

# Targeting Nerve Growth Factor, a new option for treatment of osteoarthritis: A Network meta-analysis of comparative efficacy and safety with traditional drugs

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## Research article

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# Abstract

**BACKGROUND:** Osteoarthritis (OA) is the most common joint disease and leading cause of pain and disability in the elderly population. Most guidelines recommend the use non-steroidal anti-inflammatory drugs (NSAIDs) and opioids for the non-operative treatment of OA. Monoclonal NGF antibodies are potential for pain relief and function improvement of OA. We conducted this network meta-analysis to comprehensively compare the efficacy and safety of monoclonal NGF antibodies with NSAIDs and opioids for OA.

**METHODS:** Relevant studies, published up to January 2020, were included from PubMed, CKNI and Web of Science databases. Bayesian network and conventional meta-analyses were conducted. Pain relief, function improvement and risk of adverse effects (AEs) were assessed.

**RESULTS:** 38 articles, comprising 41 trials (20489 patients with OA) were included. Overall, Anti-NGF was the most efficacious drug for pain relief (SMD compared with placebo 4.25, 95% CIs [2.87 to 5.63], SUCRA=93.7%) and (SMD 4.90, 95% CIs [3.46 to 6.33], SUCRA=98.3%). Although Anti-NGF was associated with higher risk of peripheral sensation abnormality (paresthesia and pruritus), it was not associated with higher withdrawal rates due to AEs and other AEs.

**CONCLUSIONS:** The results show that monoclonal NGF antibodies significantly relieve pain due to OA and improve function, compared to selective cox-2 inhibitions, NSAIDs, and opioids. The monoclonal NGF antibodies are not associated with severe AEs. However, there is need to conduct more studies to confirm the findings of this study.

## Introduction

Osteoarthritis (OA) is the most common joint disease and leading cause of pain and disability in the elderly population. Globally, approximately 302 million people suffer from Osteoarthritis every year (1).

OA is a common degenerative disease characterized by cartilage degeneration, osteophyte formation, and synovial inflammation. The disease usually affects the knee, hip, or hand joints. The OA-caused pain symptoms and subsequent physical dysfunction increase the mortality risk (2) as well as the societal economic burden (3). To address the health issue, most guidelines recommend the use non-steroidal anti-inflammatory drugs (NSAIDs) and opioids for the non-operative treatment of OA (1). However, the use of NSAIDs and opioids is limited by the tolerability and safety concerns(4).

In 1950s Levi-Montalcini et al(5) discovered the nerve growth factor (NGF), a new neurotrophin molecule. Subsequent studies have confirmed the crucial effect of NGF in the development of sensory neurons responsible for nociception and temperature sensation. Moreover, evidence shows that the withdrawal or blockage of NGF significantly decreases the sensitivity of peripheral nociceptors and down-regulates expression of neuropeptide (6). This results in adequate pain relief. Subsequently, numerous monoclonal NGF antibodies have been developed. Among the monoclonal NGF antibodies, clinical trials on OA have

been conducted using tanezumab, fulranumab and fasinumab, and the high efficacy results were reported (7–15).

Numerous systematic reviews and meta-analyses investigating the efficacy and safety of NSAIDs and/or opioids for treatment of OA pain have been conducted. A recent network meta-analyses compared the pain-reduction efficacy of NSAIDs with opioids (16). The results showed that NSAIDs and opioids are efficacious in pain relief in OA patients. Based on this study, we included 13 types of drugs in our network meta-analysis. Based on these drugs' activity mechanism, we divided them into 5 groups: Anti-NGF group (tanezumab, fulranumab, fasinumab), potent opioid (oxycodone, hydromorphone, oxymorphone), weak opioid (tramadol), selective COX-2 inhibitor (celecoxib, etoricoxib, rofecoxib), and traditional NSAIDs (ibuprofen, naproxen, diclofenac, paracetamol/acetaminophen). We subsequently assessed the efficacy, including pain reduction and physical function improvement, and the drug's safety for OA in a bayesian network meta-analysis.

## Method

### Literature search

We searched the PubMed, CKNI and Web of Science databases, up to January 2020. Our search terms consisted of "Osteoarthritis", "tanezumab", "fulranumab", "fasinumab", "oxycodone", "hydromorphone", "oxymorphone", "tramadol", "celecoxib", "etoricoxib", "rofecoxib", "ibuprofen", "naproxen", "diclofenac", and "paracetamol/acetaminophen". We screened the reference lists of the relevant systematic reviews and meta-analyses to identify eligible articles. All eligible articles were included irrespective of the language of publication.

### Inclusion/exclusion Criteria

The inclusion criteria for this network meta-analysis were as follows: 1. randomized clinical trials (RCTs); 2. studies comparing the target drugs with placebo, or each other; 3. studies on patients with OA at any joint; 4. studies reporting the following endpoints: pain reduction, withdrawal due to adverse effects (AEs), and function improvement. The exclusion criteria were as follows: 1. dose-escalation studies of only one drug; 2. target drugs combined with other drugs; 3. studies for postoperative pain; 4. reviews, systematic reviews and meta-analyses, conference abstraction, letters, pharmacokinetical or pharmacodynamical studies, and studies with insufficient data.

### Quality Assessment

We strictly used the Cochrane risk of the bias assessment tool to perform the methodological quality assessment of the RCTS. Based on the Cochrane handbook V.5.1.0 (17), we evaluated six indications: sequence generation, allocation concealment, blinding, incomplete outcome data, selection outcome

reporting, and other sources of bias. The quality of each indication was evaluated and ranked as low risk of bias, unclear risk of bias, or high risk of bias.

## Data Extraction

Author, publication year, total sample size, mean age, gender ratio, affected joint, route of administration, experimental drugs, intervention time, additional follow-up period, and endpoint data were collected and tabulated. To reduce the effect of withdrawal bias, we preferentially collected the data from the intention-to-treat analysis.

## Outcome Measures

The primary efficacy endpoint was the pain reduction. The secondary efficacy endpoint was the functional improvement. The change-from-baseline score (mean  $\pm$  SD) at the last follow-up period was used to evaluate the extent of pain relief. There were restrictions on the types of questionnaire used in pain evaluation. Functional improvement was evaluated using the function subscale of Western Ontario and McMaster Universities Arthritis Index (WOMAC). If the WOMAC function score was not measured or reported, the Lequesne Index or other functional measurement scales was used. For studies involving multiple treatment groups with different doses of the same drug, we selected the most effective dose group based on respective study's recommendations (18). We calculated the standardized mean difference (SMD) since results from different scales were used in the same network.

Since the patient compliance contributes to the effect of treatment in clinical practice, we selected the withdrawal rates due to AEs as the primary safety endpoint. The most commonly related AEs were labeled as the secondary safety endpoints. We calculated the odds ratio (OR) with 95% confidence intervals (CI) for the safety of target drugs versus placebo or against each other.

## Statistical analysis

Direct pairwise meta-analyses was performed to compare the efficacy of the target drugs with placebo using Review Manager Software (version 5.3). The heterogeneity across studies was tested by the Q and I<sup>2</sup> statistic, in which  $P < 0.05$  or  $I^2 > 50\%$  was considered significantly heterogeneous. After that, a random-effects model was used to test the significant heterogeneity across studies, otherwise, a fixed-effects model was preferred. The Bayesian network meta-analyses were conducted using Stata/MP (version 14.0, Stata Corp, College Station, Texas, USA) and GeMTC (version 0.14.3). This method increases the number of studies within each comparison and narrows the CIs' width, resulting in stable results (19–22). In the Bayesian network meta-analysis, non-informative uniform and normal prior distributions was used. Subsequently, four different sets of starting values were set to fit the model to yield 40000 iterations (10000 per chain) and obtain the posterior distributions of model parameters (23, 24). The thinning interval was set at 10 and the burn-ins at 1000, for each chain. Convergence of iterations was assessed

using the Gelman-Rubin-Brooks statistic (25). Global inconsistency tests and local inconsistency tests (Loop-inconsistency tests and Node-split tests) were used to reconfirm the consistency of the network meta-analysis. Three subgroup analyses were conducted. The first one was used to verify the impact of the results of the network analyses whether the included trials were commercially funded or not. The second one was to find the optimum one for both pain relief and physical function improvement from different selective COX-2 inhibitor and traditional NSAIDs (celecoxib, etoricoxib, rofecoxib, ibuprofen, naproxen, diclofenac, paracetamol/acetaminophen) versus placebo.

All estimate outcomes (SMDs or ORs) with 95% CIs were generated from the posterior distribution medians. Significant differences were considered at the 95% CI excluding 0 for the SMD or 1 for OR. Surface under the cumulative ranking (SUCRA) was used to rank the efficacy and safety of different drugs. To select the most effective drug simultaneously for the two or more endpoints, cluster-ranking plots constructed.

## Results

### Study selection

This network meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26).

A total of 38 articles, including 41 trials (7–15, 27–55), were included. The selection criteria is shown in Supplementary appendix Fig. 1. Five treatment arms (Anti-NGF, potent opioid, weak opioid, selective COX-2 inhibitor, and NSAIDs) and eight treatment arms (celecoxib, etoricoxib, rofecoxib, ibuprofen, naproxen, diclofenac, paracetamol/acetaminophen and placebo) were included into the network of the main and subgroup analyses, respectively (Fig. 1).

### Study Characteristics

A total of 20489 patients were included in to the study. Among the 41 eligible articles, only one study with 385 patients was on hand-joint OA. Across the trials, the mean age of the patients was 61.25 years (ranged from 57.41 to 70.00 years), the proportion of male patients was 32.26% (ranged from 19.57–54.03%), and the median follow-up was 84 days (IQR 42–84 days). The number of assessed patients for each treatment were 5408 (NSAIDs), 4131(selective COX-2 inhibitor), 3108 (anti-NGF), 1405 (weak opioids), and 1274 (potent opioids).

The baseline characteristics of the included studies are shown in Supplementary appendix Table 1. The methodological quality and risk of bias were evaluated for all included trials (Supplementary appendix Table 2). Based on this results, the main contributing factors to risks of bias were performance bias, selection bias, and attrition bias.

Table 1

Characteristics of the included comparisons and the results of direct pair-wise meta-analysis(FU, follow-up; No. of pts, number of patients included; No. of trials, number of trials included into direct pair-wise meta-analysis; SMD, standardised mean difference)

Comparison	No. of trials	No. of pts	Target joint	Mean age (range)	Male %	Mean FU periods (days, range)	SMD (95%CI) for pain relief
Anti-NGF vs placebo	9	2348	Hip and Knee	59.98 (57.41–62.32)	0.3667	102.67 (56–224)	4.182(3.778,4.586)
Potent opioids vs placebo	5	1528	Hip and Knee	61.10 (57.41–65.52)	0.3662	81.2 (14–112)	0.807 (-1.527,3.140)
Weak opioids vs placebo	2	805	Hip and Knee	59.09 (58.10–60.02)	0.3723	84	3.451(1.722,5.180)
Selective cox-2 inhibition vs placebo	9	2917	Hip and Knee	62.81 (60.02–64.77)	0.2863	60.67 (42–84)	4.775(2.836,6.714)
NSAIDs vs placebo	20	6833	Hand, Hip and Knee	62.55 (58.66–70.00)	0.299	55.65 (21–84)	2.573(1.789,3.357)

Table 2

Detailed results of network meta-analysis for pain (Red) and function (Blue) (Data are standardised mean difference, from the top left to the bottom right, higher comparator vs lower comparator, and their related 95% CI)

<b>Anti-NGF</b>	<b>2.34</b> <b>(0.38,4.29)</b>	<b>2.48</b> <b>(-0.93,5.89)</b>	<b>2.87</b> <b>(1.16,4.57)</b>	<b>3.70</b> <b>(1.43,5.96)</b>	<b>4.90</b> <b>(3.46,6.33)</b>
1.33 (-0.55,3.21)	<b>Selective cox-2 inhibition</b>	0.15 (-3.09,3.38)	0.53 (-0.77,1.84)	1.36 (-1.07,3.80)	2.56 (1.17,3.95)
1.22 (-2.07,4.51)	-0.11 (-3.23,3.00)	<b>Weak opioids</b>	0.39 (-2.83,3.60)	1.22 (-2.47,4.91)	2.42 (-0.68,5.52)
2.33 (0.69,3.96)	1.00 (-0.24,2.23)	1.11 (-1.99,4.20)	<b>NSAIDS</b>	0.83 (-1.42,3.09)	2.03 (0.97,3.09)
3.35 (1.16,5.53)	2.02 (-0.33,4.36)	2.13 (-1.44,5.69)	1.02 (-1.15,3.19)	<b>Potent opioids</b>	1.20 (-0.81,3.21)
4.25 (2.87,5.63)	2.92 (1.58,4.26)	3.03 (0.04,6.02)	1.92 (0.92,2.93)	0.90 (-1.04,2.84)	<b>Placebo</b>

## Primary Efficacy Endpoint

### Direct pair-wise meta-analysis

The efficacies of all the drugs were superior to placebo, for pain relief except for potent opioid with no significant difference (0.807, 95% Cis [-1.527 to 3.140]). Notably, Anti-NGF had the highest significant, for pain relief (SMD 4.817, 95% Cis [3.077 to 6.557]). The details of the pairwise meta-analysis for all drugs compared with placebo are shown in Table 1.

### Network Meta-analysis

A total of 38 trials were analyzed. No significant inconsistency was reported in loop-inconsistency estimates, node-split tests, and global inconsistency tests. The consistency model was statistically significant than the inconsistency model.

Anti-NGF was the most efficacious drug (SMD compared with placebo 4.25, 95% CIs [2.87 to 5.63]) for OA pain relief. The potent opioid drug had the lowest efficacy (SMD 0.90, 95% CIs [-1.04 to 2.84]) (Figure 2 and Table 2). Based on the SUCRA value, Anti-NGF was the most efficacious drug in pain relief

(SUCRA=93.7%), followed by selective COX-2 inhibitor (SUCRA=69.0%), and lastly opioids (SUCRA=67.3%). The details of the SURCA rank are shown in Supplementary appendix Table 3.

The subgroup analysis results showed a consistent trend, even after eliminating all non-funded trials (10 trials). Anti-NGF was still the most efficacious drug for pain relief (SURCA 92.4%, SMD=4.30, 95% CIs [2.85 to 5.74]). The detailed results are shown in the Supplementary appendix Table 4.

## Secondary Efficacy Endpoint

### Direct pair-wise meta-analysis

Except for the potent opioids (SMD 1.058, 95% CIs [-1.012 to 3.127]), there was a significant difference in efficacy both in the Anti-NGF and selective COX-2 inhibitor drugs compared to placebo. Anti-NGF had the highest efficacy for physical function improvement (SMD 5.108, 95% CIs [3.165 to 7.051]). The details of the pairwise meta-analysis for all drugs compared with placebo are presented in Table 1.

### Network meta-analysis

A total of 38 trials were analyzed. No significant inconsistency was reported. The consistency model was statistically significant compared to the inconsistency model. Similarly, Anti-NGF drug had the highest efficacy for physical function improvement (SMD 4.90, 95% CIs [3.46 to 6.33]) (Figure 2). The lowest efficacy was reported in potent opioid drug (SMD 1.20, 95% CIs [-0.81 to 3.21]) (Figure 2 and Table 2). For physical function improvement, the most efficacious drug based on SURCA, was Anti-NGF (SUCRA=98.3%), followed by selective COX-2 inhibitor (SUCRA=63.5%) and opioids (SUCRA=56.7%) (Supplementary appendix Table 3). There was no significant difference in the subgroup analysis of the trials with commercial funding. For physical function, Anti-NGF had the highest efficacy (SUCRA 97.6%, SMD 4.96, 95% CIs [3.42 to 6.50]) (Supplementary appendix Table 4).

## Primary Safety Endpoint

### Direct pair-wise meta-analysis

Except for selective COX-2 inhibitor (OR 0.742, 95% CIs [0.436 to 1.261]), There were significant differences in both Anti-NGF and Opioids in the withdrawal rate due to AEs (Supplementary appendix Table 5).

### Network meta-analysis

In the withdrawal due to AEs network, a total of 36 trials were assessed. Loop-inconsistency estimates, node-split tests, and global inconsistency tests were performed, and no inconsistency was reported.

Significantly higher withdrawal rates due to AEs were reported in potent opioids (OR 8.63, 95%CI [5.42, 13.77]), weak opioids (OR 3.27, 95%CI [1.89, 5.66]), and NSAIDs (OR 1.36, 95%CI [1.04, 1.77]) compared to placebo. Selective COX-2 inhibitor (SURCA = 93.4%) was reported as the most safe drug, followed by anti-NGF (SURCA=53.5%), and NSAIDs (SURCA=50.5%) (Supplementary appendix Table 3). The subgroup analysis showed that there was no significant change in results, after adjusting the network based on whether trials were funded (Supplementary appendix Table 4). There was no statistical difference reported after excluding the trials with short follow-up. The cluster-rank plots of primary efficacy and primary safety indicated the safest drug was selective Cox-2 inhibition (Supplementary appendix Figure 2).

## Network meta-analysis

In the headache network, the most efficacious drug was NSAIDs (OR 0.82, SURCA 90.3%, 95% CI [0.63 to 1.06]). However, no significant differences were reported between the remaining treatments and placebo.

NSAIDs (OR 1.48, 95% CI [1.04 to 2.13]), weak opioids (OR 3.90, 95% CI [1.82 to 8.36]) and potent opioids (OR 6.33, 95% CI [3.37 to 11.90]) had significantly higher risks for nausea AEs. The incidence rates of peripheral sensation abnormality AEs was significantly higher in anti-NGF (OR 3.64, 95% CI [1.87 to 7.10]), weak opioids (OR 5.25, 95% CI [1.95 to 14.15]) and potent opioids (OR 5.39, 95% CI [2.41 to 12.06]) (Table 3). No subgroup analysis was conducted for secondary safety endpoints because of the insufficient number of trials included.

Table 3. Adverse effects of different treatment compared with placebo according to direct pair-wise meta analysis and network meta-analysis (AE, adverse effect; PSA, peripheral sensation abnormality; SUCRA, surface under the cumulative ranking.)

Treatment	OR(95%CI)		SURCA(%)
	Direct	Network meta-analysis	
Withdrawal due to AEs			
Placebo	Reference	Reference	82.3
Anti-NGF	1.677(1.045,2.692)	1.36 (0.82,2.27)	53.5
Potent Opioids	5.265(3.705,7.482)	8.63 (5.42,13.77)	0.1
Weak Opioids	2.798(1.348,5.807)	3.27(1.89,5.66)	20.1
Selective cox-2 inhibition	0.742(0.436,1.261)	0.89 (0.64,1.24)	93.5
NSAIDs	1.272(1.028,1.573)	1.36(1.04,1.77)	50.5
Headache AEs			
Placebo	Reference	Reference	53.3
Anti-NGF	0.970(0.634,1.483)	1.03 (0.68,1.57)	49.3
Potent Opioids	1.283(0.897,1.837)	1.19 (0.78,1.82)	29.2
Continued			
Weak Opioids	1.305(0.709,2.399)	1.41 (0.88,2.25)	12.4
Selective cox-2 inhibition	0.748(0.528,1.060)	0.93 (0.68,1.27)	65.4
NSAIDs	0.928(0.733,1.175)	0.82 (0.63,1.06)	90.3
Nause AEs			
Placebo	Reference	Reference	74.2
Anti-NGF	0.962(0.504,1.837)	0.79 (0.41,1.53)	88.7
Potent Opioids	4.519(3.212,6.358)	6.33 (3.37,11.90)	3.3
Weak Opioids	3.131(2.054,4.775)	3.90 (1.82,8.36)	17.0
Selective cox-2 inhibition	0.825(0.398,1.708)	0.99 (0.64,1.52)	75.8
NSAIDs	1.432(0.947,2.165)	1.48 (1.04,2.13)	41.1
Psa AEs			
Placebo	Reference	Reference	82.7
Anti-NGF	4.184(2.010,8.707)	3.64 (1.87,7.10)	30.7
Potent Opioids	5.331(2.731,10.407)	5.39 (2.41,12.06)	14.2

Treatment	OR(95%CI)		SURCA(%)
	Direct	Network meta-analysis	
Weak Opioids	8.371(2.935,23.870)	5.25 (1.95,14.15)	15.4
Selective cox-2 inhibition	0.777(0.021,28.890)	0.96 (0.39,2.39)	82.6
NSAIDs	0.966(0.633,1.473)	1.13 (0.67,1.90)	74.4

## Subgroup analysis of efficacy between NSAIDs and selective COX-2 inhibitor

A total of 24 trials, assessing the efficacy of NSAIDs or selective COX-2 inhibitor, were included. Etoricoxib was the most efficacious drug for both pain relief (SMD 3.20, 95% Cis [1.17 to 5.24]) and function improvement (SMD 3.41, 95% Cis [1.88 to 4.93]). All drugs had significantly higher efficacies compared to placebo for both pain relief and function improvement (Figure 2 and Supplementary appendix Table 6). However, no significant difference was reported between different drugs. Based on the cluster-rank plot, etoricoxib was the efficacious drug (Supplementary appendix Figure 2).

## Secondary Safety Endpoint

After selection of the studies, the incidence rates of the three most common AEs, including nausea, headache, and peripheral sensation abnormality (paresthesia and pruritus) were selected for secondary safety endpoints. A total of 33 trials were assessed.

## Direct Pair-wise Meta-analysis

There were no significant difference in headache AEs among the three drugs from the pair-wise meta-analyses. However, potent opioids and weak opioids had significantly higher risks for nausea or peripheral sensation abnormality AEs. Besides, Anti-NGF had significantly higher risk for peripheral sensation abnormality AEs (Table 3).

## Discussion

This is the first network meta-analysis study comparing the efficacy and safety of the monoclonal NGF antibodies, NSAIDs, opioids, and selective cox-2 inhibitors directly or indirectly, simultaneously. The Bayesian Network used in this study increases the number of studies within each comparison. This network increases the robustness and power of the results. Our results showed that, (1) monoclonal NGF

antibody drugs have the highest efficacy for treatment of OA, and had no significant difference compared to selective cox-2 inhibitors, NSAIDs, and opioids; (2) regarding safety and efficacy, the potent opioid drugs are safe and efficacious for the treatment of OA; (3) monoclonal NGF antibodies have the highest efficacy for both pain relief and function improvement, while selective cox-2 inhibitions are the safest and the most suitable choice for long-term treatment of OA (because of the lowest risk of withdrawal due to AEs); (4) etoricoxib seemingly was the most efficacious for both pain relief and function improvement based on cluster-rank and SURCA. However, no significant difference was reported between etoricoxib and other selective cox-2 and NSAIDs.

A previous network meta-analysis (16) reported that NSAIDs, weak opioids, and potent opioids have equivalent efficacies for pain relief in OA patients. However, no direct comparison between the potent opioids and other drugs was conducted in this study. Moreover, only one indirect comparison of the drugs with the placebo was performed in the study (16). Therefore, the findings about opioids in this study lack robustness. Based on this study, we included more eligible studies, directly or indirectly comparing potent opioids with other drugs into this study. Additionally, we analyzed for function improvement and the safety of the drugs, which are equally important as pain relief in OA treatment.

The novelty of this study; monoclonal NGF antibodies have the highest efficacy for pain relief and function improvement, exceeding that of selective cox-2 inhibitors, NSAIDs, and weak opioid (tramadol), which are recommended in the American College of Rheumatology/Arthritis Foundation Guideline of 2019 (1). However, monoclonal NGF antibodies have a higher risk of peripheral sensation abnormality (including paresthesia and pruritus). Additionally, its overall withdrawal rate due to AEs is not significantly different compared to placebo. Our findings are consistent with the results of previous systematic reviews (56, 57). Based on our results, monoclonal NGF antibodies constitute the most effective treatment option for OA. The monoclonal NGF antibodies should be the first choice for patients with pain symptoms and/or disability due to OA. However, for patients with paresthesia and pruritus, selective cox-2 inhibitors and NSAIDs are best treatment options. The choice of selective cox-2 inhibitors and NSAIDs can be made based on the mean rank order presented in Supplementary appendix Table 5.

However, this study had several limitations. Firstly, we included only RCTs in our study, based on the unmanageable confounding factors. We omitted observational studies or any other non-RCTs from this network meta-analysis despite of their significance in examining drug effectiveness and safety of treatment for OA. This may have contributed to the small number of studies included. Secondly, only high-quality studies were included. This was done to control the quality of this analysis and minimize the impacts of small study effects. However, the omitted small increase generalizability and robustness of results. The publication bias may be a significant problem. It is difficult to control since it was on a small number of studies. Thirdly, the length of follow-up is closely related to safety profiles as it is not possible to measure long-term outcomes for drug safety, especially for those with short (1–6 weeks) follow-up period. Even though the median follow-up of this network-analysis was 84 days (IQR 42–84 days), it is still not enough to assess long-term outcomes for safety, particularly for these AEs with mild and

chronic symptoms, such as hypertension and sensation abnormality events. More high-quality trials, with long-term follow-up, are needed.

## Conclusion

A total of 38 studies comprising of 20489 patients were included in this network meta-analysis. The results show that monoclonal NGF antibodies significantly relieve pain due to OA and improve function, compared to selective cox-2 inhibitions, NSAIDs, and opioids. The monoclonal NGF antibodies are not associated with severe AEs. However, there is need to conduct more studies to confirm the findings of this study.

## Declarations

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Competing interests:** The authors declare that they do not have any competing interests.

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### Author contributions:

Jian Zhou and Wanchun Wang conceived the study, participated in its design and coordination, and critically revised the manuscript. Ziqin Cao, Zeling Long and Yihan Li had full access to all of the data collection, analysis, interpretation and drafted the manuscript. Jian Zhou, Jingjing Sun, Pengcheng Dou and Wanchun Wang were study investigators and contributed to the process of data collection. All authors read and approved the final manuscript.

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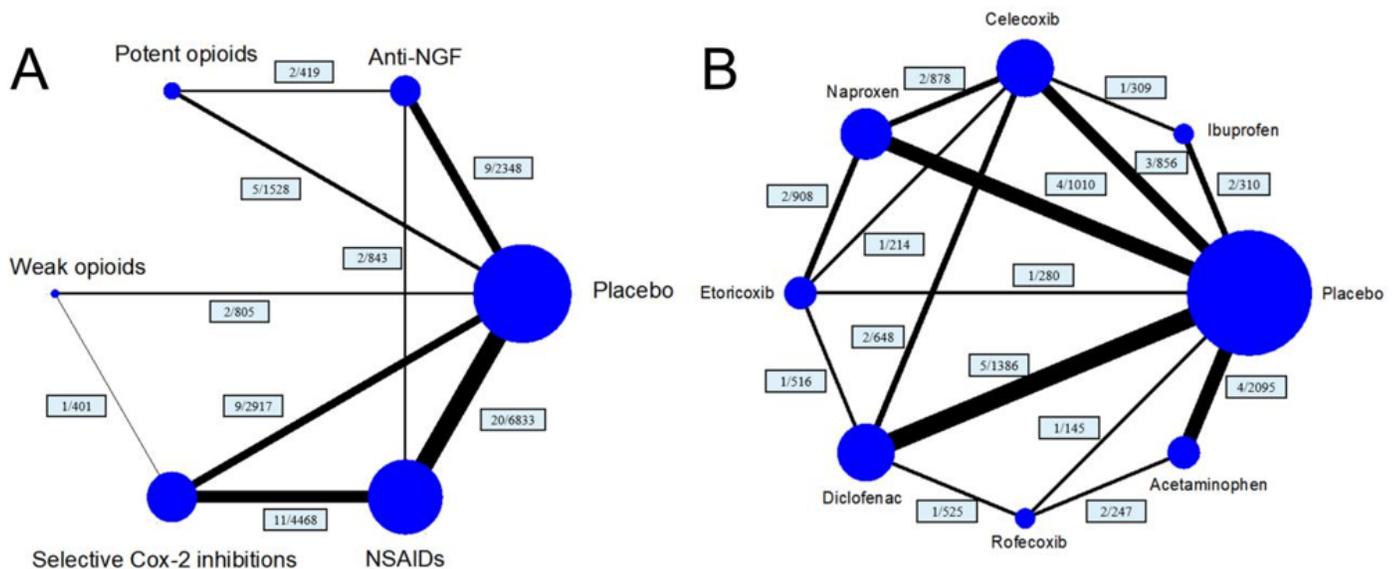
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## Figures



**Figure 1**

Structure of network formed by interventions. The lines between treatment nodes indicate the direct comparisons made within randomised controlled trials. Numbers (n/n) near the line indicate ‘number of trials/number of participants’ of the related comparisons. (A) the network plot of main network meta-analysis. (B) the network plot of subgroup analysis comparing different selective COX-2 inhibitor and traditional NSAIDs.

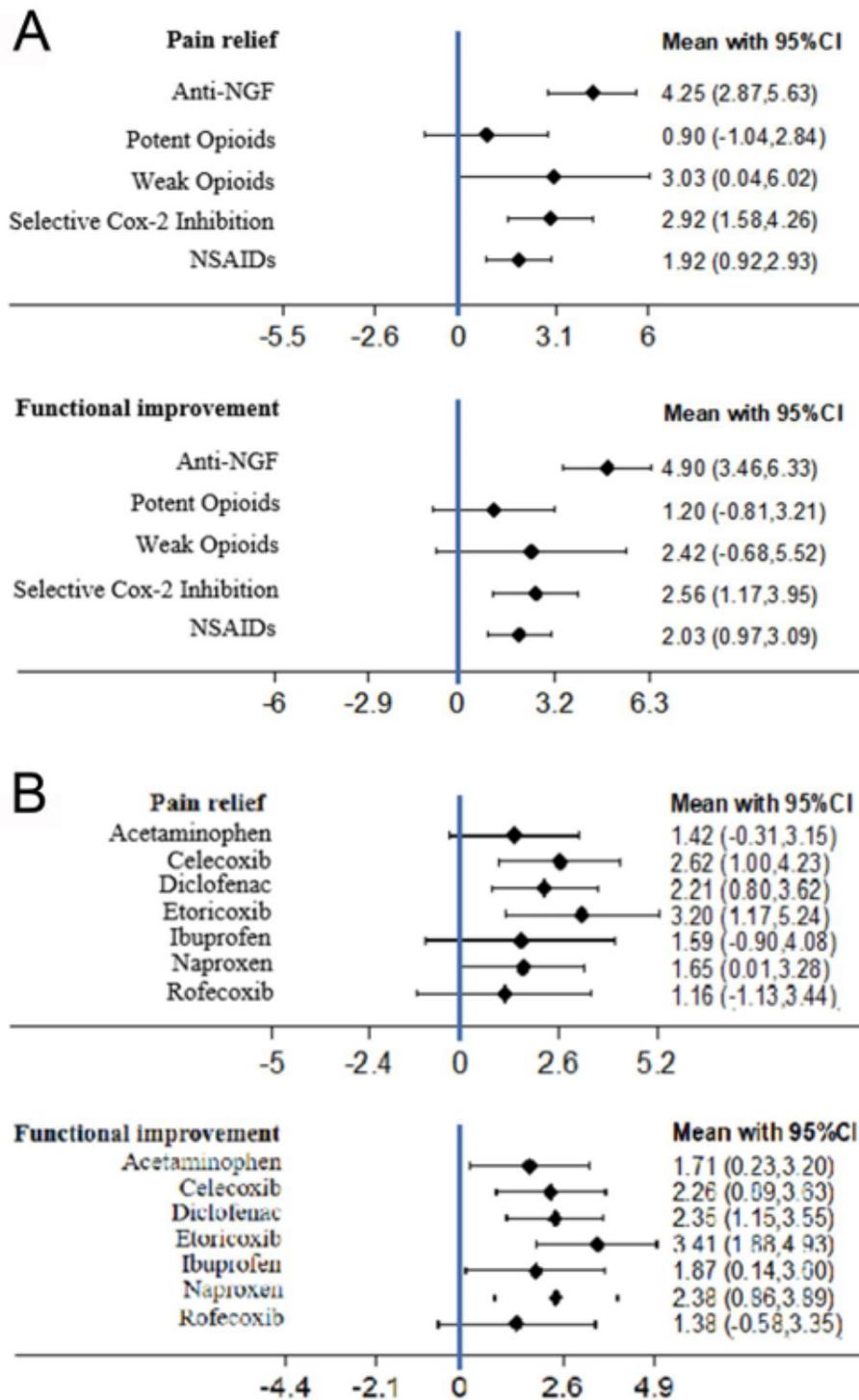


Figure 2

(A) The forest plots of pain relief and function improvement for main network meta-analysis. (B) The forest plots of pain relief and function improvement for subgroup analysis comparing different selective COX-2 inhibitor and traditional NSAIDs (SMD, standardised mean difference).

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