to severe gastrointestinal bleeding, acute coronary syndrome or myocardial infarction, cerebrovascular accident or transient ischemic attack, renal insufficiency, Stevens-Johnson syndrome, anaphylaxis or severe allergic reaction, agranulocytosis, and hepatitis, the research assistant and the pharmacist will be available through a direct phone line at all times in case emergency unblinding is required for one of the subjects.

If a clinical situation that has not been listed develops but is not life-threatening and the subject's health care provider considers that the knowledge of all medications currently in use is extremely necessary for further treatment, we propose the following algorithm to be used: first, the health care providers should contact the investigator responsible for the trial. Secondly, the physician will expose the arguments for which unblinding is mandatory (e.g., the patient can no longer receive the medication because of a major

adverse effect or because it is imperative to know the exact medication to change the treatment course).

Finally, if the investigator agrees with the physician about emergency unblinding, then, the patient's allocation will be revealed.

Adherence

For adherence, participants will have a weekly check-in session which may be via a telephone call, SMS, or E-mail depending on the participants' choice. These sessions would ascertain if participants are taking the allocated medication as instructed; would confirm data entry into the standardized patient diary, and would also serve as reminders for participants to attend the follow-up clinic visits every 4 weeks. Standardized patient diaries will include information, such as the time they took their medication, breakthrough pain symptoms, and the frequency of use of analgesics for this breakthrough pain, as well as a record of possible side effects of this medication. Patients will also be asked to return any unused trial medication at the following clinic visit. All these activities will be recorded in the clinical trial report.

Other strategies to improve adherence will be: addressing the participants' concerns, explaining how the medication works to control or prevent symptoms, providing written instructions about the dose, frequency of administration, and adverse effects to report to the clinician, and contact information of a 24 hour, 7 days a week call-center for securing urgent care if needed. Participants' adherence will also be assessed at 4 and 8 weeks into the trial during the clinic visit when they receive the next 4-week supply of medication.

Participant's timeline

Recruitment

The study timeline is shown in **Figure 1**. A health-care-providers-based strategy will be used for recruitment by sending invitation letters to the orthopedic surgeons and Primary health care physicians within the city, asking them to refer all patients diagnosed with knee OA that are potentially eligible for study participation for screening.

Subjects who meet the eligibility criteria will be asked to sign the informed consent and would be enrolled into the trial after the approval of the Institutional Review Board. Enrolled subjects will be randomly assigned to one of the study treatment arms. (**Figure 1**)

Randomization

The investigator will contact the research assistant after the patient has been screened and has given informed consent to enter the trial. Once the allocation has been assigned, the research assistant will notify the pharmacist for appropriate dispensing of the non-identified trial medication (Naproxen or LDN).

Assessments

Assessments will be conducted every 4 weeks for each patient. At each clinic visit, participant adherence and medication efficacy (pain reduction and quality of life) will be assessed. Data will only be analyzed at the end of the trial.

Sample Size Calculation

The sample size estimation is based on the primary outcome of the proposed study. The non-inferiority margin was obtained by considering a Minimal Clinically Important Difference (MCID) when opting to use LDN for the relief of pain in the treatment of mild to moderate OA in place of standard treatment. For an estimated effect size of Naltrexone, a weighted mean was calculated (Baerwald et al., 2010; Bensen et al., 1999; A. Kivitz et al., 2002; A. J. Kivitz et al., 2001; Leung et al., 2002; Makarowski et al., 2002; Reginster et al., 2007; Schnitzer et al., 2011; Sowers et al., 2005), and it was estimated that a mean change of -27.73 mm when using the VAS score to measure the pain of OA patients in the active control group (pooled SD was estimated to be 8.6 mm) is expected. It was estimated that a non-inferiority margin of 7.3 mm would be an acceptable estimate that clinicians would be willing to lose on the VAS score in patients who receive LDN, as 19.9 mm was previously defined as MCID in pain from the OA population (Tubach et al., 2005).

We used an alpha of 0.025, as we're only interested if LDN is non-inferior to Naproxen; and a power of 0.9, which yielded a sample size of 98 participants that were increased by 20% to 118 participants to account for drop-outs and protocol violations.

Outcome measures

Primary outcome

We are going to evaluate the mean pain difference in VAS between baseline and 12-week score in the two treatment arms measured.

Patients will be instructed not to take breakthrough pain medication (acetaminophen) in the preceding 24 hours before the clinic visit at 4 weeks, 8 weeks, and 12 weeks for follow-up visits.
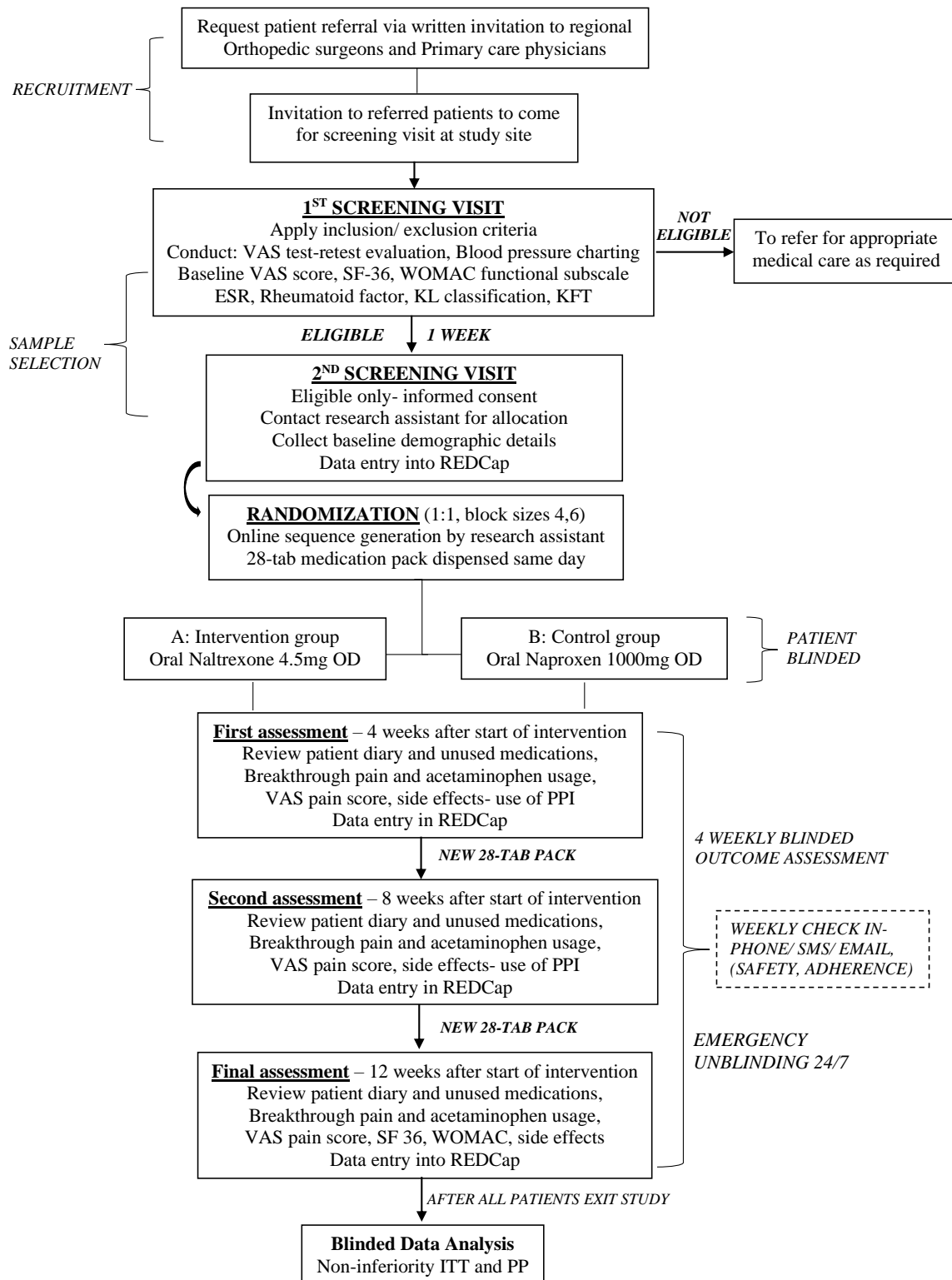
RECRUITMENT

Request patient referral via written invitation to regional
Orthopedic surgeons and Primary care physicians

Invitation to referred patients to come
for screening visit at study site

SAMPLE SELECTION

1ST SCREENING VISIT
Apply inclusion/ exclusion criteria
Conduct: VAS test-retest evaluation, Blood pressure charting
Baseline VAS score, SF-36, WOMAC functional subscale
ESR, Rheumatoid factor, KL classification, KFT

NOT ELIGIBLE → To refer for appropriate medical care as required

ELIGIBLE **1 WEEK**

2ND SCREENING VISIT
Eligible only- informed consent
Contact research assistant for allocation
Collect baseline demographic details
Data entry into REDCap

RANDOMIZATION (1:1, block sizes 4,6)
Online sequence generation by research assistant
28-tab medication pack dispensed same day

A: Intervention group
Oral Naltrexone 4.5mg OD

B: Control group
Oral Naproxen 1000mg OD

PATIENT BLINDED

First assessment – 4 weeks after start of intervention
Review patient diary and unused medications,
Breakthrough pain and acetaminophen usage,
VAS pain score, side effects- use of PPI
Data entry in REDCap

NEW 28-TAB PACK

4 WEEKLY BLINDED OUTCOME ASSESSMENT

Second assessment – 8 weeks after start of intervention
Review patient diary and unused medications,
Breakthrough pain and acetaminophen usage,
VAS pain score, side effects- use of PPI
Data entry in REDCap

WEEKLY CHECK IN- PHONE/ SMS/ EMAIL, (SAFETY, ADHERENCE)

NEW 28-TAB PACK

EMERGENCY UNBLINDING 24/7

Final assessment – 12 weeks after start of intervention
Review patient diary and unused medications,
Breakthrough pain and acetaminophen usage,
VAS pain score, SF 36, WOMAC, side effects
Data entry into REDCap

AFTER ALL PATIENTS EXIT STUDY

Blinded Data Analysis
Non-inferiority ITT and PP

Figure 1. Participants timeline from recruitment of physicians and participants to assessments of efficacy.

Secondary outcomes
The secondary outcomes of the trial are:

o Functional improvement using the 17-item Physical Function WOMAC subscale before and after 12 weeks of intervention.

o Participants' health-related quality of life using SF-36 before and after 12 weeks of intervention.
o Mean pain difference in VAS between baseline, 4 weeks score, and 8 weeks in the two treatment arms.
o Average consumption of acetaminophen in grams for breakthrough pain will also be compared between the two groups during 12 weeks.

Statistical Analysis

Both the Intention to treat and Per protocol approach will be used for the analyses of the primary outcome in this study.

We will analyze the primary outcome by comparing the mean differences between patient baseline and VAS scores at 12 weeks in both experimental and control groups, using an unpaired T-test with a non-inferiority margin of 7.3 mm ($p < 0.025$, one-sided test).

To address our secondary endpoints, we will use an unpaired T-test with a non-inferiority margin of 7.3 mm ($p < 0.025$, one-sided test) to assess the mean differences between patient baseline and VAS scores at 4 and 8 weeks. We will also run a subgroup analysis, for patients receiving physical therapy at the end of the 12-week. We will use an unpaired T-test to compare superiority in the mean differences between patient baseline and VAS scores at 12 weeks in both experimental and control groups for patients under physical therapy and for patients that do not follow this therapy.

Furthermore, we will calculate the mean score differences for SF-36, the WOMAC functional subscale, and the average acetaminophen consumption in grams and compare these mean scores between the treatment and control arms using a linear regression model adjusted for physical therapy ($p<0.05$, two-sided test).

The proportion of adverse events between the two treatment groups including overall adverse events (AE), as well as specific cardiovascular, gastrointestinal, and renal AEs will be compared between groups using the chi-square test or Fisher's exact test when deemed appropriate ($p<0.05$, two-sided test).

A linear regression model will also be used to adjust the VAS, WOMAC, and SF-36 mean score differences comparison for covariates, such as age, body mass index, Kellgren-Lawrence score, back pain of at least 30 days, and Charlson comorbidity index.

In this proposed study, it is anticipated that missing data may result from medication-related adverse-effect patient dropouts in both arms. (Gupta, 2011). For this, the Last Observation Carried Forward (LOCF) method will be used. (Haukoos & Newgard, 2007).

DISCUSSION

Study impact

OA is a disease with significant incapacitating physical and psychosocial burden. The aim of pharmacological treatment in OA is to reduce pain and inflammation. Non-steroidal anti-inflammatory drugs are the current standard of care but they have considerable adverse effects. To improve the safety profile of pain medication for OA without compromising efficacy resulted in our decision to evaluate the efficacy of LDN, an opioid antagonist that exerts an endogenous analgesic and anti-inflammatory effect while maintaining a favorable adverse effect profile.

Strengths

The preliminary evidence of LDN in a variety of chronic pain conditions supports its safety and tolerability (Parker et al., 2018). As of today, there is no published data on LDN use for pain relief in osteoarthritis. Our study will be one of the first studies comparing LDN with an existing option for pain relief. The non-inferiority design helps to show the comparability of this cheaper drug with a better side effect profile.

Considering that the outcome of pain assessment is highly subjective and patient-reported, this study will be triple blinded, to reduce reporting and observer bias. The allocation being handled by team members not involved in the recruitment.

The primary outcome of the VAS score is widely accepted and validated to study pain, and this study will further look at individual participant variability in the score. This study also looks at the overall effect of the disease on the functionality and quality of life of the participants- the results would be able to show how much LDN helps improve these aspects of the patient's life.

The once-daily dosing schedule is planned to improve adherence and reduce the variability associated with multiple dosing schedules. Even though the primary focus of the study is on efficacy, there is a plan in place for vigorous safety checks at weekly intervals. Participants will be able to contact a research assistant 24/7 throughout the 12 weeks trial period, and they will be provided with the necessary medical care.

Limitations

The study sample will be selected using a convenience sampling method, making use of local orthopedic surgeons and primary health care services. The recruitment would be a challenge considering the strict inclusion/exclusion criteria; however, we hope that the requirement of long-standing pain medication combined with the possibility of a cheaper alternative will be a good incentive for physicians to refer their patients to the study. Even though the strict inclusion criteria will reduce the generalizability of the results, it will help with improving internal validity which is more concerning for this phase II study. If this study results favor LDN, larger phase III studies would be required in a wider population.

Another potential concern is the non-standardization of the additional therapies like physical therapy that the participants might be undergoing at the time of recruitment into the trial, which can have an impact on chronic pain. We hope to tackle this problem with an effective randomization process and adjustment for these covariates in the statistical analysis.

Adherence is a concern as there is a possibility that lack of improvement might result in dropouts. We have inflated our sample size by 20% to tackle this problem, as reported in the 2019 review looking into predictors of drop-out in pain studies ((Oosterhaven, J. et.al., 2019).

Conclusion

This is a proposal of a non-inferiority randomized controlled trial, looking at LDN, as an effective, safer, and cheaper alternative to the standard NSAIDs, in chronic pain management of patients with mild-moderate knee osteoarthritis.

Registration

The trial will be registered on www.clinicaltrials.gov.

Acknowledgment

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Conflict of interest

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors agree with the submission of this manuscript. The final version has been approved by all authors. The authors have no conflicts of interest to declare.

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