Is Lutikizumab, an Anti–Interleukin-1α/β Dual Variable Domain Immunoglobulin, efficacious for Osteoarthritis? Results from a bayesian network meta-analysis

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Abstract

OBJECTIVE

Osteoarthritis (OA) is the most common form of joint disease which usually affects load-bearing joints such as hip and knee joints. Most guidelines recommend the use non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine and tramadol for the non-operative treatment of OA, the use of them is limited by the tolerability and safety concerns. Lutikizumab is a novel anti–IL-1α/β dual variable domain immunoglobulin that can simultaneously binds and inhibits IL-1α and IL-1β to relieve the pain and dysfunction symptoms. We conducted this network meta-analysis to comprehensively compare the clinical efficacy and safety of lutikizumab with other drugs recommended by guidelines.

DESIGN

Systematic review and Bayesian network meta-analysis.

DATA SOURCES

All eligible studies in PubMed, CKNI, EMBASE and Web of Science databases, from January 2000 to January 2020.

METHODS

Bayesian network and conventional meta-analyses were conducted. Pain relief, function improvement and risk of adverse effects (AEs) were assessed.

RESULTS

24 articles with 11858 patients were included. Lutikizumab showed no benifit compared with placebo for both pain relief (SMD 1.11, 95% CI [-2.29 to 4.52]) and function improvement (SMD 0.992, 95% CI [-0.433 to 4.25]). Lutikizumab and all other drugs are of favorable tolerance for patients in treatment of OA compared with placebo.

CONCLUSIONS

The results show that lutikizumab, the new anti–Interleukin-1α/β dual variable domain immunoglobulin, did not improve pain or function in the comparison with placebo. Selective cox-2 inhibitors remain the most effective and safest treatment for osteoarthritis. More high-quality trials are still needed to reconfirm the findings of this study.

Introduction

Osteoarthritis (OA) is the most common form of joint disease which usually affects load-bearing joints such as hip and knee joints (1). OA could lead to local pain, stiffness in early stages, and could cause to

dysfunction even disability of limbs in the late stages. Approximately 302 million people suffer from Osteoarthritis in the worldwide every year (2). The OA-related pain and dysfunction symptoms increase the mortality risk (3) as well as the societal economic burden (4). To address the health issue, most guidelines recommend the use non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine and tramadol for the non-operative treatment of OA (2). However, the use of aforementioned drugs is limited by the tolerability and safety concerns (5) .

Previous literature has confirmed that the proinflammatory cytokines, interleukin-1α and 1β (IL-1α/β), are pain mediators and play a important role in the the pathogenesis of OA (6, 7). The unactivated IL-1α is stored in the cell or on the membrane. Upon cell damageand IL-1α would be activated and released, and then induce IL-1β activation and promote the production of other important cytokines important for the pathogenesis of OA (8, 9). IL-1α and IL-1β both bind to the IL-1 receptor 1 (IL-1R1), causing to joint pain, inflammation, cartilage destruction and bone resorption (10–13). In addition, the researchers also found that the concentration of IL-1 in the serum and joint fluid of patients with osteoarthritis would be elevated (14, 15). Subsequently, numerous IL-1R antagonists and IL-1R1 antibodies have been developed. However, their clinical trials in patients with OA did not report the desired results (16, 17). Lutikizumab is a new anti–IL-1α/β dual variable domain immunoglobulin that can simultaneously binds and inhibits IL-1α and IL-1β without interfering with other IL-1 family members such as IL-1Ra (18). Multiple animal experiments and clinical trials already have showed the potential of lutikizumab in treatment of OA (19–21).

To comprehensively assessing the clinical efficacy, including pain reduction and physical function improvement, and the safety of lutikizumab for treatment of OA, we designed and conducted a bayesian network meta-analysis. 10 drugs were included into our network meta-analysis. Based on these drugs' activity mechanism, we divided them into 5 groups: anti-Interleukin-1α/β dual variable domain immunoglobulins (Lutikizumab), selective cox-2 inhibitors (celecoxib, etoricoxib), duloxetine, opioid (tramadol) and traditional NSAIDs (Iburofen, naproxen, diclofenac, paracetamol/acetaminophen).

Method

Literature search

We conducted a systematic search of the PubMed, CKNI, EMBASE and Web of Science databases, from January 2000 to January 2020, with the search terms consisted of ((‘Lutikizumab’ OR ‘anti-Interleukin-1α/β dual variable domain immunoglobulin’ OR ‘anti-Interleukin-1α/β’) OR (‘selective cox-2 inhibitor’ OR ‘cox-2 inhibitor’ OR ‘etoricoxib’ OR ‘celecoxib’) OR (‘NSAIDs’ OR ‘non-steroidal anti-inflammatory drugs’ OR ‘acetaminophen’ OR ‘diclofenac’ OR ‘naproxen’ OR ‘paracetamol’ OR ‘ibuprofen’) OR (‘duloxetine’) OR (‘opioids’ OR ‘Tramadol’) AND (‘osteoarthritis’ OR ‘degenerative joint disease’ OR ‘OA’)) .

Reference lists of relevant systematic reviews and meta-analyses were also reviewed to identify additionally eligible studies. Only randomized clinical trials (RCTs) were included, but no restriction was placed on the language of publication.

Eligibility criteria

The inclusion criteria were as follows: (1) Only randomized clinical trials (RCTs); (2) Studies comparing the target drugs with each other or placebo in participants with OA at any joint. The exclusion criteria were as follows: (1) Dose-escalation studies of only one drug; (2) Studies on postoperative patients with OA; (3) Reviews, systematic reviews and meta-analyses, case report, conference abstractions, letters, pharmacokinetical or pharmacodynamical studies, and animal experimental studies.

Quality assessment

Two author conducted the methodological quality and bias assessment of included studies with the Cochrane risk of the bias assessment tool strictly. The following indexes were evaluated and ranked as low risk of bias, unclear risk of bias, or high risk of bias: Sequence generation, allocation concealment, blinding, incomplete outcome data, selection outcome reporting and other sources of bias (22). All disputes were resolved through discussion.

Data extraction

Author, publication year, number of patients, mean age, gender ratio (male/female), diseased joint, funded or not, intervention methods, follow-up period, and outcome data were extracted from included studies. We would give priority to select the data from the intention-to-treat analysis to reduce the withdrawal bias if available.

Outcome measures

The primary efficacy endpoint was pain relief, and the seconday efficacy outcome was function improvement. Considering the differences between the baseline value of each included study, which may lower the reliability of the results and conclusions, the change-from-baseline score at the last follow-up (mean ± SD) was used to evaluate the efficacy to minimize the biases caused by heterogeneity of baseline values. No restriction was placed on the types of questionnaire used in pain evaluation. The function subscales of Western Ontario and McMaster Universities Arthritis Index (WOMAC) were used to evaluated the function improvements preferentially. Any other functional measurement scales, such as lequesne index, would be used if no WOMAC function score was reported. 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 (23). Standardized mean difference (SMD) was used because results from different scales were included into the same network.

The safty outcomes included the withdrawal due to adverse effects (AEs), serious AEs and any drug-related AEs. Serious AEs included any AEs that resulted in death, was life-threatening, needed for hospitalization or prolonged the existing hospitalization, caused disability/incapacity, or caused anomaly/birth defect. The odds ratio [OR] with 95% confidence intervals (CI) was used to measure the safety of target drugs versus placebo or against each other.

Statistical analysis

Conventional direct meta-analyses comparing the efficacy and safety of treatments with placebo were conducted in Stata/MP (version 14.0, Stata Corp, College Station, Texas, USA). The heterogeneity across studies was tested by the Q and I2 statistic, in which $P<0.05$ or I^2 >50% implies significantly heterogeneity. If significant heterogeneity across studies was found, a random-effects model would be used. Otherwise, a fixed-effects model would be preferred.

Bayesian network meta-analyses were conducted in Aggregate Data Drug Information System (ADDIS, version 1.16.8). This method can augment the number of studies within each comparison and narrow the CIs' width, and then increase the reliability of result and conclusion (24-27). Non-informative uniform and normal prior distributions was used in this study, then 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 (28, 29). The thinning interval was set at 20 and the burn-ins at 1000 for each chain. Convergence of iterations was assessed using the Gelman-Rubin-Brooks statistic. Consistency of the network meta-analysis was reconfirmed via global inconsistency tests and node-split tests in Stata/MP (version 14.0). SMDs and ORs with 95% CI would be generated from the posterior distribution medians. Significant differences were considered between treatments being compared when the corresponding 95% CI did not contain 0 for the SMD or 1 for OR. Surface under the cumulative ranking (SUCRA) and the cluster-ranking plots was used to rank the efficacy and safety of different treatments.

The following subgroup analyses would be performed if available: according to the drug delivery route (topical, oral or injective) and according to the diseased jonit (hip, knee, hand or ankle).

Results

Study selection

This network meat-analysis was conducted stricktly with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (30).

24 eligible studies, including 26 trials, were finally identified (31-54). The details of the selection process is shown in Supplementary appendix Figure 1. Six treatment arms (anti-Interleukin-1α/β dual variable domain immunoglobulins (ALI), selective cox-2 inhibitors (SCI), NSADIs (NSA), duloxetine (DUL), opioids (OPI) and placebo (PLA)) were included into the network (Figure 1).

Study characteristics

11858 patients were assessed in this study. Most of included 26 trials studied on knee or hip OA, only two trials with 541 patients studied on hand OA.

Across the trials, the mean age of the patients was 62.35 years (ranged from 58.15 to 60.00 years), the proportion of male patients was 30.22% (ranged from 15.31% to 54.03%), and the median follow-up was

84 days (IQR 42–89.25 days). The number of patients enrolled for each treatment were 326 (ALI), 2518 (SCI), 3985 (NSA), 621 (DUL), 1405 (OPI) and 3033 (Placebo) respectively.

The details of baseline characteristics are presented in Supplementary appendix Table 1. The methodological quality and bias-risk evalutions of all included studies are presented in Supplementary appendix Table 2. Based on this results, the main contributing factors to risks of bias were performance bias, selection bias, and attrition bias.

Primary efficacy endpoint

Conventional direct meta-analysis

22 trials comparing 5 drugs with placebo were analysized. The random-effects model was used because of the heterogeneity of the included studies and interventions.

No significant difference was found in the comparison of placebo, with ALI (SMD 1.118, 95% CI [-0.374 to 2.610]) and OPI (SMD 1.914, 95% CI [-2.833 to 6.660]). The efficacies of other treatments were all stronger to placebo for pain relief. DUL had the largest efficacy for pain relief (SMD 4.764, 95% CI [3.895 to 5.632]). The details of the direct meta-analyses for all treatments compared with placebo are presented in Table 1.

Network meta-analysis

26 trials were analyzed in pain-relief network. No significant inconsistency was reported in global inconsistency tests and node-split tests, and then the consistency model was used.

DUL was the most efficacious treatment for pain relief (SMD compared with placebo 4.76, 95% CI [2.35 to 7.17]), while both ADL (SMD 1.11, 95% CI [-2.29 to 4.52]) and OPI (SMD 1.65, 95% CI [-1.53 to 4.83]) showed no benifit compared with placebo (Figure 2 and Table 2). According to the SUCRA value, DUL had the largest effect for pain relief (SUCRA=88.7%), followed by SCI (SUCRA=88.4%), and lastly ALI (SUCRA=28.6%). The detailed results of the SURCA rank are presented in Supplementary appendix Table 3.

Secondary efficacy endpoint

Conventional direct meta-analysis

Except for ALI (SMD 0.99, 95% CI [-2.27 to 2.417]) and OPI (SMD 1.700, 95% CI [-2.920 to 6.320]), all of other treatments were superior to placebo. SCI had the highest efficacy for physical function improvement (SMD 4.498, 95% CI [2.402 to 6.594]). The details of the direct meta-analyses for all treatments compared with placebo are presented in Table 1.

Network meta-analysis

A total of 26 trials were included into the function-improvement network. No significant inconsistency was found, the consistency model was more statistically suitable than the inconsistency model.

Similar to the results of direct meta-analysis, non significant difference was found in the comparision of placebo with ALI (SMD 0.992, 95% CI [-0.433 to 4.25]) and OPI (SMD 1.12, 95% CI [-1.92 to 4.17]), and SCI was the most efficacious treatment for physical function improvement (SMD 3.94, 95% CI [2.48 to 5.40]) (Figure 2 and Table 2). The result of most SURCA ranking showed that the most efficacious treatment was SCI (SUCRA=88.4%), and the least effective one was ALI (SUCRA=29.6%) (Supplementary appendix Table 3).

Safety endpoint

Conventional direct meta-analysis

20 trials involving all 5 therapies were analysized in the conventional direct meta-analyses. There was no significant heterogeneity reported, and fixed-effects model was used. DUL, NSA and OPI had greater rates for all of safety endpoints compared with placebo, while ALI and SCI did not show a a significantly higher risk for any safety endpoint. The details of the pairwise meta-analysis for all drugs compared with placebo are shown in Table 1.

Network meta-analysis

24 trials involving all 5 treatments were analyzed in the safety network. Node-split tests and global inconsistency tests were performed, and no inconsistency was reported. The consistency model was preferred rather than the inconsistency model.

All treatments had neither more withdrawals due to AE, nor higher incidence of serious AEs, nor any drug-related AEs. Based on the results of network comparision, SCI has the lowest rate of withdrawal due to AEs (SURCA 92.6%, OR -0.11, 95% CI [-0.40 to 0.17]), the lowest rate of serious AEs (SURCA 80.2%, OR -0.01, 95% CI [-0.70 to 0.68]) and the lowest rate of drug-related AEs (SURCA 75.5%, OR 0.07, 95% CI [-0.10 to 0.24]). The cluster rank plots showed that SCI was the optimum treatment from the perspective of safety and efficacy (The results of cluster-rank plots can be seen in Supplementary appendix Figure 2). The relative safety between different treatments was presented in Table 3. The SURCA and relative safety compare to placebo are presented in Supplementary appendix Table 4.

Subgroup analysis

Two subgroup analyses were conducted.

The first subgroup analysis was conducted exploited the impacts of different drug delivery route. Three of the 26 trials used topical drug delivery methods. After excluding these studies, no substantial change was revealed samely. DUL had the largest efficacy for pain relief (SMD 4.76, 95% CI [2.33 to 7.19]), and SCI for

function improvement (SMD 4.19, 95% CI [2.70 to 5.68]). No tratment showed a higher risk of any safety endpoint (Supplementary appendix Table 5).

In the second one, there were only two trials studied on hand joint while others all studied on knee or hip joints. After excluding these studies, no substantial change was reported. Simlarily, DUL had the highest effect for pain relief (SMD 4.76, 95% CI [2.32 to 7.20]), and SCI for function improvement (SMD 4.07, 95% CI [2.59 to 5.55]). No tratment showed a higher risk of any safety endpoint (Supplementary appendix Table 5).

Discussion

This is the first network meta-analysis comparing the efficacy and safety of lutikizumab, the new anti–Interleukin-1α/β dual variable domain immunoglobulin, for treating OA with drugs recommended by guidelines (2). We included all available evidence from RCTs directly or indirectly comparing lutikizumab with traditional treatments for OA and used the bayesian method to increase the numer of the comparision in the study, which can enhance the power of this study. As mentioned above, considering the difference in the baseline values from different included study populations and its influence to the results, we chose the change-from-baseline score as the outcome measures, and only included the literature that reported the results of change-from-baseline score. Our main findings are: (1) ALI (lutikizumab) was not associated with pain relief or function improvement of OA compared with placebo; (2) DUL, SCI and NSA therapies all can improve every symptoms of OA effectively, and have an signifcant advantage over OPI and ALI; (3) SCI, ALI, DUL, NSA and OPI are of favorable tolerance for patients in long-term treatment of OA compared with placebo. These results indicated that lutikizumab is not suitable for the treatment of OA because it brings no improvement in joint pain and dysfunction, while selective cox-2 inhibitiors (such as celecoxib and etoricoxib) are the ideal choice for the treatment of OA from the perspective of safety and efficacy. Combining with the results from other chinical trials (55, 56), the inhibition of IL-α/β does not seem to be a new way to treat osteoarthritis in the future.

There are still several limitations in this study. Considering of the unmanageable confounding factors in non-RCTs and their unpredictable influences on the result of network meta-analysis, only RCTs were included, While non-RCTs especially observational studies can examine the long-term effectiveness and safety of treatment for OA. Besides that, to enhance the the credibility of this meta-analysis, only high-quality studies were included. These may be contributed to the small number of included studies. Consequentially publication bias can be a significant problem for this study, especially the funnel plots showed a dubious asymmetry. We tried to adjust the publication bias by trimming and filling method. However, a previous study suggested that the result of trimming and filling method should be interpreted as a sensitivity analysis rather than a corrected estimate of publication bias (57). So the results of this study should be interpreted cautiously, particular for part of ALI in which the number of included study is smaller compared with other treatments. Although we have conducted two subgroup analyses to reduce the impact of potential confounding factors, there are still many other factors that could affect the reliability of the results, such as the differences of comorbidities, duration of osteoarthritis and grade of

osteoarthritis in study population. For a instance, comorbidities usually cause to worse symptom management and consequentially affect the results of analgesic effectiveness assessment. Paradoxically, researches on analgesics often excludes people with clinically significant comorbidities and do not systematically describe the distribution of comorbidities in the study population. Most of included studies, coincidentally, failed to report accurate grade or duration of osteoarthritis. We were unable to adjust for these factors because of the insufficiency of related data, and thus, those results should be interpreted with caution. More high-quality trials are needed.

Conclusion

24 studies, involving 26 trials assessing 11858 patients were included in this network meta-analysis. The results show that lutikizumab, the new anti–Interleukin-1α/β dual variable domain immunoglobulin, did not improve pain or function in the comparison with placebo. Selective cox-2 inhibitors remain the most effective and safest treatment for osteoarthritis. More high-quality trials are needed to reconfirm the findings of this study.

Declarations

Author contributions: Wanchun Wang and Ren Wu conceived the study, participated in its design and coordination, and critically revised the manuscript. Ziqin Cao, Xuantao Hu and Yihan Li had full access to all of the data collection, analysis and interpretation. Ziqin Cao drafted the manuscript. Jian Zhou and Jingjing Sun were study investigators and contributed to the process of data collection. Tong Wu, Dilihumaer Ailiand Zeling Long contributed to the process of study selection. All authors read and approved the final manuscript.

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

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Characteristics of the included comparisons and the results of direct pair-wise meta-analysis(No. of pts, number of patients included; No. of trials, number of trials included into direct pair-wise meta-analysis; SMD, standardised mean difference; OR, odds ratio)

Comparison	No. of trials	No. of pts	Target joint	SMD (95%CI) for pain relief	SMD (95%CI) for function improvement	OR (95%CI) for withdrawal due to AEs	OR (95%CI) for serious AEs	OR (95%CI) for any drug-related AEs
ALI vs PLA	2	478	Hand, Hip and Knee	1.118 (-0.374 to 2.610)	0.992 (-0.433 to 2.417)	1.408 (0.647 to 3.061)	0.595 (0.211 to 1.681)	1.014 (0.732 to 1.405)
SCI vs PLA	7	4402	Hip and Knee	4.594 (2.381 to 6.807)	4.498 (2.402 to 6.594)	0.899 (0.631 to 1.282)	0.947 (0.329 to 2.727)	1.062 (0.890 to 1.267)
DUL vs PLA	2	1247	Hip and Knee	4.764 (3.895 to 5.632)	3.455 (2.470 to 4.440)	2.766 (1.721 to 4.445)	1.018 (0.309 to 3.352)	1.337 (1.098 to 1.627)
NSA vs PLA	14	6305	Hand, Hip and Knee	2.688 (1.741 to 3.635)	2.849 (1.819 to 3.878)	1.473 (1.119 to 1.940)	1.758 (0.987 to 3.133)	1.332 (1.129 to 1.572)
OPI vs PLA	2	2012	Hip and Knee	1.914 (-2.833 to 6.660)	1.700 (-2.920 to 6.320)	2.419 (1.600 to 3.656)	1.012 (0.063 to 16.241)	1.281 (1.028 to 1.596)

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).

ALI	2.95 (-0.62 to 6.53)	2.46 (-1.53 to 6.45)	2.16 (-1.31 to 5.64)	0.14 (-4.32 to 4.60)	-0.99 (-4.25 to 2.27)
-3.11 (-6.85 to 0.62)	**SCI**	-0.49 (-3.22 to 2.24)	-0.79 (-2.18 to 0.59)	-2.82 (-6.01 to 0.37)	-3.94 (-5.40 to -2.48)
-3.65 (-7.82 to 0.53)	-0.53 (-3.39 to 2.33)	**DLU**	-0.30 (-2.91 to 2.30)	-2.33 (-6.14 to 1.49)	-3.45 (-5.76 to -1.15)
-1.77 (-5.40 to 1.85)	1.34 (-0.07 to 2.76)	1.87 (-0.84 to 4.59)	**NSA**	-2.02 (-5.23 to 1.18)	-3.15 (-4.36 to -1.94)
-0.54 (-5.20 to 4.13)	2.58 (-0.76 to 5.91)	3.11 (-0.89 to 7.10)	1.23 (-2.10 to 4.57)	**OPI**	-1.12 (-4.17 to 1.92)
1.11 (-2.29 to 4.52)	4.23 (2.70 to 5.76)	4.76 (2.35 to 7.17)	2.89 (1.65 to 4.13)	1.65 (-1.53 to 4.83)	**PLA**

Table 3. Detailed results of network meta-analysis for safety endpoints (Data are odds ratio, from the top left to the bottom right, higher comparator vs lower comparator, and their related 95%CI).

Withdrawal Due to AEs

ALI	-0.47 (-1.31 to 0.37)	0.72 (-0.20 to 1.65)	0.02 (-0.81 to 0.85)	0.59 (-0.28 to 1.47)	-0.36 (-1.15 to 0.43)
0.47 (-0.37 to 1.31)	SCI	1.19 (0.63 to 1.75)	0.49 (0.28 to 0.70)	1.06 (0.65 to 1.48)	0.11 (-0.17 to 0.40)
-0.72 (-1.65 to 0.20)	-1.19 (-1.75 to -0.63)	Dul	-0.70 (-1.25 to -0.15)	-0.13 (-0.74 to 0.48)	-1.08 (-1.56 to -0.60)
-0.02 (-0.85 to 0.81)	-0.49 (-0.70 to -0.28)	0.70 (0.15 to 1.25)	NSA	0.57 (0.15 to 0.99)	-0.38 (-0.64 to -0.12)
-0.59 (-1.47 to 0.28)	-1.06 (-1.48 to -0.65)	0.13 (-0.48 to 0.74)	-0.57 (-0.99 to -0.15)	OPI	-0.95 (-1.33 to -0.57)
0.36 (-0.43 to 1.15)	-0.11 (-0.40 to 0.17)	1.08 (0.60 to 1.56)	0.38 (0.12 to 0.64)	0.95 (0.57 to 1.33)	Placebo

Serious AEs

ALI	0.54 (-0.72 to 1.80)	0.58 (-1.03 to 2.19)	1.03 (-0.18 to 2.24)	0.56 (-2.22 to 3.34)	0.55 (-0.50 to 1.60)
-0.54 (-1.80 to 0.72)	SCI	0.04 (-1.36 to 1.44)	0.49 (0.10 to 0.88)	0.02 (-2.59 to 2.64)	0.01 (-0.68 to 0.70)
-0.58 (-2.19 to 1.03)	-0.04 (-1.44 to 1.36)	Dul	0.45 (-0.91 to 1.81)	-0.02 (-2.87 to 2.84)	-0.03 (-1.25 to 1.19)
-1.03 (-2.24 to 0.18)	-0.49 (-0.88 to -0.10)	-0.45 (-1.81 to 0.91)	NSA	-0.47 (-3.08 to 2.14)	-0.48 (-1.08 to 0.12)
-0.56 (-3.34 to 2.22)	-0.02 (-2.64 to 2.59)	0.02 (-2.84 to 2.87)	0.47 (-2.14 to 3.08)	OPI	-0.01 (-2.59 to 2.57)
-0.55 (-1.60 to 0.50)	-0.01 (-0.70 to 0.68)	0.03 (-1.19 to 1.25)	0.48 (-0.12 to 1.08)	0.01 (-2.57 to 2.59)	PLA

Any drug-related AEs

ALI	-0.08 (-0.88 to 0.72)	0.44 (-0.38 to 1.25)	0.20 (-0.60 to 1.00)	0.59 (-0.24 to 1.42)	-0.15 (-0.93 to 0.63)
0.08 (-0.72 to 0.88)	SCI	0.51 (0.23 to 0.80)	0.28 (0.15 to 0.40)	0.67 (0.36 to 0.98)	-0.07 (-0.24 to 0.10)
-0.44 (-1.25 to 0.38)	-0.51 (-0.80 to -0.23)	Dul	-0.24 (-0.52 to 0.05)	0.15 (-0.21 to 0.52)	-0.59 (-0.82 to -0.36)
-0.20 (-1.00 to 0.60)	-0.28 (-0.40 to -0.15)	0.24 (-0.05 to 0.52)	NSA	0.39 (0.08 to 0.70)	-0.35 (-0.51 to -0.19)
-0.59 (-1.42 to 0.24)	-0.67 (-0.98 to -0.36)	-0.15 (-0.52 to 0.21)	-0.39 (-0.70 to -0.08)	OPI	-0.74 (-1.03 to -0.46)
0.15 (-0.63 to 0.93)	0.07 (-0.10 to 0.24)	0.59 (0.36 to 0.82)	0.35 (0.19 to 0.51)	0.74 (0.46 to 1.03)	Placebo

Figures

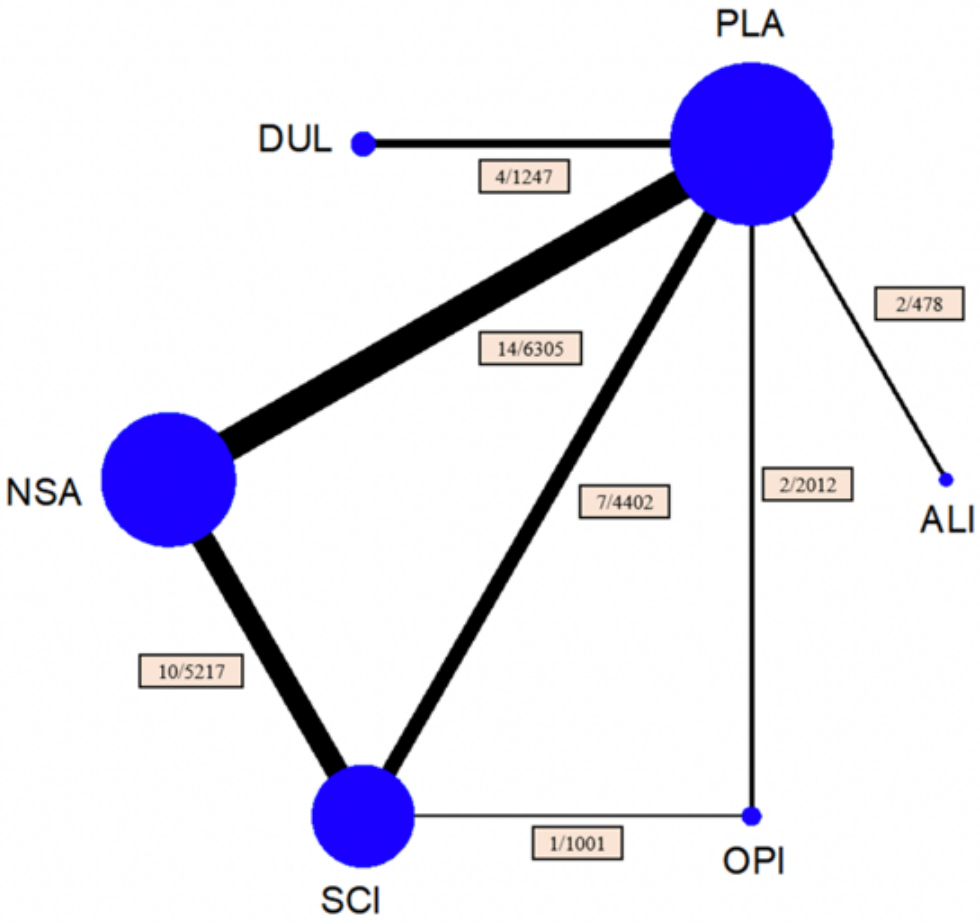

Figure 1

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.

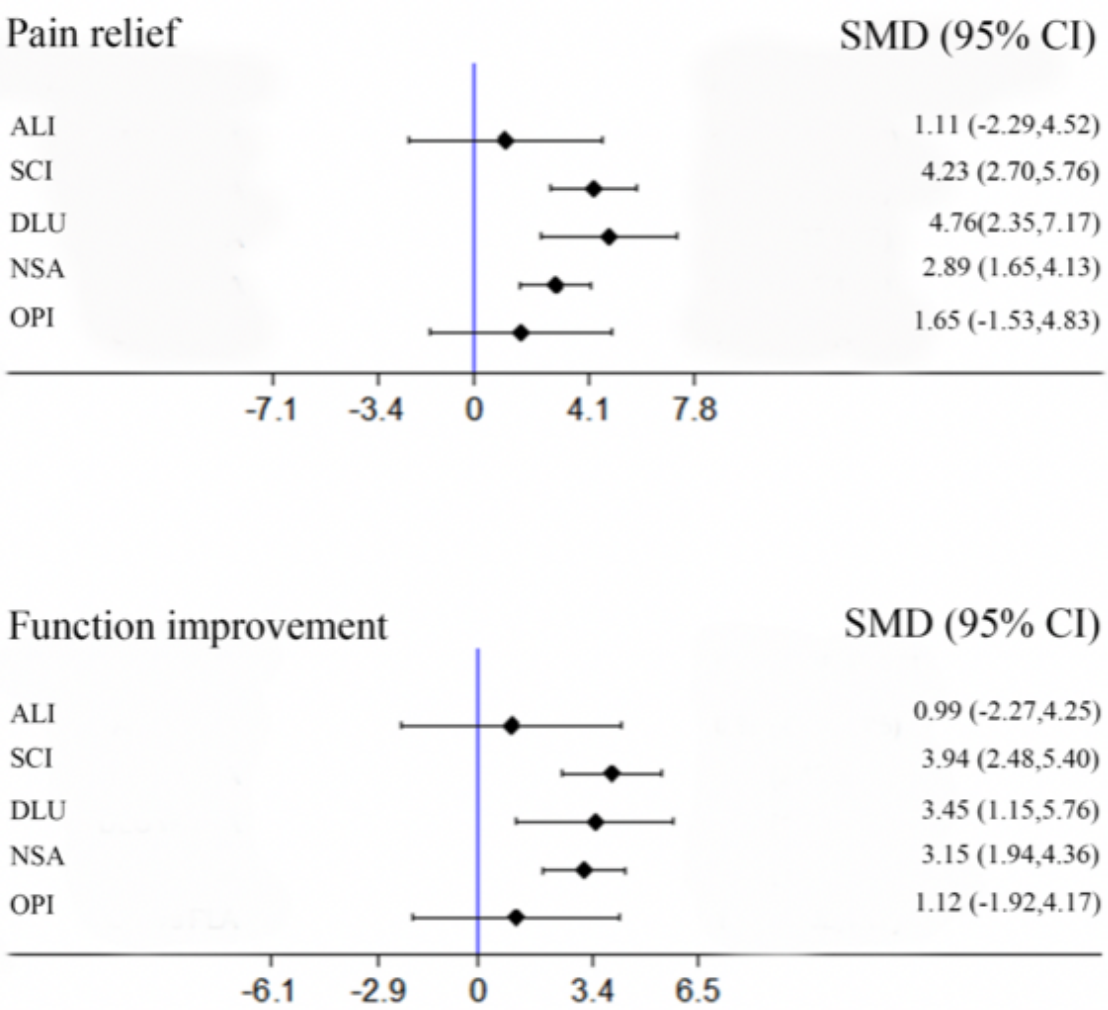

Figure 2

The forest plots. The forest plots of pain relief and function improvement for network meta-analysis. (SMD, standardised mean difference; CI, confidence interval).

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