BMJ Open

Duloxetine combined with intra-articular injection versus intra-articular injection alone for pain relief in knee osteoarthritis: a study protocol for a randomised controlled trial

Duo Yi Li ,[1] Rong Han,[2] Zhi Gang Zhao,[2] Fang Luo[3]

To cite: Li DY, Han R, Zhao ZG, *et al*. Duloxetine combined with intra-articular injection versus intra-articular injection alone for pain relief in knee osteoarthritis: a study protocol for a randomised controlled trial. *BMJ Open* 2020;**10**:e036447. doi:10.1136/bmjopen-2019-036447

► Prepublication history and supplemental material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-036447).

Received 15 December 2019
Revised 25 September 2020
Accepted 30 September 2020

Check for updates

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Professor Fang Luo; luofangwt@yahoo.com and Dr Zhi Gang Zhao; 1022zzg@sina.com

ABSTRACT

Introduction Intra-articular (IA) injection of hyaluronic acid (HA) and corticosteroid (CS) is a common treatment for osteoarthritis (OA) of the knee. As a drug treatment for patients with depression, duloxetine has been shown in many studies to effectively relieve the pain of OA and improve function of the knee joint. However, evidence regarding the efficacy of IA injection of HA+CS combined with duloxetine for pain management in patients with OA of the knee is lacking. The aim of this study was to test the hypothesis that IA injection of HA+CS combined with duloxetine could achieve pain management superior to that of IA injection of HA+CS alone in patients experiencing knee OA pain.

Methods This study will adopt a prospective, randomised, open-label blind endpoint study design. In total, 150 patients with OA of the knee will be enrolled in the study. The participants will be randomly allocated to receive either a single IA injection of HA+CS combined with duloxetine or a single IA injection of HA+CS alone, and both groups will complete a 24-week follow-up to assess pain and functional improvements. The primary outcome measure is the change in the weekly mean of the 24 hours average pain scores from baseline to the end of 24 weeks in patients with OA of the knee, and the secondary outcomes include the response to treatment, changes from baseline in the brief pain inventory, improvement in the Western Ontario and McMaster Universities Osteoarthritis index scores, patient global impression of improvement scale, Hospital Anxiety and Depression Scale and adverse events during the 24-week follow-up. The data will be analysed by the intention-to-treat principle.

Ethics approval and dissemination This study was approved by the institutional ethics committee of the Beijing Tiantan Hospital (approval number: KY 2019-086-02). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number ClinicalTrials.gov Identifier: NCT04117893; Pre-results.

Strengths and limitations of this study

- To the best of our knowledge, this study will be the first investigation to compare the efficacy of intra-articular (hyaluronic acid+corticosteroid) alone and combined with duloxetine for the management of pain in patients with knee osteoarthritis (OA).
- This study may provide a new treatment strategy and enrich the knowledge base of the research field of combined therapies for OA of the knee.
- This trial will be conducted using rigorous methods, including a prospective,randomised, open-label blind endpoint design, the implementation of interventions using clearly prespecified approaches and the blinding of the assessors of outcomes, to increase the accuracy of the outcomes.
- This study is a single-centre trial, which could be a limitation.
- Patients receiving oral placebo as a control group were not included in our study design because of limited funding.

INTRODUCTION

Osteoarthritis (OA) is an increasingly common degenerative joint disease worldwide due to the ageing population and increase in obesity.[1–3] This disease mainly occurs in the older population and affects approximately 15% of adults older than 45 years and approximately 50% of those older than 75 years.[4] All joints can be affected, especially weight-bearing joints, such as the knee.[5] The symptoms include pain, movement limitation and functional impairment, rendering OA a leading cause of disability in the older population.[6 7] With the ageing of the population and increasing prevalence of obesity, OA of the knee has a significant negative impact from a socioeconomic perspective, including substantial healthcare costs and loss of productivity.[8 9] Therefore, it is essential to develop effective treatments that can relieve symptoms, slow disease progression and consequently reduce healthcare resource needs.[3]

Disability due to OA of the knee is more closely related to the level of pain experienced by the patient than the radiographical severity of the disease.[10] Consequently, the management of OA of the knee should focus on pain reduction to improve functionality. To manage chronic pain due to OA, the current treatment guidelines recommend a combination of pharmacological and non-pharmacological therapies, which are often applied using a multimodal approach.[11 12] Pharmacological therapies can be summarised as oral paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and drugs for slowing the progression of the disease (glucosamine and chondroitin sulfate). However, many of the above treatments, particularly NSAIDs and opioids, are associated with significant safety risks.[13]

In addition to oral medication, treatments include topical NSAIDs, intra-articular (IA) hyaluronic acid (HA), IA corticosteroids (CS) and so on. IA injection is the preferred effective non-surgical modality.[14 15] IA injection treatments have fewer systemic adverse events (AEs), and depositing the medication inside the joint has a more direct effect, especially in older patients and those at a greater risk for NSAID-induced AEs.[16 17] HA has been proposed to reduce pain through several mechanisms of action, including the restoration of the viscoelastic properties of the synovial fluid and reductions in friction within the joint.[18] CS have both anti-inflammatory and immunosuppressive effects that affect protein expression, inhibit the expression of pro-inflammatory proteins and enhance the expression of anti-inflammatory proteins within the structures of the knee.[19] IA injections of CS and HA individually demonstrate efficacy in patients with severe OA.[20] CS provide shorter term pain relief than HA, which provides longer term pain relief with the onset of pain reduction occurring over several weeks.[21 22] The combination of CS+HA for the management of OA of the knee may provide superior improvement in symptomatic relief for patients who are candidates for IA therapy.[23 24] However, recent studies have shown adverse effects on cartilage and joints, and acceleration of OA progression following repeated injections of triamcinolone acetonide (TA) administered over an extended period.[25 26] Infection, post-injection flare, crystal-induced synovitis, tendinopathy, steroid arthropathy and systemic hyperglycaemia were noted as complications after repeated IA injections of CS.[27 28] Therefore, further studies are needed to identify a new strategy to reduce the frequency of IA injections to potentially lower the incidence of adverse reactions.

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, has been demonstrated to have a centrally acting analgesic effect in addition to its antidepressant properties.[29 30] Several studies have reported a significant improvement in pain in patients with OA of the knee treated with duloxetine compared with placebo.[5 13 31] Duloxetine is effective and well tolerated without severe or life-threatening events in patients with OA.[13 32] However, to date, no study has investigated the benefits of IA injections of CS+HA combined with oral duloxetine in patients with OA of the knee.

Based on the current literature, we hypothesise that compared with IA injection of CS and HA alone in the knee, IA injection of CS+HA combined with oral duloxetine could further relieve pain and improve the physical function and quality of life of patients with OA of the knee. Thus, this prospective, randomised, controlled study is proposed to optimise the current treatment scheme.

METHODS

Trial design

This prospective, randomised, open-label blind endpoint (PROBE) study is designed to compare the efficacy and safety of IA injection of either HA+CS combined with oral duloxetine (experimental group) or HA+CS (control group) alone for patients with OA of the knee. All OA of the knee participants will be randomly assigned to the experimental group or the control group at a 1:1 ratio (figure 1). The investigation will be performed at Beijing Tiantan Hospital Affiliated with Capital Medical University from October 2020 to December 2022. The study plan has been approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2019-086-02). This study is in accordance with the World Medical Association's Declaration of Helsinki. All patients will sign written informed consent to participate in the study, and all participants will have sufficient time to decide whether to participate in this study. The patients who participate in the study will have the right to obtain the relevant information and will be allowed to withdraw their consent or discontinue participation without restrictions at any time point during the study. The confidentiality of the participant records will be protected.

Objectives

The purpose of the IA (HA+CS) combined with duloxetine versus the IA (HA+CS) alone trial is to determine whether the efficacy of duloxetine combined with IA (HA+CS) is superior to that of conventional IA (HA+CS) alone in the treatment of knee OA pain in patients who are candidates for IA therapy.

Patient population

Eligibility criteria

The patients must meet all following criteria to be eligible:

- Male and female outpatients aged 50 to 75 years who meet the American College of Rheumatology clinical and radiographical criteria for the diagnosis of OA of the knee with knee pain (pain for ≥14 days per month for ≥3 months before the study entry with a mean score ≥4 on the 24 hours average pain score (0 to 10) using the average of daily ratings before the trial[33]).
- Body mass index (BMI) <40 kg/m^2.
- Radiographical criteria including Kellgren-Lawrence grades II to III.

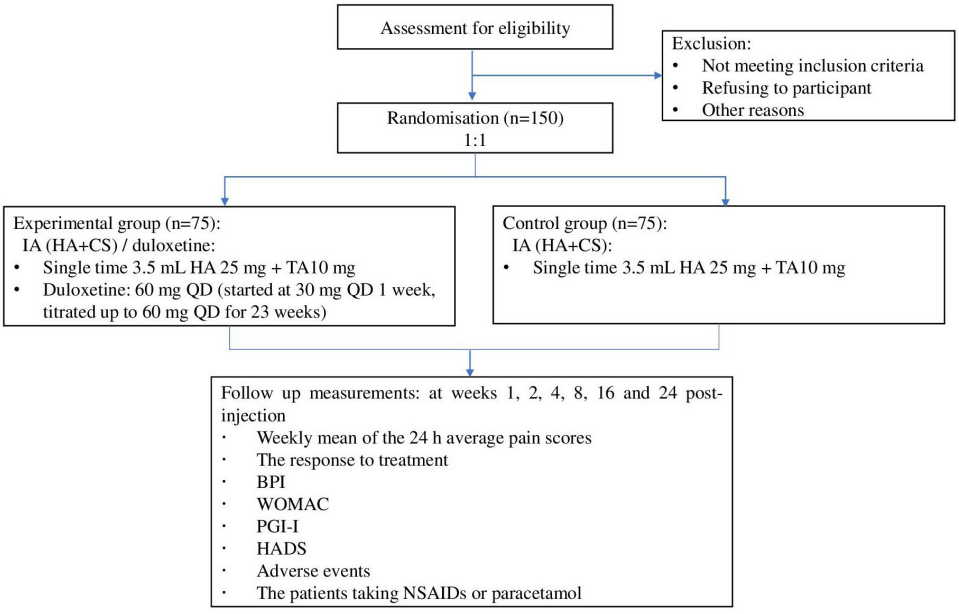

Figure 1 Trial design of the treatment for knee osteoarthritis. BPI, brief pain inventory; CS, corticosteroids; HA, hyaluronic acid; HADS, hospital anxiety and depression scale; IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug; PGI-I, patient global impression of improvement scale; QD, once per day; TA, triamcinolone acetonide; WOMAC, western Ontario and McMaster universities osteoarthritis index.

- Knee stability, no deformity and no lumbar spondylosis with radiculopathy.
- Good cognition, the ability to understand the study protocol and willingness to participate.

Subjects with one or more of the following conditions will be excluded:

- Inflammatory arthritis, autoimmune disorder, septic arthritis or any other concomitant disease (such as liver and kidney disease).
- Prior synovial fluid analysis indicative of a diagnosis other than OA.
- Contraindications to duloxetine (current use of monoamine oxidase inhibitors or poorly controlled angle-closure glaucoma), previous exposure to duloxetine, concurrent use of other drugs acting on the central nervous system (such as benzodiazepines) and allergy to any medications used in this study.
- Metabolic diseases or anticoagulation therapy.
- History of invasive therapies to the knee during the past 6 months, joint replacement of the knee at any time or current infection in the affected limb.

Randomisation and blinding

The randomisation will be performed by permuted blocks. The allocation sequence will be generated by an independent researcher before the inclusion of the first participant.[34] After randomisation, all patients will be randomly assigned to the experimental group IA (HA+CS) combined with oral duloxetine or control group (IA (HA+CS)) in a distribution ratio of 1:1. One assessor will be responsible for the pre-trial evaluation of eligibility, and another assessor will be responsible for the post-intervention evaluation. To ensure that the blinding is maintained, the patients will be given clear instructions not to disclose the treatment they have been randomised to receive while being interviewed by the blind assessors. Information regarding the treatment allocation will be stored in a secure locker in the case emergency unblinding is needed.

Intervention

All included patients will be allocated to one of the following two study groups. The patients in the experimental group will receive a single 3.5 mL IA injection of HA+CS (25 mg of HA (Artz Dispo, Seikagaku Co, Tokyo, Japan) plus 10 mg of TA and oral duloxetine (Cymbalta; Eli Lilly and Co, Indiana, USA). The patients in the control group will receive only a 3.5 mL IA injection of HA+CS (25 mg of HA plus 10 mg of TA). These two groups will receive non-cross-linked (native) avian-derived HA with a molecular weight of 0.8 Md. In this study, HA is produced by Artz that has been available on the Chinese market since 1997. The patients will agree to maintain their usual activity level throughout the course of the study.

The patients in the experimental group assigned to receive duloxetine 60 mg once per day will start with duloxetine 30 mg once per day for 1 week and then titrate up to duloxetine 60 mg once per day for 23 weeks. The patients will be instructed to take the medication with meals. At the end of the 24-week treatment phase, the patients will enter a 1-week dose-tapering phase, followed by an observational phase of 1 week to minimise discontinuation-emergent AEs. Patients who discontinue the study early must contact the investigator to obtain discontinuation advice and will be entered into a 2-week taper phase if they received the duloxetine treatment for at least 2 weeks.

All procedures will be performed in an outpatient clinic. The injection will be performed by a physician who has experience with >500 cases of knee joint injections or aspirations per year. The patients will rest in the supine position. The knee will be flexed at approximately 60° and prepared under sterile conditions; 1 mL of 2% lidocaine hydrochloride with 1:80 000 epinephrine will be injected into the skin and subcutaneous tissue at the lateral soft spot of the knee joint just inferior to the lower pole of the patella with a 27-gauge needle for patient comfort. A 21-gauge needle (0.8·50 mm) will then be inserted through the same area into the joint capsule. The injection will be performed using the inferolateral approach under ultrasound guidance. The accuracy of the injection will be assessed by an unobstructed injection of 1 mL of air into the knee joint. If effusion is present, it will be aspirated into a separate syringe. The same needle will be left in place, and then, a syringe prefilled with the HA and TA mixture will be inserted to administer the injection. Patients will be treated and closely monitored if a severe reaction to the injections occurs or if there is evidence of an active infection in the injected joint at any point throughout the study period.

If the treatment effect is not satisfactory, the patients will be allowed to use concomitant rescue medication, including paracetamol and NSAIDs (all other pain medications will be excluded), to avoid increasing the dose of duloxetine. No pain medication will be allowed within the 48 hours before each assessment to avoid masking the symptoms of pain. All patients will receive a chart to record the number of analgesics taken daily and the use of rescue treatment during the previous weeks at each study visit.

The safety of treatment will be assessed during the study. The decision to continue treatment, continue after adjusting treatment or end the trial will be made according to the available data including the risk-benefit evaluation. The trial will be continued if the patients are satisfied with clinical outcome. If patients are unable to adhere to oral duloxetine due to side effects, the treatment plan will be modified. The dosage of duloxetine will be decreased, and analgesics will be used according to the outcome of pain evaluation. The trial will be terminated in case of complication such as infection of the knee joint or serious side effects (eg, allergy) caused by duloxetine.

Outcome measures

Baseline data

The pre-enrolment information, including age (years), gender (male or female), height, weight, BMI, pre-existing pain and duration, baseline weekly mean of the 24 hours average pain scores, Kellgren-Lawrence grade, presence of depression or anxiety, and the percentage of analgesic use preceding study entry, will be collected. The schedule of measurements is presented in table 1.

Table 1 Measurements to be taken at each point in the trial

	Enrolment	Allocation	Post allocation					
Time point	**Pre-injection**	**Day 0**	**1 week**	**2 weeks**	**4 weeks**	**8 weeks**	**16 weeks**	**24 weeks**
Enrolment:								
Eligibility screening	X							
Informed consent	X							
Allocation		X						
Interventions:								
IA (HA+CS)/duloxetine		X						
IA (HA+CS)		X						
Assessments:								
Baseline variables	X							
Weekly mean of the 24 hours average pain scores	X		X	X	X	X	X	X
Response to treatment			X	X	X	X	X	X
BPI	X		X	X	X	X	X	X
WOMAC	X		X	X	X	X	X	X
PGI-I				X	X	X	X	X
HADS	X			X	X	X	X	X
Occurrence of AEs		X	X	X	X	X	X	X
Concomitant medication use	X	X	X	X	X	X	X	X

AEs, adverse events; BPI, brief pain inventory; CS, corticosteroids; HA, hyaluronic acid; HADS, hospital anxiety and depression scale; IA, intra-articular; PGI-I, patient global impression of improvement scale; WOMAC, western Ontario and McMaster universities osteoarthritis index.

Primary outcome

The primary outcome measure is the change in the weekly mean of the 24 hours average pain scores from baseline to the end of 24 weeks in patients with OA knee pain as reported in the patients' diaries based on an 11-point Likert scale (an ordinal scale with 0 indicating 'no pain' and 10 indicating the 'worst pain imaginable').

Secondary outcomes

- Response to treatment: The response to treatment is defined as a 30% (moderate) or a 50% (substantial) reduction in the weekly mean score of the 24 hours average pain severity ratings from baseline to the endpoint on weeks 1, 2, 4, 8, 16 and 24 post-injection.
- Brief pain inventory (BPI):[35] This self-reported scale will be used to measure the severity of pain and the interference of pain in function on weeks 1, 2, 4, 8, 16 and 24 post-injection. The severity of the pain will be assessed by four questions as follows: the patients will rate their most severe pain, least severe pain, average pain over the past 24 hours and current pain. The pain scale ranges from 0 (no pain) to 10 (extreme pain). Over the past 24 hours, seven questions will be used to assess the impact of pain on daily activities, mood, walking ability, ability to work normally, relationships with others, sleep and pleasure in life. The interference level ranges from 0 (no interference) to 10 (complete interference), and the average of the interference terms is obtained as a summary interference measurement.
- Western Ontario and McMaster Universities Osteoarthritis index (WOMAC):[10 36] This instrument is designed to assess pain, stiffness, and physical function in patients with OA of the knee and will be evaluated on weeks 1, 2, 4, 8, 16 and 24 post-injection. This index consists of 24 questions as follows: five questions regarding pain, two questions regarding stiffness, and 17 questions regarding physical function; each question will be answered using a 5-point scale ranging from 0 (none) to 4 (extreme). Higher scores on the WOMAC indicate worse pain, stiffness and functional limitations.
- Patient global impression of improvement scale (PGI-I):[37] This patient-rated 7-point scale of symptomatic improvement will be assessed at all visits starting 2 weeks after the treatment. On the PGI-I scale, a rating of 1 indicates that the patient is 'very much improved', a rating of 4 indicates that the patient has experienced 'no change' and a rating of 7 indicates that the patient has 'very much worsened'.
- Hospital anxiety and depression scale (HADS):[38] This self-rating patient-reported outcome measure will be developed to assess depression and anxiety in patients. Fourteen items are equally divided in two subscales: anxiety (HADS-A) and depression (HADS-D). The HADS-A includes items such as tension, worry, fear, panic, difficulties in relaxing and restlessness. The HADS-D includes items predominantly measuring anhedonia (not experiencing joy). Responses are rated on a 4-point Likert scale and range from 0 to 3, with higher scores indicating higher severity. Anchor points for the Likert items vary depending on the item. This scale is assessed to establish the analgesic effect of duloxetine independent of the effects on mood or anxiety.

Adverse events and data safety monitoring

During the trial, the treatment-related AEs reported by the patients will be recorded and evaluated at each visit. The safety and tolerability of the treatment will be assessed according to the incidence and type of AEs. Treatment-related AEs are any events that first occur or worsen during treatment compared with the baseline period. All AEs that the investigator considers causal in relation to the study drug will be recorded using a case report form. Severe AEs or adverse operation effects must be reported to the research ethics committee as soon as possible. The research ethics committee will review the AEs and determine whether termination of the study is necessary. If any patients are harmed by participating in the trial, they will be treated and closely monitored without delay by the researchers until they are healed.

Missing values

Missing data will not be replaced. Mixed models will be used in the analysis of repeated data to avoid deleting subjects with any missing values.

Sample size calculation

Based on previous research,[31] we estimate that the mean of the weekly mean of the 24 hours average pain scores after 24 weeks will be approximately −2.92±1.725 in the experimental group (IA (HA+CS) combined with oral duloxetine) and −2.08±1.745 in the control group (IA (HA+CS)). In total, 68 patients per group will be needed to achieve 80% power at a two-sided α level of 0.05. Considering a drop-out rate of 10%, in total, 75 patients per arm are needed; thus, in total, 150 patients will be needed for this trial.

Statistical analyses

The statistical analyses will be performed with SPSS software V.25 (IBM, Chicago, Illinois, USA). The Shapiro-Wilk test will be used to test whether all data are normally distributed. The normally distributed data will be expressed as the mean and SD. The data that do not follow a normal distribution will be presented as the median and IQR.

All analyses will be conducted on the intention-to-treat population. The baseline data and study outcomes of the experimental group and control group will be compared by a significance test of differences. The stratified cluster randomisation will be considered when analysing the data (multilevel analysis). If the baseline characteristics are statistically significantly different between the two treatment groups, we will perform a confounder analysis. If the effect on the outcome changes by 10% or more, the

baseline characteristic will be considered a confounder, and the analyses will be adjusted accordingly. A t-test will be used for the continuous variables with a normal distribution, and the Mann-Whitney U test will be used for the variables with a non-normal distribution. The categorical variables will be tested using the χ^2 test or Fisher's exact test. In addition, the outcomes at each postoperative time point will be compared with the preoperative data from the same group. A repeated-measures analysis of variance of the outcomes at different time points between the two groups will be performed, and Bonferroni correction will be used to correct multiple comparisons. Descriptive analyses will be used to assess the safety indicators in all randomised and treated patients. The relief of pain and functional improvement of OA of the knee after treatment may be related to BMI, effusion and use of concomitant rescue medication. The results, such as the Likert scale, BPI, WOMAC, PGI-I and AEs, will be stratified according to BMI, including normal (18.5 to 24.9), overweightness (25 to 29.9), obesity (>30), presence of effusion (negative or positive) and usage of concomitant rescue medication (yes or no) to test if the clinical effect is influenced by these confounding factors. P<0.05 will be considered indicative of statistical significance.

DISCUSSION

Consistent with a pragmatic approach, the PROBE design will be applied in the present study. Furthermore, the PROBE design can better reflect clinical practice and carry on the excellence of randomised controlled trials with randomised sequences and exact endpoint analyses by blinded experts.[39]

Chronic pain and depression often co-exist and influence each other.[29] Depressed mood has been associated with alterations in central pain processing and renders patients more sensitive to particular pain stimuli.[40] Duloxetine alleviates pain in OA by acting on serotonin and norepinephrine receptors, thereby affecting the central pain pathway.[41 42] However, patients with long-term severe symptoms may need repeated IA injections to relieve pain.[3] It is necessary for clinicians to reduce the incidence of adverse reactions caused by injections.[3] Therefore, we designed this protocol to evaluate the therapeutic effect of a single IA injection of CS and HA combined with oral duloxetine. If the combined treatment is more effective, this study will provide clinically important information regarding the pain management role of duloxetine in patients with OA of the knee receiving IA injection of CS and HA.

In addition, an analysis of the data from all placebo-controlled trials of duloxetine (52 studies involving 17 822 patients) showed that patients with OA who received duloxetine had the lowest treatment-emergent AE rate compared with other indications.[43] The dose-dependent adverse effects of duloxetine include constipation, dry mouth, decreased appetite and drowsiness.[13] Mild-to-moderate nausea may develop and be relieved within 8 days.[44] Therefore, in our study, the patients will start receiving duloxetine 30 mg once per day for 1 week and then titrate up to duloxetine 60 mg once per day to slowly improve their tolerance and reduce the occurrence of adverse reactions. The patients will be instructed to take the medication with meals.[45] In a retrospective analysis,[46] the use of duloxetine for the treatment of OA of the knee resulted in significant pain relief in both elderly and young groups (p<0.05). However, among the patients in all age groups who did not respond well to duloxetine at 7 weeks, no significant pain relief was found when the dose was increased to 120 mg/day.[46] Therefore, we chose the effective and relatively low dose of duloxetine (60 mg/day) for the treatment to avoid increasing the burden on the liver and kidney, and reducing the occurrence of adverse reactions.

Some elderly patients with severe symptoms of OA of the knee do not want to undergo surgical treatment or have contraindications for surgical treatment. Thus, it is urgent to identify safe, effective, and persistent non-surgical treatment options with minimal side effects. Various conservative treatment modalities are used as basic methods for treating OA of the knee. If used properly, these treatments can improve the quality of life of patients. Future studies should focus on improving the efficacy of non-surgical treatment options and providing scientific and medical evidence supporting innovative non-surgical technologies as choices before surgery for patients who are reluctant or unsuitable to undergo surgical treatment.

There are several limitations in this study. First, the present study will examine the effectiveness and safety only up to 24 weeks after treatment; however, a longer follow-up period could provide more informative results. Second, additional studies will be needed to determine whether duloxetine may reduce the frequency of injections and related adverse reactions and explore the optimal dosage of duloxetine. Third, we will be use low molecular-weight (MW) HA for patients in this study; however, some authors have reported that high MW cross-linked HA may lead to better results. The effect of duloxetine combined with high or low MW HA may be different, and further study will be performed for this issue. Fourth, MRI and X-ray examinations may provide further information regarding changes in structural damage to the articular cartilage, which is worth studying in the future. Fifth, there is no oral placebo for the control group because of limited funding, and the placebo effect may not be well parcelled out. However, our primary objective will be to identify whether there is a difference between IA (HA+CS) combined with duloxetine and IA (HA+CS). Thus, IA (HA+CS) alone could serve as the primary active control. In addition, this study will be a single-centre trial, and data from a multi-centre trial may be more precise.

In summary, the results of the IA (HA+CS) combined with duloxetine versus IA (HA+CS) trial may provide an effective method for relieving pain and improving knee function in patients with OA of the knee aged over 50

years and provide guidance for patients regarding multimodal analgesia and treatment.

Patient and public involvement

The patients and public were not involved in the planning and design of this study.

Ethics and dissemination

Ethical considerations

The study plan has been approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2019-086-02). A Standard Protocol Items: Recommendations for Interventional Trials checklist is available for this protocol (online supplemental file 1). All patients will sign written informed consent to participate in the study (online supplemental file 2), and all participants will have sufficient time to decide whether to participate in this study. The subjects will be informed of the objectives of the project and the risks and benefits of the explorations to be carried out, including data collection. None of the tests will pose risks that could endanger the lives of the participants. The patients who participate in the study will have the right to obtain the relevant information and will be allowed to withdraw their consent or discontinue participation without restrictions at any time point during the study. The confidentiality of the participant records will be protected.

Dissemination plan

Scientific statements and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the consent of the principal investigators and the methodologist. The co-authors of the report and publications will be the investigators and clinicians involved on a pro rata basis of their contribution in the study and the biostatistician and associated researchers. The aggregated research findings will be presented at national and international scientific conferences and will be submitted for publication in peer-reviewed journals.

Author affiliations
[1]Department of Anesthesiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Department of Pharmacy, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[3]Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Acknowledgements We are thankful for the support of the staffs from the Department of Pain Management, Beijing Tiantan Hospital Affiliated with Capital Medical University and the patients enrolled in this study.

Contributors DYL and RH contributed equally to this work and should be considered co-first authors. DYL and RH contributed to the conception and drafting of the first manuscript for this trial. ZGZ and FL contributed equally in designing the project. All the authors have read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer-reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Duo Yi Li http://orcid.org/0000-0002-2151-548X

REFERENCES

1 Uchio Y, Enomoto H, Ishida M, *et al*. Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open-label, long-term, phase III extension study. *J Pain Res* 2018;11:1391–403.
2 Uchio Y, Enomoto H, Alev L, *et al*. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese patients with knee pain due to osteoarthritis. *J Pain Res* 2018;11:809–21.
3 Bruyère O, Honvo G, Veronese N, *et al*. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). *Semin Arthritis Rheum* 2019;49:337–50.
4 Saccomanno MF, Donati F, Careri S, *et al*. Efficacy of intra-articular hyaluronic acid injections and exercise-based rehabilitation programme, administered as isolated or integrated therapeutic regimens for the treatment of knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2016;24:1686–94.
5 Wang G, Bi L, Li X, *et al*. Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study. *Osteoarthritis Cartilage* 2017;25:832–8.
6 Bjordal JM, Klovning A, Ljunggren AE, *et al*. Short-Term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. *Eur J Pain* 2007;11:125–38.
7 Litwic A, Edwards MH, Dennison EM, *et al*. Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013;105:185–99.
8 Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. *Clin Orthop Relat Res* 2004;427 Suppl:S6–15.
9 Murphy L, Schwartz TA, Helmick CG, *et al*. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum* 2008;59:1207–13.
10 Jinks C, Jordan K, Croft P. Measuring the population impact of knee pain and disability with the Western Ontario and McMaster universities osteoarthritis index (WOMAC). *Pain* 2002;100:55–64.
11 Zhang W, Moskowitz RW, Nuki G, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137–62.
12 McAlindon TE, Bannuru RR, Sullivan MC, *et al*. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage* 2014;22:363–88.
13 Chappell AS, Desaiah D, Liu-Seifert H, *et al*. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract* 2011;11:33–41.
14 Zhang W, Nuki G, Moskowitz RW, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis: Part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010;18:476–99.
15 Kon E, Filardo G, Drobnic M, *et al*. Non-Surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2012;20:436–49.

16 Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. *J Pain Res* 2018;11:2189–96.
17 Ariani A, Manara M, Fioravanti A, *et al*. The Italian Society for rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. *Reumatismo* 2019;71:5–21.
18 Altman RD, Manjoo A, Fierlinger A, *et al*. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC Musculoskelet Disord* 2015;16:321.
19 Suntiparpluacha M, Tammachote N, Tammachote R. Triamcinolone acetonide reduces viability, induces oxidative stress, and alters gene expressions of human chondrocytes. *Eur Rev Med Pharmacol Sci* 2016;20:4985–92.
20 Campos ALS, E Albuquerque RSP, da Silva EB, Campos A, E A R DSE, *et al*. Viscosupplementation in patients with severe osteoarthritis of the knee: six month follow-up of a randomized, double-blind clinical trial. *Int Orthop* 2017;41:2273–80.
21 Bannuru RR, Natov NS, Dasi UR, *et al*. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. *Osteoarthritis Cartilage* 2011;19:611–9.
22 Bannuru RR, Osani MC, Vaysbrot EE, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
23 Smith C, Patel R, Vannabouathong C, *et al*. Combined intra-articular injection of corticosteroid and hyaluronic acid reduces pain compared to hyaluronic acid alone in the treatment of knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2019;27:1974–83.
24 Ertürk C, Altay MA, Altay N, *et al*. Will a single periarticular lidocaine-corticosteroid injection improve the clinical efficacy of intraarticular hyaluronic acid treatment of symptomatic knee osteoarthritis? *Knee Surg Sports Traumatol Arthrosc* 2016;24:3653–60.
25 McAlindon TE, LaValley MP, Harvey WF, *et al*. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA* 2017;317:1967–75.
26 Conaghan PG, Hunter DJ, Cohen SB, *et al*. Effects of a single intra-articular injection of a microsphere formulation of triamcinolone acetonide on knee osteoarthritis pain: a double-blinded, randomized, placebo-controlled, multinational study. *J Bone Joint Surg Am* 2018;100:666–77.
27 McGarry JG, Daruwalla ZJ. The efficacy, accuracy and complications of corticosteroid injections of the knee joint. *Knee Surg Sports Traumatol Arthrosc* 2011;19:1649–54.
28 Richards MM, Maxwell JS, Weng L, *et al*. Intra-Articular treatment of knee osteoarthritis: from anti-inflammatories to products of regenerative medicine. *Phys Sportsmed* 2016;44:101–8.
29 Enteshari-Moghaddam A, Azami A, Isazadehfar K, *et al*. Efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis. *Clin Rheumatol* 2019;38:2873–80.
30 Wong DT, Bymaster FP. Dual serotonin and noradrenaline uptake inhibitor class of antidepressants potential for greater efficacy or just hype? *Prog Drug Res* 2002;58:169–222.
31 Chappell AS, Ossanna MJ, Liu-Seifert H, *et al*. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain* 2009;146:253–60.
32 Wang G, Bi L, Li X, *et al*. Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study. *Osteoarthritis Cartilage* 2017;25:832–8.
33 Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic criteria committee of the American rheumatism association. *Arthritis Rheum* 1986;29:1039–49.
34 Garcia-Yu IA, Garcia-Ortiz L, Gómez-Marcos MA, *et al*. Vascular and cognitive effects of cocoa-rich chocolate in postmenopausal women: a study protocol for a randomised clinical trial. *BMJ Open* 2018;8:e24095.
35 Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap* 1994;23:129–38.
36 Bellamy N, Buchanan WW, Goldsmith CH, *et al*. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833–40.
37 William G. *ECDEU assessment manual for psychopharmacology*. Washington, DC: US Department of Health, Education, and Welfare, 1976.
38 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
39 Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (probe) study. A novel design for intervention trials. prospective randomized open blinded end-point. *Blood Press* 1992;1:113–9.
40 Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age Ageing* 2012;41:646–52.
41 Kidd BL. Osteoarthritis and joint pain. *Pain* 2006;123:6–9.
42 Mease PJ, Hanna S, Frakes EP, *et al*. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *J Rheumatol* 2011;38:1546–51.
43 Brunton S, Wang F, Edwards SB, *et al*. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. *Drug Saf* 2010;33:393–407.
44 Whitmyer VG, Dunner DL, Kornstein SG, *et al*. A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *J Clin Psychiatry* 2007;68:1921–30.
45 Rizea-Savu S, Duna SN, Ghita A, *et al*. The effect of food on the single-dose bioavailability and tolerability of the highest marketed strength of duloxetine. *Clin Pharmacol Drug Dev* 2019;00:1–8.
46 Micca JL, Ruff D, Ahl J, *et al*. Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials. *BMC Musculoskelet Disord* 2013;14:137.