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Identifying predictors of response to oral non-steroidal anti-inflammatory drugs and paracetamol in osteoarthritis: a hypothesis-driven protocol for an OA Trial Bank individual participant data meta-analysis

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ABSTRACT

Introduction Symptomatic treatments for osteoarthritis (OA) provide only small-to-moderate efficacy over placebo in randomised controlled trials (RCTs). Treatment guidelines therefore have emphasised the need to identify predictors of treatment response through subgroup and multiple regression analysis. Individual participant data (IPD) meta-analysis is recommended as an efficient approach for this purpose. To our knowledge, this has not been undertaken for oral non-steroidal anti-inflammatory drugs (NSAIDs), including paracetamol, in OA. In this IPD meta-analysis, we aim to identify RCTs with specific mechanistic features related to OA pain, such as joint inflammation. We hypothesise that NSAIDs may work better for participants with joint inflammation, whereas paracetamol may not.

Methods and analysis A comprehensive literature search will be conducted on the databases of Web of Science, Embase, Medline, CINAHL, AMED and the Cochrane Library from 1 January 1998 to 1 December 2020. All RCTs related to oral NSAIDs or paracetamol including placebo-controlled trials in people with OA that have evaluated pain-related peripheral risk factors (eg, clinically detected knee effusion, synovial hypertrophy or effusion on imaging, knee morning stiffness, elevated serum C-reactive protein (CRP) level) and/or central pain risk factors (eg, pain elsewhere, depression, anxiety, sleep disturbance) will be retrieved. The outcome will be change in pain from baseline. Change in function and patient global assessment will also be included as outcomes if available. Investigators of all eligible trials will be contacted for IPD. Multilevel regression models will be used to identify predictors for the specific (active–placebo) and the overall treatment effect (change from baseline in active group).

Ethics and dissemination No identifiable data will be included in this study and no formal ethics approval is required as no new data collection will be processed. Results of this hypothesis-driven IPD meta-analysis will be disseminated through conference presentations and publication in peer-reviewed journals.

PROSPERO registration number CRD42020165098.

Strengths and limitations of this study

- Certain subgroups of people with knee osteoarthritis (OA) may benefit more from oral non-steroidal anti-inflammatory drugs than paracetamol. Individual clinical trials are not powered to address this issue.
- Individual participant data (IPD) meta-analysis allows for greater statistical power to identify participant-level predictors of treatment response. It allows utilisation of existing datasets aggregated from pre-existing randomised controlled trials (RCTs), instead of implementing a new large-scale and costly trial.
- The study will be conducted within the framework of the OA Trial Bank, an international organisation that aims to facilitate research into predictors of response to different treatments in OA.
- Most RCTs collect data on only a limited number of individual participant characteristics. Therefore, the IPD analysis is confined to the predictors that are available in the included studies.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide.[1–3] People with OA often experience chronic pain and impaired joint function, and subsequent reduction in quality of life.[4] Unfortunately, there are few effective and safe treatments that can reduce the progression of OA,[1 5] and at present, the main focus of clinical management of OA is to relieve joint symptoms.[6]

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used systemic analgesics for OA,[7 8] and currently, these are recommended by the American Academy of Orthopaedic

Surgeons and the American College of Rheumatology (ACR) guidelines as the first-line drug treatment for management of OA pain.[9 10] However, the efficacy of oral NSAIDs varies across different studies, probably due to the differences in the choice of oral NSAIDs and differences in individual patient response.[11–13] Experimental work has shown oral NSAIDs to have higher efficacy than paracetamol in controlling OA synovial macrophage infiltration and proinflammatory expression,[14] thus one could speculate that oral NSAIDs might be more effective than paracetamol in patients with inflammatory signs. Indeed, one recent study found that a higher serum lysophosphatidylcholines to phosphatidylcholines ratio, which suggests an elevated inflammatory process, can predict a better clinical response to naproxen in people with symptomatic knee OA.[15] In contrast, the presence of central pain sensitisation might be expected to predict a poor response to oral NSAIDs in people with OA. It is reported that facilitated temporal summation of pain prior to treatment is an independent predictor of poor pain alleviation following oral NSAID administration,[16] and that patients with lower conditioned pain modulation showed less reduction in pain with topical NSAID treatment.[17]

Paracetamol is another widely used oral analgesic for OA, which shares with NSAIDs an inhibitory effect on peripheral prostaglandin-synthesising cyclo-oxygenase-2 enzymes.[18] Paracetamol has been recommended as the first-line drug treatment by most OA guidelines,[19] including the National Institute for Health and Care Excellence and the European League Against Rheumatism, largely based on its perceived safety.[20 21] However, a recent network meta-analysis reported that paracetamol was clinically ineffective for patients with OA.[11] As with NSAIDs, paracetamol is also reported to be less effective in patients with OA with central sensitisation.[16] In addition, as a simple analgesic, paracetamol does not have a pronounced anti-inflammatory effect, which may be the reason why its analgesic effect is significantly weaker than NSAIDs for OA.[22] Including paracetamol in this project would permit us to examine the relative analgesic effect between oral NSAIDs and paracetamol and to confirm whether the difference relates to joint inflammation.

In view of the variation in the treatment effect of oral NSAIDs or paracetamol across different populations,[11 13 23–25] it is speculated that oral NSAIDs or paracetamol may have a higher efficacy when targeted at certain patient subgroups. Some guidelines have stressed the necessity to identify predictors of treatment response in order to tailor treatment according to individual patient characteristics—individualised medicine.[26 27] However, identifying clinical predictors of treatment response requires a much larger sample size that often is not achievable within a single trial. A meta-analysis that uses individual participant data (IPD) from multiple trials may overcome the power problem inherent in single individual trials and is therefore considered a suitable alternative approach.[28] By employing this approach, an earlier study has demonstrated increased short-term efficacy from intra-articular glucocorticoid injection in patients with knee OA with more severe pain.[29] Similarly, this protocol aims to retrieve the IPD from randomised controlled trials (RCTs) performed for oral NSAIDs or paracetamol in people with OA in order to identify the responders and the predictors of response to these two most commonly used analgesics in OA. It is hypothesised that patients with inflammatory signs (eg, clinically detected knee effusion, synovial hypertrophy or effusion on imaging, knee morning stiffness, elevated serum C-reactive protein (CRP) level) may respond better to oral NSAIDs, and that those with central pain risk factors (eg, pain elsewhere, depression, anxiety, sleep disturbance) may have a lower response to either oral NSAIDs or paracetamol than those without these factors.

METHODS AND ANALYSIS

A meta-analysis will be performed on the IPD extracted from existing RCTs to examine the efficacy and predictors of response to oral NSAIDs or paracetamol in individual participants with OA. The summary of this protocol has been approved by the steering committee of the OA Trial Bank. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-IPD (PRISMA-IPD) checklist for this IPD meta-analysis protocol.[30]

Selection of studies

All trials that fulfil the eligibility criteria will be included in this IPD meta-analysis.

Inclusion criteria

Study design

RCTs, whether published or unpublished, evaluating pain-related peripheral risk factors (eg, clinically detected knee effusion, synovial hypertrophy or effusion on imaging, knee morning stiffness, elevated serum CRP level) and/or central pain risk factors (eg, pain elsewhere, depression, anxiety, sleep disturbance) at baseline, and the efficacy of oral NSAIDs or paracetamol in participants with OA will be included in the meta-analysis. Both blinded studies and open-label studies will be considered for inclusion.

Participants

In this protocol, definition of OA may vary between studies and be based, for example, on the criteria endorsed by the ACR,[31 32] or on typical clinical and/or radiographic features of OA, such as chronic usage-related joint pain and/or radiographic joint space narrowing plus osteophyte. Studies using all such criteria will be considered. Participants with chronic joint pain that is not caused by rheumatoid arthritis or other forms of arthritis will also be included.

Interventions

Oral NSAIDs or paracetamol, including all oral formulations and dosages, will be examined.

Comparators

The control group will include placebo, usual care, no treatment or waiting list control. RCTs directly comparing oral NSAIDs and paracetamol will also be included.

Outcomes

All the included trials must include an assessment of pain. Referring to the recommendations of the OMERACT-OARSI Initiative,[33] this meta-analysis protocol also includes measures of functional impairment and the patient global assessment, if available. The follow-up duration will be set as 1 week minimum, and the primary outcomes will be measured at 6 weeks or any other time points nearest to 6 weeks, as 6 weeks is the most commonly reported time point for oral NSAIDs. Other time points will also be documented for further analyses as appropriate.

Exclusion criteria

Participants suffering from back pain and/or other arthritic pain (eg, rheumatoid arthritis pain) will be excluded. We will also exclude studies assessing the effect of oral NSAIDs or paracetamol in animals, reviews, editorials, conference abstracts with no other source of data available and non-randomised trials. No geographical or language restrictions will be applied.

Literature search

A comprehensive literature search will be conducted on the databases of Web of Science (Core Collection, 1900 onwards), Embase (OVID interface, 1974 onwards), Medline (OVID interface, 1946 onwards), CINAHL (EBSCOhost interface, all time), AMED (OVID interface, 1985 onwards) and the Cochrane Library (Wiley interface, current issue) to retrieve all the RCTs that are related to oral NSAIDs or paracetamol in people with OA published from the inception of each database to 1 December 2020. The specific search strategies can be found in online supplemental appendix 1. In addition, the pharmaceutical suppliers of oral NSAIDs or paracetamol, which are identified from the British National Formulary, the electronic Medicines Compendium and Clinicaltrials.gov, will be contacted or consulted to identify unpublished appropriate trial data. The references of the included trials will also be manually searched to explore any relevant trials that are not found from the aforementioned databases, and the authors and collaborating authors will be contacted to request any additional information regarding eligible studies. Any available data on clinicalstudydatarequest.com will also be browsed.

The duplicates in the references will be removed prior to the assessment of study eligibility. Two investigators will be responsible for screening the titles, abstracts and full texts of the preliminary retrieved studies to determine whether the studies satisfy the inclusion criteria.

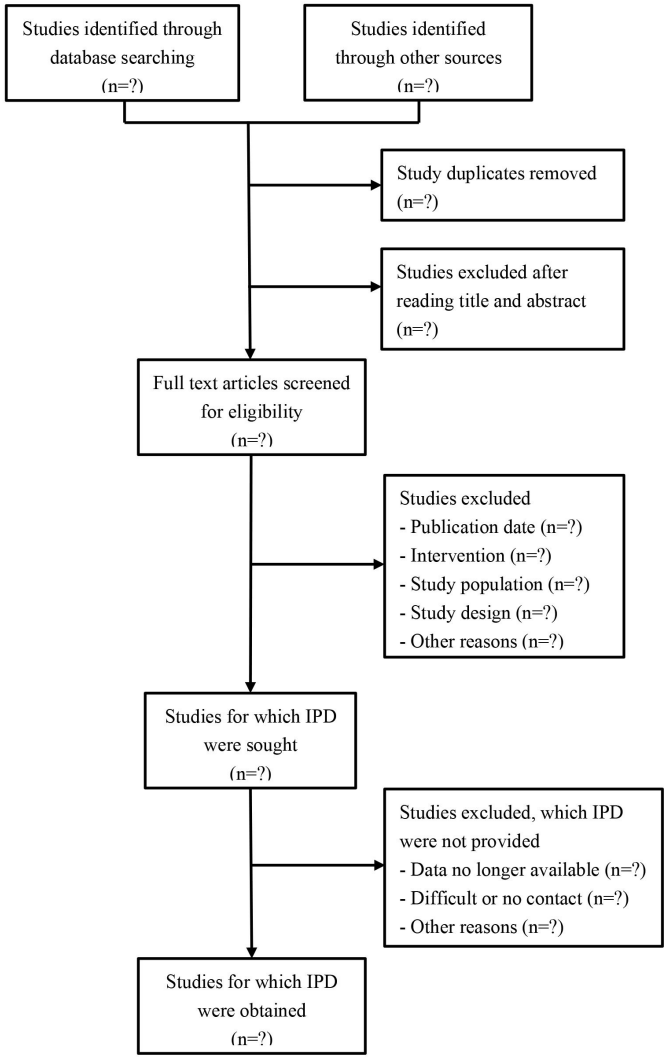

Figure 1 Flow diagram of search and study selection. IPD, individual participant data.

Subsequently, two investigators will independently review the list of included and excluded studies and evaluate all the full texts. Any disputes between the two investigators with respect to study inclusion will be resolved through discussion, and a third investigator will be engaged if consensus cannot be reached. The eligible studies identification process is shown in figure 1.

Data collection

The lead or corresponding investigators of all eligible trials will be contacted for this project, and if none of the investigators can be reached, an email will be sent to all the coauthors. If there is no reply from any author, the research institution where the trial was conducted will be contacted instead. A data sharing agreement will be signed between the OA Trial Bank and the data contributors. The IPD will be obtained and converted into Microsoft Access for storage and management under the General Data Protection Regulation (GDPR) and the Agreement between the OA Trial Bank and individual trialists.

Data extraction

The types of data to be extracted from the eligible trials include participant demographics, OA characteristics, relevant central and/or peripheral characteristics, study design and descriptions, intervention details and outcome measures. The extracted data will be amassed by the main investigator and verified independently by another investigator.

The types of data to be contributed by the authors of the original studies, if any, include participant characteristics such as age, sex and body mass index (BMI), and as long as available, other characteristics such as site of OA, radiographic changes of OA, duration of complaints, level of pain and pain-related risk factors (eg, clinically detected knee effusion, synovial hypertrophy or effusion on imaging, knee morning stiffness, elevated serum CRP level as peripheral risk factors; pain elsewhere, depression, anxiety, sleep disturbance as central pain risk factors). Additional information including study-level characteristics (eg, community or hospital), allocation concealment, sample size, blinding, intervention type, control type, doses and formulations and follow-up duration will also be collected from the published papers and investigators as needed. In addition, outcome measures of pain, function and the global assessment of participants at the baseline and all subsequent assessments will be requested. It is very common that the authors wish to send the whole database to us to save their time. Should this be the case, we will ask for a deidentified dataset in accord with the GDPR.

All participants that are randomised will be pooled into the database for intention-to-treat (ITT) analyses. Per-protocol analyses will be undertaken only if the ITT is not possible. Multiple imputation will be used to impute the missing data (please see statistical analysis for further details).

Patient and public involvement

There have been no patient or public involvement in the study design of this IPD meta-analysis.

Quality evaluation

The quality of study will be evaluated by employing a modified risk of bias tool that is recommended by the Cochrane Collaboration[34] (table 1 and online supplemental appendix 2). This risk of bias tool contains nine questions for evaluating each of the predetermined domains. In comparison with the original Cochrane tool, the modified version for this study will score questions as yes, no or unclear. In view of the fact that the quality evaluation may vary with the language of the study, the modifications applied in this study aim to minimise inter-rater variability in the quality rating.

The first five questions of the modified risk of bias tool target the selection bias, performance bias and detection bias, and each question will be scored based on the criteria set by Cochrane.[34] The sixth question targets the attrition bias, and similar to the PEDro and van Tulder quality scales,[35] a threshold for the acceptable dropout rate will be set to evaluate the risk of bias (15% on discussions with review authors).[36] The seventh question targets selective reporting and will be evaluated by comparing the outcomes presented in the results with those prespecified in the methods. The last two questions mean to address 'other biases', including the use of ITT analysis and the similarity between the treatment and controls at baseline. Although these two types of bias are not specified in Cochrane's risk of bias,[34] they have been included in a number of other RCT quality scales.[35]

In addition to the quality of each study, the attrition bias of the IPD will also be evaluated based on a set of indicators including the number of eligible trials per treatment, the number of trials with IPD acquired and the percentage of data obtained per trial.

To measure the representativeness of the IPD analysis, participant characteristics of all eligible trials will be compared with those included. In addition, sensitivity analyses will be performed to compare the summary effects between the included studies and all published studies.

Table 1 Modified risk of bias assessment

Source of bias	Yes*	No	Unclear	Comments
1. Was the randomisation procedure adequate?	☐	☐	☐	
2. Was the treatment allocation adequately concealed?	☐	☐	☐	
3. Were participants adequately blinded to the intervention?	☐	☐	☐	
4. Were physicians adequately blinded to the intervention?	☐	☐	☐	
5. Were outcome assessors adequately blinded to the intervention?	☐	☐	☐	
6. Incomplete outcome data: Is the attrition rate <15%?	☐	☐	☐	
7. Are all prespecified outcomes of interest reported in the prespecified way?	☐	☐	☐	
8. Was intention-to-treat analysis used?	☐	☐	☐	
9. Were the treatment and control group similar at baseline?	☐	☐	☐	

*See online supplemental appendix 2 for criteria for a judgement of 'yes'.

Data analyses

The databases will be cleaned and merged with study ID, participant ID, participant characteristics, interventions, predictors, covariates and outcomes, etc, all in the exact same format in MS Access. The mean and SD will be chosen to express the continuous data with a normal distribution, while the median and the IQR will be chosen to express the continuous data of other distributions. The frequency and percentage will be used to express categorical data. The 95% CI will be applied for statistical analyses and p<0.05 will be regarded as statistically significant. The multiple imputation method will be applied to treat any missing data in each trial before data pooling, and all missing data will be considered as missing at random.[37] The heterogeneity of the included trials will be measured by I^2. Stata SE V.14 (StataCorp, College Station, Texas, USA) will be applied as the statistical software for all data analyses.

In this protocol, the primary outcome is pain at 6 weeks of treatment duration, or any other duration nearest to 6 weeks. This is because most of the trials for NSAIDs and paracetamol use this time point to report their outcomes.[13 38 39] The secondary outcomes include pain at other follow-up durations, area under the curve for pain scores at the different time points, as well as function and global assessment measures.

The IPD meta-analysis will be performed with both study-level and IPD-level variables to examine the treatment effect and its potential predictors. We will undertake a one-stage multilevel modelling as our primary analysis, as it is more efficient.[40] In addition, we will undertake a two-stage modelling as a sensitivity analysis. The comparison of the two modellings is shown in table 2.

One-stage modelling

In one-stage modelling, all patient-level data from the trials will be analysed in a single step to determine the treatment effect by considering both study-level and individual-level covariates in the regression model. Both the specific treatment effect (ie, the effect of a treatment vs placebo) and the overall treatment effect (ie, the changes from baseline observed in the treatment group) will be estimated.[41] Two multilevel regression models will be established—one for the specific treatment effect and the other for the overall treatment effect. All models will be clustered at the trial level using a random trial intercept.

In the first model, participants from both oral NSAIDs and paracetamol intervention groups will be included. The pain reduction or other outcome improvement will be considered as the dependent variable. The model will be built to contain a fixed treatment term (active or placebo), a fixed predictor term, a random within-study treatment-by-predictor interaction term and a random across-study treatment-by-predictor interaction term. The model will be adjusted for baseline pain, age and sex (separate terms per trial). All variables have to be centred to the study mean.

In the second model, however, only participants in the treatment group will be included. It is based on the assumption that any treatment effect includes both specific and non-specific contextual effects (ie, placebo effect).[41] The pain reduction or other outcome improvement will be considered as the dependent variable, while the potential predictor and other covariates will be considered as independent variables. All variables have to be centred to the study mean. There is no treatment variable in the model, hence, no interaction term with treatment is needed for prediction. Each predictor (eg, clinically detected knee effusion, synovial hypertrophy or effusion on imaging, knee morning stiffness, elevated serum CRP level as peripheral risk factors; depression, anxiety, sleep disturbance as central pain risk factors) will be examined on their own. And those that are significant (p<0.05) will be examined further, by adjusting for age and sex, to determine their influence on the overall treatment effect. This follows clinical practice, where participants are not

Table 2 The pros and cons of the two IPD-MA modellings

IPD-MA modellings	Pros	Cons
One-stage modelling	► Offers the highest degree of flexibility for making necessary assumptions. ► Allows a more exact likelihood specification. ► Have better convergence properties when the studies have small numbers of participants.	► The methodology is not as straightforward as it may seem. ► Computationally intensive and prone to convergence problems. ► May lead to aggregation bias, also known as ecological bias.
Two-stage modelling	► Conceptually more intuitive and requires less statistical expertise. ► Study-specific estimates are not influenced by external information.	► Little power for detecting non-linear associations between continuous exposures and the outcomes. ► Little power for detecting treatment–covariate interactions. ► May lead to bias in pooled effects, SEs, between-study heterogeneity and correlation between random effects when few studies or few participants per study are available.

IPD-MA, individual participant data meta-analysis.

given an active ingredient of a drug or placebo, but an entire treatment that includes both the active ingredient and the placebo/therapeutic context.[42]

Two-stage modelling

In two-stage modelling, a regression model will be established for each trial. For a specific treatment effect (the effect of a treatment in comparison with placebo), the predictors will be determined by an interaction term between the treatment variable (yes=active and no=placebo) and the potential predictor. The partial regression coefficients of the interaction term will be estimated for each trial. They will then be pooled to generate an overall estimate of partial regression coefficient. The prediction model for the overall treatment effect (ie, the improvement from baseline), however, will be established within the treatment arm. The partial regression coefficients of a predictor will be estimated for each trial. They will then be pooled to generate an overall estimate. The inverse-variance based random-effect meta-analytic technique will be applied to pool the partial regression coefficients. Heterogeneity test will be applied.

Exploratory analyses

The following three analyses will be explored:

1. An IPD network meta-analysis for relative effect between NSAIDs and paracetamol. A network will be developed to include both direct comparisons between NSAIDs and paracetamol as well as indirect comparisons of these two through a common comparator (eg, placebo or no treatment arm). A multilevel regression model will be developed to examine the relative effect and its interaction with potential predictors such as inflammation.
2. An IPD network meta-analysis for placebo effect (placebo–no treatment group): A network will be developed to include both direct comparisons between placebo and no treatment, as well as indirect comparisons of these two arms through a common comparator (eg, NSAIDs or paracetamol). A multilevel regression model will then be developed to examine the placebo effect and its interaction with potential predictors such as female sex.

   Both frequentist and Bayesian statistics will be used for these two IPD network meta-analyses.
3. Since predictors of response to treatments may differ between knee, hip and hand OA, subgroup analyses will be conducted for different sites of OA, if sufficient data are available.

ETHICS AND DISSEMINATION

No identifiable data will be included in this study and no formal ethics approval is demanded as no new data collection will be processed. A data delivery agreement will be provided and signed by data contributor of each original trial in this study. Results of this hypothesis-driven IPD meta-analysis will be disseminated through conference presentations and publication in peer-reviewed journals.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting or dissemination plans of our research.

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Contributors YX, CZ, GL and WZ contributed to the conceptualisation and design of the study. YX and CZ developed the search strategy and drafted the first version of the manuscript. YX, CZ, MD, MSMP, JW, MvM, GL and WZ all involved in the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. The study proposal has been peer reviewed and approved by the OA Trial Bank Steering Committee.

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