# INPLASY PROTOCOL

To cite: Deng et al. The long-term effectiveness and safety of the available treatments for the pain of knee osteoarthritis: a protocol for a systematic review and network meta-analysis. Inplasy protocol 202160070. doi: 10.37766/inplasy2021.6.0070

Received: 20 June 2021

Published: 20 June 2021

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**Support:** **Hubei Provincial Health Commit.**

**Review Stage at time of this submission:** **The review has not yet started.**

**Conflicts of interest:**
**None declared.**

# The long-term effectiveness and safety of the available treatments for the pain of knee osteoarthritis: a protocol for a systematic review and network meta-analysis

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**Review question / Objective:** **Osteoarthritis is a common skeletal muscle disease affecting the hip and knee, and one of the most typical clinical manifestation is chronic pain. There are many non-surgical treatments against joint pain in clinic, which are oral medicine, intra-articular injection, acupuncture and so on. Several studies have shown that some oral medicine, intra-articular injection and acupuncture have certain effect on KOA, but previous systematic reviews have not compared these treatments together. We aim to access the long-term effectiveness and safety of acupuncture, intra-articular injection and some oral medicine on knee osteoarthritis pain in a network meta-analysis.**
**Eligibility criteria:** **All randomized controlled trials comparing 2 or more of the following: acupuncture, moxibustion, fire needles, sham acupuncture, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen, duloxetine Hydrochloride and oral placebo, will be included. Trials must have randomly assigned, on average, at least 100 patients per group to minimize bias due to small study effects. Non- randomized studies or trials published as abstracts only will be excluded.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 June 2021 and was last updated on 20 June 2021 (registration number INPLASY202160070).

## INTRODUCTION

**Review question / Objective:** **Osteoarthritis is a common skeletal muscle disease affecting the hip and knee, and one of the most typical clinical manifestation is chronic pain. There are many non-surgical treatments against joint pain in clinic, which are oral medicine, intra-articular injection, acupuncture and so on. Several**

studies have shown that some oral medicine, intra-articular injection and acupuncture have certain effect on KOA, but previous systematic reviews have not compared these treatments together. We aim to access the long-term effectiveness and safety of acupuncture, intra-articular injection and some oral medicine on knee osteoarthritis pain in a network meta-analysis.

**Condition being studied:** Knee osteoarthritis (OA) is the most common degenerative joint disease, accompanied with cardinal symptoms of chronic pain and restricted joint activity. It is assessed that about 250 million person are suffered from KOA all over the world and the prevalence of knee OA rose greatly over the last decades and continues to increased, partially since obesity and other risk factors, but also independently, of other causes grow substantially. The major treatment methods of knee OA in western medicine include drugs, intra-articular (IA), surgical treatment. Initial pharmacological management in osteoarthritis includes non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol), and cyclo-oxygenase-2 (COX-2) inhibitors [6]. In addition, some guidelines advise caregivers to consider duloxetine for pain refractory to initial pharmacological management. It is thought that the anxiolytic effects coupled with central pain inhibition help address neuropathic and central pain mechanisms contributing to osteoarthritis. Intra-articular (IA) treatments are widely used, and clinically, the commonly used intra-articular injection drugs are steroids, glucocorticoid, hyaluronic acid and other drugs . Its purpose is to regulate local inflammatory response, increased local bioavailability and reduced systemic exposure. While, acupuncture is one of the most popular treatments applied in traditional Chinese medicine and has been used for relieving pain in musculoskeletal diseases. In related studies, these three treatments are effective in the treatment of knee osteoarthritis, and the effectiveness of various individual treatments for knee osteoarthritis was evaluated in previous systematic reviews (including meta-analysis). However, numerous treatments have not been directly compared. Furthermore, to choose the optimal treatment(s), it would be more helpful if all candidate treatments could be compared in the same analysis, as opposed to using a series of simple but inefficient standard pairwise meta-analyses comparing only two treatments at a time. Thus, the aim of the present study is to systematically search, review, and analyze the treatment of oral drugs, intra-articular injection and acupuncture for the pain of knee OA from randomized clinical trials (RCTs).

## METHODS

**Participant or population:** Studies that enrolled patients with a clinical diagnosis of knee osteoarthritis will be included, and there are no restrictions on gender, age, or ethnicity.

**Intervention:** We will consider studies evaluating the following treatments: acupuncture (Ear Acupunctures, Electroacupuncture), moxibustion, fire needles, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen) Acetaminophen, and duloxetine Hydrochloride, irrespective of preparations (tablet or capsule), dosage, regimen and length of treatment.

**Comparator:** Controlled interventions included control groups with no treatment, sham/placebo groups, or other conventional treatments, which act as vital links for the incorporation of indirect evidence in the networks.

**Study designs to be included:** All randomized controlled trials comparing 2 or more of the following: acupuncture, moxibustion, fire needles, sham acupuncture, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen,

duloxetine Hydrochloride and oral placebo, will be included. Trials must have randomly assigned, on average, at least 100 patients per group to minimize bias due to small study effects. Non- randomized studies or trials published.

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**Information sources:** The MEDLINE, EMBASE and Cochrane Register of Controlled Trials.

**Main outcome(s):** Our prespecified primary outcome was pain. Knee pain levels will be assessed by the visual analogue scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score of pain subscale or the WOMAC global scores.

**Additional outcome(s):** The secondary outcomes will include the following: Function measures: the WOMAC score of physical functional or Lysholm knee scoring scale. Quality of life: the short from health survey (SF-36) or the Pittsburgh Sleep Quality of Index (PSQI).

**Quality assessment / Risk of bias analysis:** The quality of systematic review reflects the risk of bias or validity in its process and results, as well as the reliability of the included studies, which will be assessed using the Cochrane's risk of bias tool. It will be assessed with methodological quality as low risk, high risk, or unclear risk of bias, which contains 7 specific domains: random sequence generation, allocation concealment, blinding of the subjects and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The overall rating is intended to inform readers of the risk of bias across individual studies and will not be used to weight the studies in the meta-analysis. Two reviewers will complete the easement of risk of bias separately. The conflicts or any discrepancies will be resolved by discussion or will be judged by other reviewer to reach the agreement.

**Strategy of data synthesis:** Network meta-analysis considers all trials simultaneously and enables integration of trials involving the availability of both direct and indirect data for comparisons of interest. Firstly, we will conduct classic pair-wise meta-analyses to synthesize studies with the same pair of interventions by using RevMan 5.3 Software. The results will be reported as standard mean differences (SMD) with the corresponding 95% confidence interval (CI). Statistical heterogeneity between studies was assessed by the $\chi 2$ test with a P value of $\leq 0.01$ indicating significant heterogeneity. Secondly, the network meta-analyses are conducted using a hierarchical random-effects model within the Bayesian framework. Then, we will perform the Bayesian network meta-analysis for assessing the therapeutic effect among these treatments in KOA using STATA 16.0 software or WinBUGS1.4.3 software, which uses Markov chain Monte Carlo (MCMC) simulation methods to run thousands of simulated iterations based on the data and description of the proposed distributions for relevant parameters.

**Subgroup analysis:** NA.

**Sensitivity analysis:** According to the quantitative estimation, we will adjust the inclusion of studies and ultimately obtain an ideal network with consistency. Sensitivity analyses were conducted to assess the impact of excluding nonrandomized studies and to examine the impact of low methodological quality.

**Country(ies) involved:** China.

**Keywords:** knee osteoarthritis, acupuncture, intra-articular injection, NSAIDs, network meta-analysis.

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