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# The efficacy of Duloxetine and exercise compared to exercise alone in patients with knee osteoarthritis: a 12-week, randomized, double-blinded, parallel trial.

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**Abstract:**

***Introduction:*** *Osteoarthritis (OA) is an irreversible disease that affects the population worldwide, directly impacting patients' quality of life, work capacity and daily activities. Nowadays the standard conservative therapy for OA consists of exercise and adjunctive medication, however drug arsenal for management of pain is very limited. Duloxetine is an effective treatment for chronic pain, and we hypothesized that Duloxetine would have a synergistic effect with exercise, improving pain in addition to mood symptoms when compared to exercise alone.*

***Methods:*** *This is going to be 12-week multicentre, double-blind, placebo-controlled, randomized trial that will evaluate pain improvement in patients with radiologically confirmed knee OA and moderate to severe OA in WOMAC pain subscale score treated with Duloxetine + exercise in comparison to Placebo + exercise. During the study period, besides Duloxetine/placebo intake, patients will be asked to perform a set of exercises three times a week (one supervised session at the site; two home-based sessions with the assistance of a program in Wii and Better Knee App in Apple Watch).*

***Outcomes:*** *It is expected that patients receiving Duloxetine+exercise will have a 40% improvement in pain (assessed through WOMAC score) compared to placebo+exercise group. Secondary outcomes include impact in quality of life (i.e. EQ-5D-5L questionnaire: mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and frequency of use of rescue drugs for pain. Exploratory endpoints will include the rate of adherence to study interventions and rate of treatment discontinuation. Final analysis of outcomes will be performed once all patients have reached week 13 and data collection is closed. If our hypothesis is confirmed, Duloxetine can turn into another effective option for management of OA pain, possibly delaying and/or avoiding surgery in this population and reducing healthcare related costs.*

***Keywords:*** *Knee osteoarthritis, Duloxetine, WOMAC score, Double-blind, Placebo control, Better Knee App.*

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## INTRODUCTION

Osteoarthritis (OA) is a prevalent chronic musculoskeletal disorder affecting the population worldwide, predominantly the elderly (WHO, 2007). It is included in the World Health Organization's (WHO) list of chronic rheumatic conditions with the greatest impact on society (Laupattarakasem et al., 2008). Studies have found a prevalence ranging from 15.4% to 19.6% (Kim et al., 2014; Allena & Golightly, 2015) for symptomatic knee OA in individuals over 60 years of age and it is estimated that by 2050, 40 million will be severely disabled (WHO, 2017).

A common symptom of OA is pain due to loss of bone joint function. This is result of an early fragmentation of the cartilage surface, variable crystal deposition, remodeling and violation of the tidemark by blood vessels

(Madry, Luyten & Facchini, 2012). Bone remodeling, sub synovial inflammation, synovial cell hyperplasia, and the excess of synovial fluid leads to capsular swelling (Hernandez-Molina et al., 2008) which results in pain and loss of joint function observed in OA.

The current standard of care in OA is a multi-modal treatment. Conservative treatment for hip and knee OA, encompasses exercise therapy focused on lower limb strengthening (i.e. strengthening, low-impact aerobics, aquatic activity and tai chi chuan) and also adjuvant drug therapy, combined with patients´ education regarding the natural history of disease, factors that influence progression and lifestyle modifications. Pharmacological therapy generally includes simple analgesics, NSAIDs, steroids, and sometimes intra-articular injections. Considering most part of these patients will have chronic pain, it is important to develop strategies that avoid opioid use, reducing the risk of abuse. Those patients that fail to present relief of symptoms after twelve weeks of conservative treatment will often be recommended knee replacement surgery. Therefore, improvement of non-surgical care has the potential of enhancing quality of life and reducing the costs related to healthcare (McAlindon et al., 2014).

In this context, duloxetine is an effective treatment for chronic pain as it acts on central pain sensitization, neuropathic pain and may also improve associated depressive or anxiety symptoms. However, interaction between the exercise program and duloxetine has never been studied in the context of OA. We hypothesized that Duloxetine would have a synergistic effect with exercise, improving pain in addition to mood symptoms when compared to exercise alone. Therefore, this 12-week multicenter, double-blind, placebo-controlled, randomized trial will evaluate if patients with radiologically confirmed knee OA and moderate to severe OA in WOMAC pain subscale score treated with Duloxetine + exercise will have a 40% improvement in pain (assessed through WOMAC score) in comparison to Placebo + exercise. WOMAC is a scale frequently used in OA to assess pain and functional limitation. Secondary outcomes include impact in quality of life (evaluated through EQ-5D-5L questionnaire that assess 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and frequency of use rescue drugs for pain. Exploratory endpoints will include the rate of adherence to study interventions and rate of treatment discontinuation. Final analysis of outcomes will be performed once all patients have reached week 13 and data collection is closed. If our hypothesis is confirmed, Duloxetine can turn into another effective option for management of OA pain, possibly delaying and/or avoiding surgery in this population.

## METHODS

### Study Design

This is a 12-week multicenter, double-blind, placebo-controlled, randomized trial that will assess the superiority of Duloxetine + Exercise (intervention group) compared to Placebo + Exercise (control group) in patients with radiologically confirmed knee OA and moderate to severe OA in WOMAC pain subscale score. The trial will be carried in USA and Canada in four community hospitals. Final analysis of the primary and secondary outcomes will be performed once all patients have reached week 13 (1 week after completion of the 12-week program) and data collection is closed. If early discontinuation occurs, the patient will not be replaced, and the reason for discontinuation should be documented in the e-CRF.

### Intervention

In the 1st week, the intervention group will receive a loading dose of 30mg of duloxetine. If well tolerated, in the subsequent weeks, the daily dose will be increased to 60mg. The control group will receive matched placebo in the same model.

Regarding the exercise program, both groups will be oriented to a 30 minute-exercise session to be done three times per week. First session and then once a week, exercises will be done in person at center site, so patients can receive orientation from a physical therapist on how to perform the exercises. The exercises encompass aerobic, strengthening of lower limbs, and active range-of-motion exercises for the knee. In the remaining two sessions, patients are supposed to repeat the same set of exercises at home. During the study period, patients will receive a Wii and an Apple watch loaded with programs of the study. Wii platform will have guided exercises, and through Wii joystick, it will be possible to assess if exercises are being done correctly. Frequency, duration and adequate execution of exercises will be converted into scores and patients will be able to check their individual progress and also compare it to other patients in the study. Moreover, through Better Knee app in Apple Watch, patients will receive reminders to perform the exercises, take the pills, and check intake of study drugs. These home-based sessions are meant to reduce the burden of site visits to patients and simulate a real-life situation when patients are oriented to perform exercises on their own. Both gadgets will allow us to encourage and

check adherence to study interventions and to monitor the physical activity level of patients.

## Outcomes

Primary outcome will be improvement in WOMAC pain subscale score, assessed at week 13 (1 week after completion of the 12-week program) in comparison to baseline. Secondary outcomes include improvement in quality of life (evaluated through EQ-5D-5L questionnaire that assess 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and use of rescue drugs (i.e., analgesic). Exploratory endpoints will include rate of adherence to study interventions (assessed through Wii and BKApp) and rate of treatment discontinuation. Final analysis of the primary and secondary outcomes will be performed once all patients have reached week 13 and data collection is closed.

## Timeline

The total length of the study will be 24 weeks. There will be a 12-week enrolment period, followed by 12 weeks of the intervention. When coming to weekly supervised exercise practice, patients will be assessed by a trained team member for WOMAC scale, quality of life, incidence of depressive symptoms, use of rescue drugs, and adverse events. If patient is not able to come to the clinic visit, these assessments will be made via phone call. If unscheduled visits occur because of worsening of symptoms and/or occurrence of AES, this must be properly documented in e-CRF.

## Eligibility Criteria

• Individuals older than 18 years old
• Knee OA confirmed by image according to the definition of the American College of Rheumatology (ARC) together with clinical criteria. Additionally, the following criteria must be met:
• WOMAC pain subscale score corresponding to moderate or severe OA;
• Adequate bone marrow function (ANC ≥ 1,500/mm3; Platelets ≥ 100,000/mm3; and Haemoglobin ≥ 9.0 g/dL).
• Adequate renal function (Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥ 60 mL/min);
• Adequate liver function at screening (total serum bilirubin ≤1.5 x ULN; AST and ALT ≤ 2.5 x ULN; Alkaline phosphatase ≤ 5x ULN; INR or PT < 1.5 x ULN)
• Left ventricular ejection fraction ≥50% and NYHA functional class no greater than 2
• If female, must be of non-child bearing potential or practicing birth control (Non-child bearing potential female patients are those >60yo, submitted to oophorectomy or >50yo in the absence of periods in the last 12 months and FSH/LH levels consistent with menopause; all other women will have pregnancy tests performed at the beginning of the study, and if negative, they must agree on practicing birth control with an effective method. This is going to be documented in CRF in in/ex criteria);
• Patient is willing and able to comply with the protocol and complete study-related materials;
• The patient has signed and dated the IRB approved, written, informed consent prior to study participation.

## Exclusion Criteria

• Pregnant and breastfeeding women;
• Secondary arthritis (inflammatory joint disease; septic arthritis; gout; pseudogout; Paget's disease; joint fracture; acromegaly; Wilson's disease; heritable arthritic disorders; collagen gene mutations; Ochronosis; Haemochromatosis; or Osteochondromatosis) or significant deformity of knee joints;
• Patients with inflammatory intestinal diseases, unable to stop medicines during the study;
• Obesity Class II BMI ≥ 35;
• Patients who have taken the following medications within the last three weeks: duloxetine, monoamine oxidase inhibitors; tricyclic antidepressants and other tricyclic compounds (e.g., cyclobenzaprine, promethazine); neuroleptics; selective serotonin reuptake inhibitors; or other drugs that reduce seizure threshold;
• Patients who were taking any investigational agent within the last 30 days;
• Known allergy history of the study drug;
• Patients with co-morbidities not tolerating physical activities;
• Any clinical or biological abnormality found at screening which, in the opinion of the investigator, is clinically significant and would preclude safe participation in this study;
• Use of any corticosteroids or analgesics, COX-2 inhibitor or NSAID [including topical NSAIDs; excluding low-dose aspirin (≤325mg per day)];
• Use of potent CYP3A4 inhibitors;
• Use of anticoagulants (warfarin, heparin) or antiplatelet aggregation agents (excluding low-dose aspirin) or a condition associated with decreased homeostasis.
• A history of clinically significant drug or alcohol abuse, as defined by DSM-V.

Patients will be removed from the study in case of uncontrollable pain, unacceptable toxicities, or if patient removes consent. Also, permanent discontinuation will

occur in the following situations: (i) initiation of alternative therapy or other treatment not provided by the protocol during the study period; (ii) violation or important protocol deviation; (iii) closure or study completion. The primary reason of the study discontinuation should be documented in the individual's medical records.

## Recruitment Strategy

Patients will be recruited directly from the clinics that treat patients with knee OA in the four site centers where study will be conducted (healthcare provider-based strategies), but will also involve community recruitment through internet advertisement in compliance with FDA and IRB regulations.

## Adherence

The adherence of the assigned patients will be encouraged in all site visits and through Wii platform and BKapp in Apple Watch®. As previously mentioned, Wii platform will score frequency, duration and adequate execution of exercises, with the intention of stimulating patients to carry on home-based exercises. BKapp in addition to exercise and drug reminders will allow completion of adherence assessments through checklists and voice commands together with a "Reward Program" should incentive him/her go through the study program and complete the scheduled tasks.

Patients should return unused medications (duloxetine/placebo) at every site visit. The site will maintain a record of the number of study medication provided, the number of capsules returned, starting and stopping dates and percentage of compliance for each patient. These data will be cross-checked with inputs from BKapp and documented on medical charts and in e-CRF. In case of low adherence, the reasons will be accessed and discussed together with the patient aiming to understand the reasons.

## Randomization

Subjects will be assigned to the two treatment groups with a 1:1 allocation ratio according to a computer-generated list using permuted blocks. The allocation list or block sizes will be concealed until the outcome is analysed, in order to not influence by principal investigators, therapists or other staff members. Patients will be stratified according to BMI (<35 and ≥35).

## Blinding

The trial will be double-blinded regarding the use of duloxetine, as a matching placebo capsule will be provided to subjects not allocated in the intervention group. Medication or placebo will be dispensed by a central pharmacy according to subject allocation.

## Emergency Unblinding

For patients with grade 4 of adverse events that are potentially life threatening, emergency unblinding will be indicated. Nausea, somnolence, insomnia, dizziness, constipation, dry mouth and weakness are the most common side effects and duloxetine dose-related.

## Sample Size Calculation

Previous studies have reported effect sizes of 40% for exercise in OA patients (Golightly et al., 2012), and of 30-40% for duloxetine (Risser et al., 2013; Sullivan et al., 2009). We assumed an effect size of 40% of the Duloxetine+exercise over exercise alone, as this was considered to be clinically significant. The sample size was calculated with 80% power, and significance level (alpha) of 5% and a dropout rate of 20%, resulting in a number of 236 patients.

## Statistical Analysis Plan

The continuous variables (i.e. WOMAC score) will be evaluated for normality using either histogram or Shapiro-Wilk test. In case the WOMAC score prove to be normally distributed, a parametric test such as unpaired t-test will be employed. If not, a non-parametric test (i.e. Wilcoxon test) will be used instead.

Chi-square test will be used to compare the categorical data and selected covariates such as age, gender, BMI, use of rescue drugs and quality of life scores, considered significant by the univariate analysis in ANOVA, will also be evaluated with multiple regression analysis with Bonferroni correction. Patients that could not be evaluated for the primary outcome due to withdrawal or loss to follow-up will be treated as missing data. We assume the data to be missing at random. Therefore, single imputation using regression technique will be applied for missing information (Dziura et al., 2013) and intention to treat analysis will be conducted for aforementioned outcomes.

## Data Management

The data will be recorded using an electronic case report form (e-CRF).

The investigator will use their login to enter the data in the system. Medical terms should use standardized Medical Dictionary for Regulatory Activities (MedDRA). Concerning the data security, all members of the study team will possess an individual user account, which may

have privileges and restrictions according to their role in data management. Once all activities and the data management are completed, the data will be pre-evaluated by a pre-lock checklist, then locked and sent to statistical analysis. Unlocking of the database should occur only under extremely unavoidable circumstances, after approval of PI authorized to unlock the database or under serious adverse events that are potentially life-threatening and clinical emergencies.

## Data and Safety Monitoring Plan

A group independent from the study will assess and review data regarding progress, safety and efficacy assuring its attendance to the ethical guidelines. In case of futility or safety issue, this committee will warn the PIs enabling them to decide if further action is needed. An interim analysis will not be performed considering the short duration of the trial.

## Registration

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

## DISCUSSION

OA is considered one of WHO chronic rheumatic conditions with most significant impact on society. Unfortunately, despite considerable improvements in Medicine, conservative treatment options for OA are still very limited, especially regarding drug management of pain. Albeit of symptom improvement with exercise programs, these patients still need to make chronic use of analgesics, which severely limits the use of NSAIDs and opioids because of the risk of renal impairment and opioid addiction, respectively. When this population fails to present relief of symptoms after 3-4 months of conservative treatment, they will often be recommended for knee replacement surgery.

Therefore, Duloxetine, as an effective treatment for chronic pain conditions and associated mood symptoms, may be an interesting alternative to be considered in association with exercise for this population. Our study will evaluate the possible synergistic effect of this combination

One of the potential limitations of this study protocol is adherence of the patients, both in terms of ingestion of study drug and execution of home-based exercises. In order to minimize this, BKapp together with Wii-platform will encourage patients to adhere the protocol by sending reminders and also through the "gamification" of activities.

If proven to be effective, Duloxetine+exercises can turn into another effective option for management of OA pain. This treatment has the potential to reduce side effects and complications related the surgical treatment, impacting directly on patient's quality of life and in relation to the limitations of movements, work and daily activities.

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## Conflict of interest and financial disclosure

The authors have no personal or financial conflicts of interest. All authors agree with the submission of this manuscript and declare that all them have approved it.

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