Systematic Review and Meta-Analysis

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The short-term effect and safety of duloxetine in osteoarthritis

A systematic review and meta-analysis

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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.

Trial registration number: CRD42019128862

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

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of OA as the second and third line. However, the side effects of NSAIDs 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.[8] 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.[9,10] Duloxetine is a selective serotonin and noradrenaline-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 neuropathic pain.[7,11,12]

Several trials have shown that duloxetine is effective in the treatment of OA pain.[13–15] 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.[16] 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.[17]

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 reviewed 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.[18] 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% confident 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 was assessed with the inference of I^2. If I^2 value was more than 50%, a random model was used. Otherwise, if I^2 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

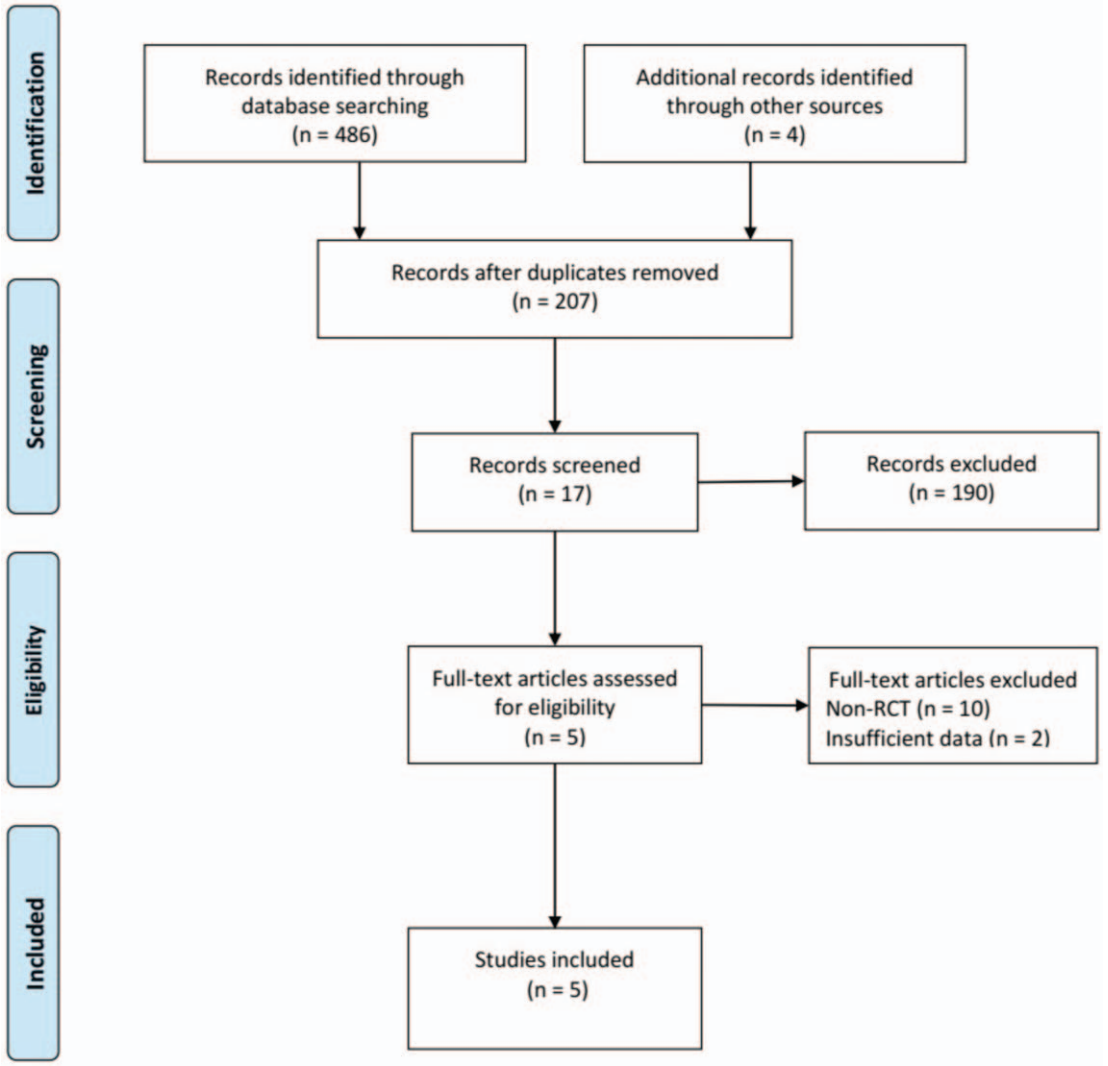

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis flow diagram.

Table 1

Baseline study characteristics.

Study	Groups	Age, years	Gender (%female)	Location of OA	Duration of OA diagnosis (years)	Mean duration of pain (years)	BPI average score	NSAID use	Dose and duration
Chappell, 2009 (USA)	Duloxetine (111)	62.1 ± 9.6	70.00%	Knee	6.9 ± 8.4	9.0 ± 8.7	6.16 ± 1.58	58 (52.3%)	30 mg/day for 1 week, 60 mg/day for 6 weeks, 60/120 mg for 6 weeks
	Placebo (120)	62.5 ± 9.3	81.00%	Knee	7.1 ± 7.2	9.3 ± 8.3	6.23 ± 1.54	59 (49.2%)	
Chappell, 2011 (USA)	Duloxetine (128)	63.2 ± 8.8	69.50%	Knee	6.2 ± 5.9	8.1 ± 7.6	6.07 ± 1.39	47 (36.7%)	30 mg/day for 1 week, 60 mg/day for 6 weeks, 60/120 mg for 6 weeks
	Placebo (128)	61.9 ± 9.2	83.60%	Knee	5.6 ± 6.2	6.7 ± 6.6	6.14 ± 1.27	53 (41.4%)	
Frakes, 2011 (USA)	Duloxetine (264)	63.2 ± 8.8	69.50%	Knee	9.8 ± 8.9	9.8 ± 8.9	6.09 ± 1.58	264 (100%)	30 mg/day for 1 week, 60 mg/day for 2 weeks, 60/120 mg for 7 weeks
	Placebo (260)	61.9 ± 9.2	83.60%	Knee	9.2 ± 8.9	9.2 ± 8.9	6.24 ± 1.51	260 (100%)	
Wang, 2017 (China)	Duloxetine (205)	61.2 ± 8.2	78.00%	Knee (204)Hip (1)	2.9 ± 4.4	8.2 ± 7.8	5.49 ± 1.27		30 mg/day for 1 week, 60 mg/day for 13 weeks
	Placebo (202)	59.8 ± 8.4	74.80%	Knee (200)Hip (2)	2.7 ± 4.2	7.8 ± 7.1	5.41 ± 1.21		
Uchio, 2018 (Japan)	Duloxetine (177)	65.5 ± 8.0	80.20%	Knee	4.0 ± 4.2		5.0 ± 1.0	98 (55.4%)	20, 40 mg/day for 1 week each, 60 mg/day for 12 weeks
	Placebo (176)	66.4 ± 8.4	75.00%	Knee	4.5 ± 4.3		5.1 ± 1.0	100 (56.8%)	

BPI = Brief Pain Inventory, OA = osteoarthritis, NSAIDs = non-steroidal anti-inflammatory drugs.

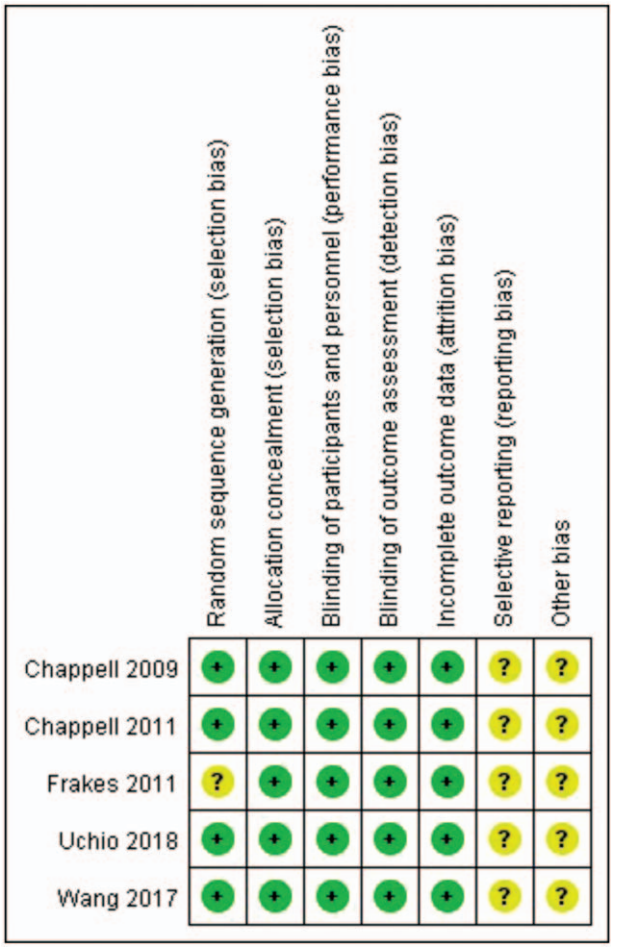

Figure 2. Risk of bias summary of the included studies.

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 patient suffered 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,

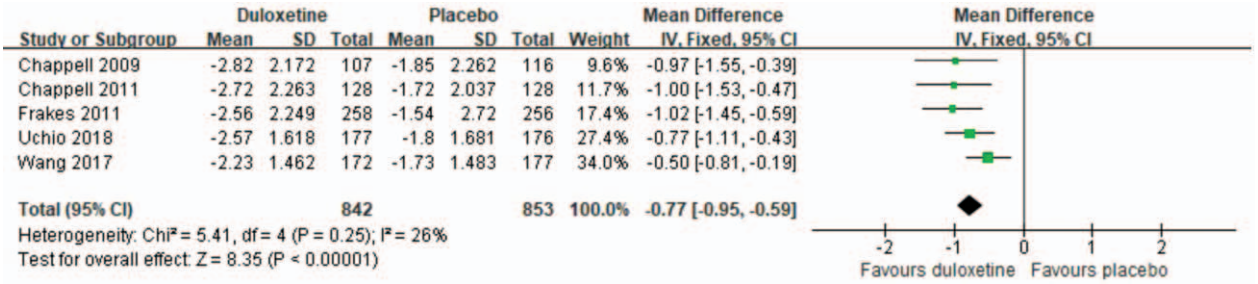

Figure 3. Forrest plot of reduction in pain intensity.

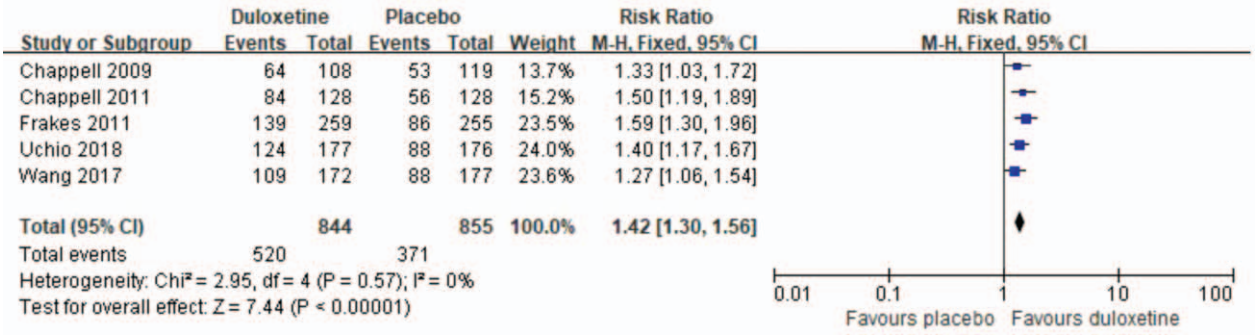

Figure 4. Forrest plot of ≥30% reduction in pain severity.

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.

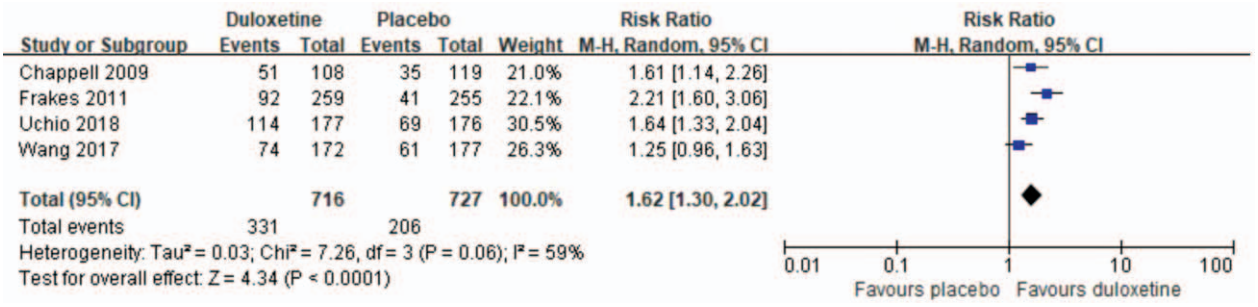

Figure 5. Forrest plot of ≥50% reduction in pain severity.

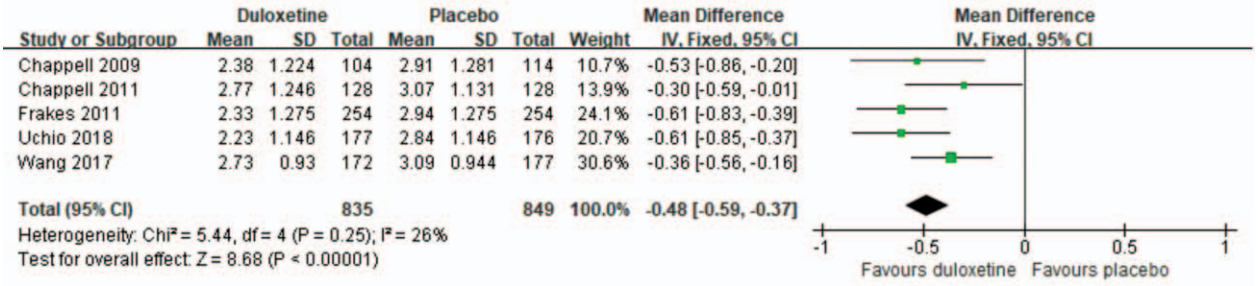

Figure 6. Forrest plot of mean values in Patient Global Improvement-Inventory.

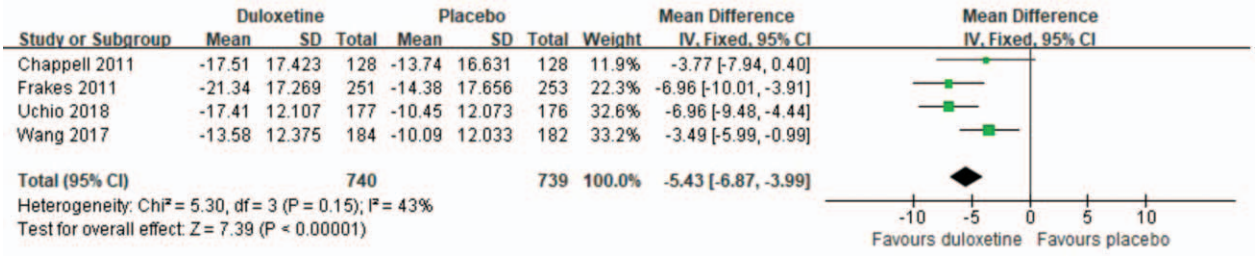

Figure 7. Forrest plot of change from baseline to endpoint in Western Ontario and McMaster Universities score total score.

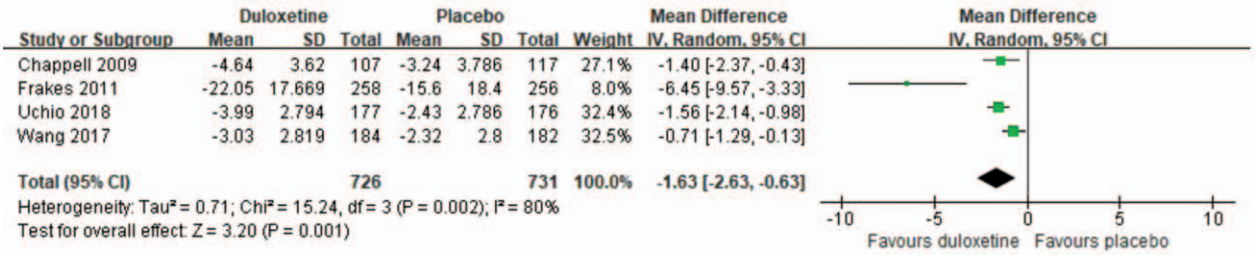

Figure 8. Forrest plot of change from baseline to endpoint in Western Ontario and McMaster Universities score pain score.

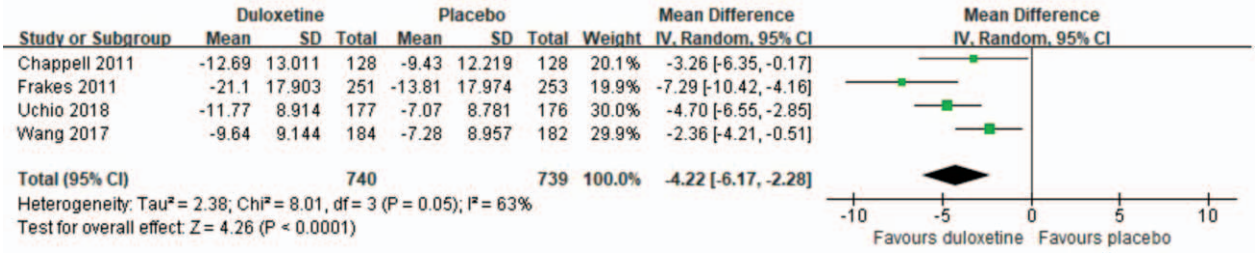

Figure 9. Forrest plot of change from baseline to endpoint in Western Ontario and McMaster Universities score physical function score.

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,[10] which leads to hyper excitability of the peripheral nerve and ultimately caused central nervous system sensitization.[2,3–2,5] 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

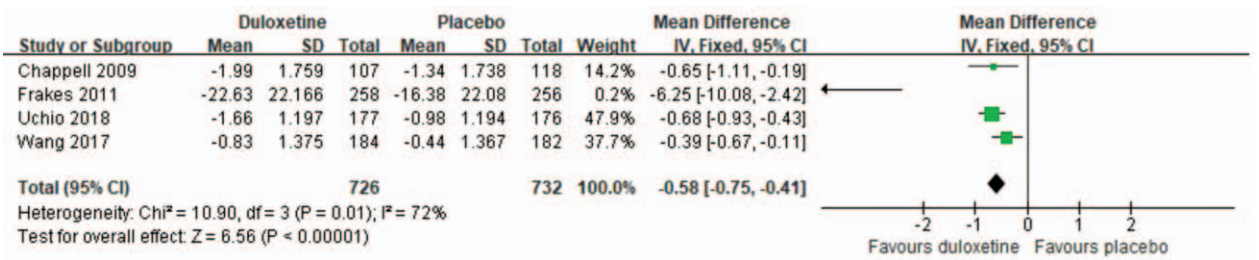

Figure 10. Forrest plot of change from baseline to endpoint in Western Ontario and McMaster Universities score stiffness score.

Table 2

Adverse events.

Study	Groups	TEAEs (events/n)	SAEs (events/n)	Discontinuation (events/n)	TEAEs occurred most frequently in each study				
Chappell, 2009 (USA)	Duloxetine (111)	55/111	1/111	70.00%	\	\	\	\	\
	Placebo (120)	49/120	2120	81.00%					
Chappell, 2011 (USA)	Duloxetine (128)	65/128	3/128	69.50%	Nausea	Constipation	Hyperhidrois	\	\
	Placebo (128)	42/128	2/128	83.60%					
Frakes, 2011 (USA)	Duloxetine (264)	167/264	5/264	69.50%	Nausea	Dry mouth	Constipation	Dizziness	Fatigue
	Placebo (260)	130/260	4/260	83.60%					
Wang, 2017 (China)	Duloxetine (205)	121/199	0/199	78.00%	Nausea	Dry mouth	Constipation	Dizziness	Somnolence
	Placebo (202)	83/198	3/198	74.80%					
Uchio, 2018 (Japan)	Duloxetine (177)	120/177	1/177	80.20%	Nausea	Dry mouth	Constipation	Nasopharyngitis	Somnolence
	Placebo (176)	98/176	1/176	75.00%					

SAEs = severe adverse events, TEAEs = treatment-emergent adverse events.

important modulators.[26] By inhibiting the reuptake of serotine 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.[27,28] 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.[29–31]

This systematic review has several limitations. First, although compared to the previous review,[16] 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.[32] Second, treatment strategies and baseline characteristics of patients were not consistent among included studies.

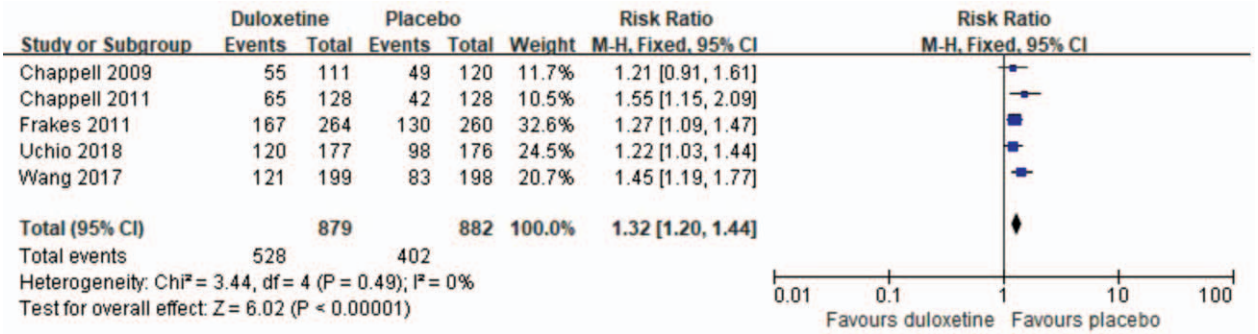

Figure 11. Forrest plot of incidence of treatment-emergent adverse events.

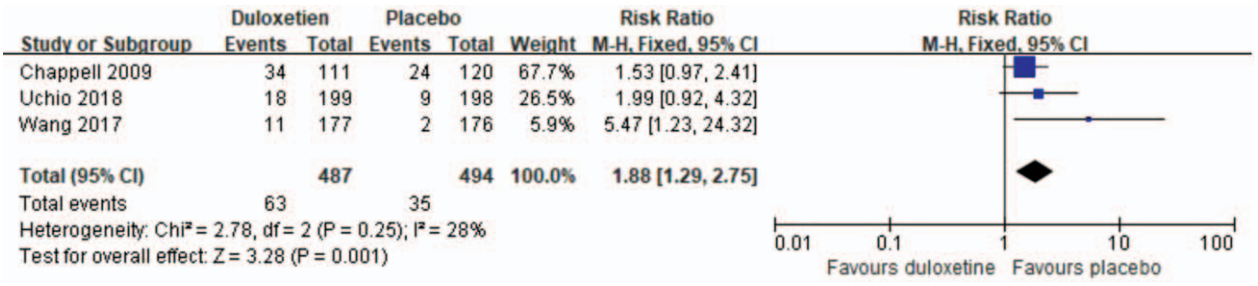

Figure 12. Forrest plot of incidence of discontinuation.

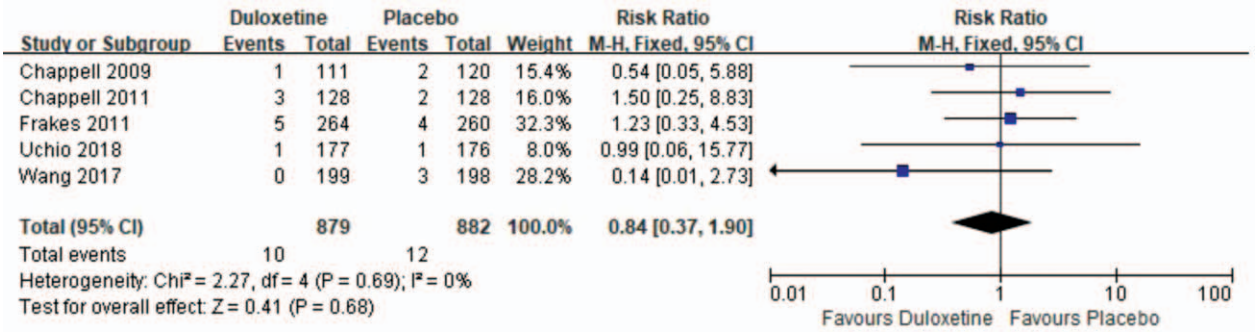

Figure 13. Forrest plot of incidence of severe adverse events.

Table 3

GRADE evidence profile.

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Reduction in pain intensity												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	842	853	–	MD **0.77 lower** (0.95 lower to 0.59 lower)	⊕⊕⊕⊕ High	Important
≥30% reduction in pain severity (%)												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	520/844 (61.6%)	371/855 (43.4%)	**RR 1.42** (1.30 to 1.56)	**182 more per 1,000** (from 130 more to 243 more)	⊕⊕⊕⊕ High	Important
Mean Values in PGI-I												
5	Randomized trials	Not serious	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 trials	Not serious	Serious [a]	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 trials	Not serious	Serious [b]	Not serious	Not serious	None	726	732	–	MD **0.58 lower** (0.75 lower to 0.41 lower)	⊕⊕⊕◯ Moderate	Important
TEAEs												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	528/879 (60.1%)	402/882 (45.6%)	**RR 1.32** (1.20 to 1.44)	**146 more per 1,000** (from 91 more to 201 more)	⊕⊕⊕⊕ High	Important
SAEs												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	10/879 (1.1%)	12/882 (1.4%)	**RR 0.84** (0.37 to 1.90)	**2 fewer per 1,000** (from 9 fewer to 12 more)	⊕⊕⊕⊕ High	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

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.

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References

[1] Boring MA, Hootman JM, Liu Y, et al. Prevalence of arthritis and arthritis-attributable activity limitation by urban-rural county classification - United States, 2015. MMWR Morb Mortal Wkly Rep 2017 May 26;66:527–32.

[2] Skevington SM. Investigating the relationship between pain and discomfort and quality of life, using the WHOQOL. Pain 1998 Jun; 76:395–406.

[3] McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014 Mar;22:363–88.

[4] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators-Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 8;388:1545–602.

[5] Ohtori S, Orita S, Yamashita M, et al. Existence of a neuropathic pain component in patients with osteoarthritis of the knee. Yonsei Med J 2012 Jul 1;53:801–5.

[6] Steinmeyer J, Bock F, Stove J, et al. Pharmacological treatment of knee osteoarthritis: special considerations of the new German guideline. Orthop Rev (Pavia) 2018 Dec 6;10:7782.

[7] Bair MJ, Wu J, Damush TM, et al. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med 2008 Oct;70:890–7.

[8] Fitzcharles MA, Lussier D, Shir Y. Management of chronic arthritis pain in the elderly. Drugs Aging 2010 Jun 1;27:471–90.

[9] Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. Annu Rev Neurosci 1991;14:219–45.

[10] Havelin J, Imbert I, Cormier J, et al. Central sensitization and neuropathic features of ongoing pain in a rat model of advanced osteoarthritis. J Pain 2016 Mar;17:374–82.

[11] Gao Y, Guo X, Han P, et al. Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo. Int J Clin Pract 2015 Sep;69:957–66.

[12] Luciano JV, D'Amico F, Feliu-Soler A, et al. Cost-utility of group acceptance and commitment therapy for fibromyalgia versus recommended drugs: an economic analysis alongside a 6-month randomized controlled trial conducted in Spain (EFFIGACT study). J Pain 2017 Jul;18:868–80.

[13] Chappell AS, Desaiah D, Liu-Seifert H, et al. Duloxetine 60 to 120 mg once daily versus placebo in the treatment of patients with osteoarthritis knee pain. Pain Med 2009;10:250.

[14] Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011 Jan-Feb;11:33–41.

[15] Frakes EP, Risser RC, Ball TD, et al. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011 Dec;27:2361–72.

[16] Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. Pain Med 2015 Jul;16:1373–85.

[17] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009 Oct;62:e1–34.

[18] Higgins JPT, Thomas J, Chandler J. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

[19] Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009 Dec;146:253–60.

[20] Wang G, Bi L, Li X, et al. Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2017 Jun;25: 832–8.

[21] Uchio Y, Enomoto H, Alev L, et al. A randomized, double-blind, placebo-controlled Phase III trial of duloxetine in Japanese patients with knee pain due to osteoarthritis. J Pain Res 2018;11:809–21.

[22] Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010 Mar;85(3 Suppl): S3–14.

[23] Dimitroulas T, Duarte RV, Behura A, et al. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. Semin Arthritis Rheum 2014 Oct;44: 145–54.

[24] Eitner A, Hofmann GO, Schaible HG. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. Front Mol Neurosci 2017;10:349.

[25] Thakur M, Dickenson AH, Baron R. Osteoarthritis pain: nociceptive or neuropathic? Nat Rev Rheumatol 2014 Jun;10:374–80.

[26] Millan MJ. Descending control of pain. Prog Neurobiol 2002 Apr; 66:355–474.

[27] Jones SL. Descending noradrenergic influences on pain. Prog Brain Res 1991;88:381–94.

[28] Richardson BP. Serotonin and nociception. Ann N Y Acad Sci 1990; 600:511–9. discussion 9-20.

[29] Brunton S, Wang F, Edwards SB, et al. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. Drug Saf 2010;33:393–407.

[30] Emslie GJ, Wells TG, Prakash A, et al. Acute and longer-term safety results from a pooled analysis of duloxetine studies for the treatment of children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol 2015 May;25:293–305.

[31] Riediger C, Schuster T, Barlinn K, et al. Adverse effects of antidepressants for chronic pain: a systematic review and meta-analysis. Front Neurol 2017;8:307.

[32] Higgins J, Thompson S, Deeks J, et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy 2002 Jan;7:51–61.

[33] Lewis-Fernandez R, Blanco C, Mallinckrodt CH, et al. Duloxetine in the treatment of major depressive disorder: comparisons of safety and efficacy in U.S. Hispanic and majority Caucasian patients. J Clin Psychiatry 2006 Sep;67:1379–90.

[34] Weinstein DL, Cohen JS, Liu C, et al. Duloxetine in the treatment of women with stress urinary incontinence: results from DESIRE (duloxetine efficacy and safety for incontinence in racial and ethnic populations). Curr Med Res Opin 2006 Nov;22:2121–9.

[35] Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet 1998 Jan 10;351:123–7.

[36] Uchio Y, Enomoto H, Ishida M, et al. Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open-label, long-term, Phase III extension study. J Pain Res 2018;11: 1391–403.