The short-term effect and safety of duloxetine in osteoarthritis
A systematic review and meta-analysis

Shi-Hua Gao, MMed, Jian-Bin Huo, MMed, Qi-Mou Pan, MMed, Xi-Wen Li, MMed, Hai-Yun Chen, MMed*, Jun-Han Huang, MMed

Abstract
Background: Previous clinical trials indicated that duloxetine may be effective in the treatment of osteoarthritis (OA) pain. This meta-analysis is conducted to evaluate short term analgesic effect and safety of duloxetine in the treatment of OA.

Methods: Electronic databases were searched in February 2019, including PUBMED, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Web of Science. All eligible studies should be randomized controlled trials (RCTs) comparing duloxetine treatment group to placebo about OA pain relief and safety outcomes.

Results: Five RCTs with 2059 patients were involved in this systematic review and meta-analysis. Compared to placebo, duloxetine treatment showed significant better result, with higher reduction pain intensity (mean difference [MD]=−0.77, P<.00001), higher rates of both 30% and 50% reduction in pain severity (risk ratio [RR]=1.42, P<.00001; RR=1.62, P<.00001), lower mean Patient Global Improvement-Inventory (PGI-I) score (MD=−0.48, P<.00001). The results of the Western Ontario and McMaster Universities (WOMAC) score change from baseline to endpoint also favored duloxetine treatment group in all four categories, including total (MD=−5.43, P<.00001), pain (MD=−1.63, P<.001), physical function (MD=−4.22, P<.00001), and stiffness score (MD=−0.58, P<.00001). There were higher rates of treatment-emergent adverse events (TEAEs) (RR=1.32, P<.00001) and discontinuation (RR=1.88, P<.00001) in duloxetine group. However, there was no significant difference in the incidence of severe adverse events (SAEs) between these 2 groups (RR=0.84, P=.68).

Conclusion: Duloxetine was an effective and safe choice to improve pain and functional outcome in OA patients. However, further studies are still needed to find out the optimal dosage for OA and examine its long-term efficacy and safety.

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Abbreviations: BPI = Brief Pain Inventory, CI = confident interval, GRADE = Grading of Recommendations Assessment Development and Evaluation, MD = mean difference, NSAIDs = non-steroidal anti-inflammatory drugs, OA = osteoarthritis, PGI-I = Patient Global Improvement-Inventory, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, RCTs = randomized controlled trials, RR = risk ratio, SAEs = severe adverse events, SNRI = serotonin and noradrenaline-reuptake inhibitors, TEAEs = treatment-emergent adverse events, WOMAC = Western Ontario and McMaster Universities.

Keywords: duloxetine, meta-analysis, osteoarthritis, pain

1. Introduction

Osteoarthritis (OA) is one of the most common painful diseases.[1] It occurs mainly in older individual and it will gradually worsen as the cartilage in the affected joint wears down.[2] Accompanied by joint pain, stiffness, and loss of function.

A worldwide survey indicated that the prevalence of OA is estimated to be 9.6% for men and 18% for women in the over 60-year-old population.[3] Moreover, the worldwide age-standardized prevalence of OA has increased by 32.9% between 2005 and 2015.[4] OA is also highly prevalent in China. Only OA of the knee affected around 5.6% to 9.1% for men and 15% to 20.5% for women.[5,6]

OA are highly associated with low quality of life, anxiety, and depression.[7] Among the symptoms of OA, pain is the major complaint. For the management of OA, the first line therapy is self-management like physical exercises and weight control. Analgesics including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly applied for the treatment
of OA as the second and third line. However, the side effects of NAIDs are quite noticeable (like peptic ulcer, gastrointestinal bleeding, and serious cardiovascular condition). Opioids, on the other hand, have significant risk of respiratory depression, constipation, dependency. Because of long term side effect and limited efficacy of these drugs, other treatment options are required.

One of the most popular explanations for chronic pain is central pain sensitization. Studies have shown that the imbalance of serotonin and norepinephrine systems within central pain pathway plays an important role in the development of pain sensitization. Duloxetine is a selective serotonin and norepinephrine-reuptake inhibitors (SNRI) that has been used for the treatment of depression. Duloxetine is a selective SNRI that has been used for the treatment of depression. Because of the association between chronic pain conditions and dysfunction of serotonin and norepinephrine system, duloxetine are now widely used in chronic pain conditions, including osteoarthritis pain, fibromyalgia, diabetic peripheral neuropathy pain.

Several trials have shown that duloxetine is effective in the treatment of OA pain. A previous systematic review and meta-analysis of three randomized controlled trials (RCTs) evaluated the efficacy and safety of duloxetine on osteoarthritis knee pain and results favored duloxetine above placebo. However, the limited number of included studies and patients lowered the robustness of the conclusion. Recently, more high quality RCTs have been conducted. Moreover, previous review lacked assessment of the strength of the body of evidence. Therefore, an update of the review is necessary.

In this study, a thorough search was conducted to retrieve trials of OA pain. Clinical efficacy and safety of duloxetine will be examined, as well as quality of included studies. We will assess the strength of the body of evidence will use the Grading of Recommendations Assessment, development and Evaluation (GRADE) tool. This study is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.

2. Method

2.1. Ethical statement

Ethical statement was unnecessary as data of this study was extracted from previously published articles.

2.2. Search strategy

Electronic databases were searched in February 2019, including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Web of Science (science and social science citation index). We used a series of logic combinations and search terms related to the topic (“duloxetine”, “Cymbalta”, “osteoarthritis”) to perform searches in each database. Published systematic reviews of the same topic were assessed to identify the additional RCTs. Example of searching strategy for PUBMED was as follows:

(“duloxetine hydrochloride”[MeSH Terms] OR (“duloxetine”[All Fields] AND “hydrochloride”[All Fields]) OR “duloxetine hydrochloride”[All Fields] OR “duloxetine”[All Fields]) OR (“duloxetine hydrochloride”[MeSH Terms] OR “duloxetine”[All Fields] AND “hydrochloride”[All Fields]) OR “duloxetine hydrochloride”[All Fields] OR “cymbalta”[All Fields]) AND (“osteoarthritis”[MeSH Terms] OR “osteoarthritis”[All Fields])

2.3. Selection process

Two reviewers initially screened the literature by examining titles and abstracts after removing duplicates. The eligibility of the studies was assessed by reviewing the full text. Authors were consulted when uncertainty appeared such as whether different publications are from the same trial. Disagreements were resolved by discussion followed by consulting the third reviewer.

All eligible trials should meet the following inclusion criteria:

1. patients with OA;
2. studies compared duloxetine to placebo for pain relief and safety outcomes;
3. studies with randomized controlled design.

Exclusion criteria were as follows:

1. non-RCTs;
2. trials involving patients with comorbid psychiatric diseases;
3. studies without sufficient data for the evaluation of pain relief and safety outcomes.

2.4. Data collection

Two reviewers independently collected the data of interest using the EpiData Software, version 3.1 (EpiData Association, Odense, Denmark). The data items include author, year, sample size, baseline information such as age, gender, location of OA, duration of OA, Brief Pain Inventory (BPI) average score, NSAID use, the dosage and duration of interventions and co-intervention, comparisons and outcomes. Authors were contacted inquiring for unpublished data.

2.5. Risk of bias assessment

Two reviewers independently conducted the assessment using the Cochrane risk of bias tool for randomized trials. The domains of bias include random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting risk. The risk of each bias domain will be graded as low, unclear and high. Disagreements were resolved by consulting a third reviewer or through discussion.

2.6. Data synthesis

Review Manager 5.3 was used for statistical analysis. Pooled mean difference (MD) with 95% confidence interval (CI) was calculated for continuous data while relative risk (RR) with 95% CI for dichotomous data. Clinical heterogeneity will be evaluated by the reviewers with the background of clinical experience in OA. Statistical heterogeneity will be assessed with the inference of I². If I² value was more than 50%, a random model was used. Otherwise, if I² value was less than 50%, a fixed model was applied. Sensitivity analysis was performed by excluded studies with the overall high risk of the bias.

2.7. Confidence in cumulative evidence

The strength of the body of evidence will be assessed by the GRADE tool. The evidence will be graded as high, moderate, low or very low according to the justification of study design, risk of bias, inconsistency, indirectness, and imprecision. The GRADE evidence profile will be generated by the GRADE Guideline Development Tool.
3. Result

3.1. Study selection process

During initial literature search, 486 records were identified. After removal of duplicate and selection based on eligibility criteria, five RCTs were included in this systematic review and meta-analysis.[14,15,19–21] The process is depicted as the PRISMA flow diagram in Figure 1.

3.2. Study characteristic

A total of 2059 patients were involved in this study. All of the five included trials were RCTs with placebo controlled. Except one trial included one patient with osteoarthritis of hip joint in duloxetine group and two in placebo group, all of the patients suffered osteoarthritis of the knee. Patients of intervention group received 20 to 120 mg duloxetine per day and treatment duration ranged from 10 to 14 weeks. As can be seen from Table 1, Patients of these trials were at a relatively old age (ranged from 59.8 to 66.4) and the majority were females (69.5%–83.6%). The mean duration of OA diagnosis ranged from 2.7 to 9.8 years, and the mean duration of pain ranged from 6.7 to 9.8 years, indicating patients involved in this study had suffered from long-term pain.[22] Ranging from 5.0 to 6.24, the average BPI pain score across the included trials had met the recommendation of the Initiative on Method, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), that only patients assessed with pain score at least 4 out of 10 could be included in RCTs. Detailed characteristics of the included trials are described in Table 1. In addition, only Uchio[21] reported the Kellgren-Lawrence (K-L) grade of included patients. Distribution in duloxetine group was as follows: 7.9% (grade 1), 49.2% (grade 2), 39.0% (grade 3), and 4.0% (grade 4). In placebo group, the distribution of K-L grade was: 5.7% (grade 1), 47.7% (grade 2), 42.0% (grade 3), and 4.5% (grade 4). As presented in Figure 2, the study quality of these included trials was relatively high.

3.3. Effect of duloxetine on pain relief

In this study, the analgesic effect of duloxetine was evaluated by reduction in BPI average pain score as primary outcome. All of the five included studies based on an 11-point numerical rating
scales (0 as no pain and 10 as worst pain imaginable). As can be seen from Figure 3, the meta-analysis of reduction in pain intensity indicated that there was significant statistical difference between the duloxetine group and placebo group (n=1695, MD=−0.77, P<.00001). According to the recommendation of IMMPACT, a reduction of at least 2 points from baseline to endpoint can be deemed as clinically meaningful in patients suffering from painful conditions, which duloxetine group have reached (ranged from 2.23 to 2.82). The pooled result indicated that duloxetine can reduce BPI average pain, and the result was both statistically and clinically significant.

Secondary results regarding the effect of duloxetine from meta-analysis were as follows: both 30% (n=1699 RR=1.42, P<.00001) and 50% (n=537 RR=1.62, P<.00001) reduction in pain severity rates were significantly higher in duloxetine group (Figs. 4 and 5). Figure 6 showed that statistically significant difference was also detected in Patient Global Improvement-Inventory (PGI-I), which showed patients in duloxetine group had a better recovery (n=1684, MD=−0.48, P<.00001). The Western Ontario and McMaster Universities (WOMAC) score change from baseline to endpoint were assessed in four categories in this study, including the total score (n=1479, MD=−5.43, P<.00001), pain score (n=1457, MD=−1.63, P=.001), physical function score (n=1479, MD=−4.22, P<.00001), and stiffness score (n=1458, MD=−0.58, P<.00001). From the pooled result of the WOMAC scores above, the duloxetine group significantly improved in overall satisfaction, pain severity, physical function and stiffness of the infected joint (Figs. 7–10).

### 3.4. Safety of duloxetine

As shown in Figures 11 and 12, in spite of the efficacy of duloxetine, the overall incidence of treatment-emergent adverse events (TEAEs) as well as discontinuation was significantly higher in intervention group (n=1761, RR=1.32, P<.00001; n=981, RR=1.88, P<.00001). As described in Table 2, nausea,
constipation, dry mouth, diarrhea, fatigue, dizziness, somnolence, and insomnia were the most frequent adverse events in patients received duloxetine treatment. However, Figure 13 showed that no significant difference was found between these 2 groups (n=1761, RR=0.84, P=.68) for severe adverse events (SAEs). Besides, no death was recorded in all five trials.

Figure 3. Forrest plot of reduction in pain intensity.

Figure 4. Forrest plot of ≥30% reduction in pain severity.

Figure 5. Forrest plot of ≥50% reduction in pain severity.

Figure 6. Forrest plot of mean values in Patient Global Improvement-Inventory.
3.5. Confidence in cumulative evidence

The GRADE evidence profile for important outcomes are shown in Table 3. The level of evidence was moderate for WOMAC physical function score and stiffness score and high for the rest of other results, which indicated that the results from this study were relatively reliable.

4. Discussion

In this meta-analysis, results showed that duloxetine has a significant analgesic effect. The use of duloxetine decreased BPI average pain, increased the rates of 30% and 50% reduction in pain severity. As for PGI-I and WOMAC scores, results also favored duloxetine group.

Prior studies have noted that OA pain may be explained by changes in joint structure and biochemical environment around peripheral joint nociceptors, which leads to hyper excitability of the peripheral nerve and ultimately caused central nervous system sensitization. Further studies showed that the increased responsiveness of nociceptive neurons in central nervous system was associated with dysfunction of endogenous pain pathway, in which serotine and noradrenaline acted as...
By inhibiting the reuptake of serotonin and noradrenaline, duloxetine enhances the inhibitory activity of endogenous pain pathway in the descending spinal cord, which explains its direct analgesic effect rather than mood improvement. Moreover, the anti-depressant effect of duloxetine had been minimized by excluding patients with depressive disorder in this study.

In terms of safety, the results from our review show that there is no significant difference in the rate of SAEs, but higher rates of TEAEs and discontinuation are detected. Most of the TEAEs observed were nausea, constipation, dry mouth, diarrhea, fatigue, dizziness, somnolence, and insomnia. The results from this review were similar to previous studies that focused on the profile of adverse events of duloxetine. As mentioned in these studies, these common adverse events were mild to moderate in severity. Moreover, these adverse events appeared early in the treatment period and then gradually became less prevalent, and there is evidence showed that nausea, one of the most common adverse events, would alleviate when duloxetine was taken with food or initiated at a lower dose. If the characteristics of the TEAEs are understood by clinicians, they can explain to patients and increase the coherence of duloxetine treatment.

This systematic review has several limitations. First, although compared to the previous review, our study has included 2 more RCTs from China and Japan, the number of included trials is relatively small. However, quality of these trials is fairly high and the number of patients is sufficient. Also, a minimum threshold for the number of included studies has not yet been established. Second, treatment strategies and baseline characteristics of patients were not consistent among included studies.
For example, the races were different across these trials. Studies found that there may be differences in TEAEs rates between Caucasian and non-Caucasian.[29,33,34] Moreover, the dosage and duration varied among included trials, yet meta-analysis should still be conducted because these different patients were compared within individual study, not across different studies.[18,35] Third, in this review, only one study (Wang 2017)[20] included 3 patients with hip osteoarthritis. Sensitivity analysis showed that the heterogeneity of some result disappeared or decreased when this study was excluded (reduction in pain, ≥50% reduction in pain severity rate, change in WOMAC total score), but results still remain consistent. Although there is no existing evidence indicates that the pathophysiology of OA pain is different in various joints, the location of OA might interfere with the result and adds heterogeneity to some of the results. So, current results should be taken with caution. Finally, the duration in each included study was relatively short and the optimal dosage of duloxetine was still not clear. Ninety-three patients from one of the included studies (Uchio 2018) entered a phase III extension study.[21,36] Results showed that the analgesic effect was significant through 52 weeks, but 91.4% patients experienced adverse events (mostly dry mouth, constipation, nasopharyngitis, and somnolence). Therefore, more studies should be conducted to further assess the long-term efficacy and especially safety of duloxetine on the treatment of OA. Also, studies with multiple treatment arms are needed to find out the optimal dosage.

5. Conclusion

The administration of 60/120 mg duloxetine significantly reduced pain in OA patients, improves physical function and alleviate stiffness of the joints. Despite of higher rates of TEAEs and discontinuation, duloxetine did not increase the rate of SAEs. This meta-analysis suggests duloxetine might be another effective and safe medication to manage OA pain. However, further studies are still needed to find out the optimal dosage and examine its long-term efficacy and safety on OA patients.

Author contributions

Conceptualization: Shi-Hua Gao, Hai-Yun Chen.
Data curation: Shi-Hua Gao.
Formal analysis: Shi-Hua Gao, Qi-Mou Pan.
Investigation: Jian-Bin Huo.
Methodology: Jian-Bin Huo.
Resources: Xi-Wen Li.
Software: Xi-Wen Li, Jun-Han Huang.

Table 3

| GRADE evidence profile. |
|-------------------------|
|                         |
| No. of studies | No. of patients | Effect |
|----------------|-----------------|--------|
| Study design | Risk of bias | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| Reduction in pain intensity 5 | Randomized | Not serious | Not serious | Not serious | None | 842 | 853 | MD 0.77 lower 0.95 to 0.59 lower | ⊕⊕⊕⊕ High | Important |
| ≥50% reduction in pain severity (%) 5 | Randomized | Not serious | Not serious | Not serious | None | 520/844 | 571/855 | RR 1.42 | 1.30 to 1.56 | 182 more per 1,000 (from 130 more to 243 more) | ⊕⊕⊕⊕ High | Important |
| Mean Values in PQA 5 | Randomized | Not serious | Not serious | Not serious | None | 835 | 849 | MD 0.48 lower 0.59 lower to 0.37 lower | ⊕⊕⊕⊕ High | Important |
| Change from baseline to endpoint in WOMAC physical function score 4 | Randomized | Not serious | Not serious | Not serious | None | 740 | 739 | MD 4.22 lower 6.17 lower to 2.28 lower | ⊕⊕⊕ Moderate | Important |
| Change from baseline to endpoint in WOMAC stiffness score 4 | Randomized | Not serious | Not serious | Not serious | None | 726 | 732 | MD 0.58 lower 0.75 lower to 0.41 lower | ⊕⊕○ Moderate | Important |
| TEAEs 5 | Randomized | Not serious | Not serious | Not serious | None | 528/879 | 402/882 | RR 1.32 | 1.20 to 1.44 | 146 more per 1,000 (from 91 more to 201 more) | ⊕⊕⊕⊕ High | Important |
| SAEs 5 | Randomized | Not serious | Not serious | Not serious | None | 10/879 | 12/882 | RR 0.84 | 0.37 to 1.90 | 2 fewer per 1,000 (from 9 fewer to 12 more) | ⊕⊕⊕⊕ Moderate | Important |

GRADE = Grading of Recommendations Assessment, Development and Evaluation, SAEs = severe adverse events, TEAEs = treatment-emergent adverse events.

For example, the races were different across these trials. Studies found that there may be differences in TEAEs rates between Caucasian and non-Caucasian.[29,33,34] Moreover, the dosage and duration varied among included trials, yet meta-analysis should still be conducted because these different patients were compared within individual study, not across different studies.[18,35] Third, in this review, only one study (Wang 2017)[20] included 3 patients with hip osteoarthritis. Sensitivity analysis showed that the heterogeneity of some result disappeared or decreased when this study was excluded (reduction in pain, ≥50% reduction in pain severity rate, change in WOMAC total score), but results still remain consistent. Although there is no existing evidence indicates that the pathophysiology of OA pain is different in various joints, the location of OA might interfere with the result and adds heterogeneity to some of the results. So, current results should be taken with caution. Finally, the duration in each included study was relatively short and the optimal dosage of duloxetine was still not clear. Ninety-three patients from one of the included studies (Uchio 2018) entered a phase III extension study.[21,36] Results showed that the analgesic effect was significant through 52 weeks, but 91.4% patients experienced adverse events (mostly dry mouth, constipation, nasopharyngitis, and somnolence). Therefore, more studies should be conducted to further assess the long-term efficacy and especially safety of duloxetine on the treatment of OA. Also, studies with multiple treatment arms are needed to find out the optimal dosage.

5. Conclusion

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Author contributions

Conceptualization: Shi-Hua Gao, Hai-Yun Chen.
Data curation: Shi-Hua Gao.
Formal analysis: Shi-Hua Gao, Qi-Mou Pan.
Investigation: Jian-Bin Huo.
Methodology: Jian-Bin Huo.
Resources: Xi-Wen Li.
Software: Xi-Wen Li, Jun-Han Huang.
Supervision: Jun-Han Huang.
Writing – original draft: Shi-Hua Gao, Qi-Mou Pan.
Writing – review & editing: Hai-Yun Chen.

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