

Duloxetine for individuals with chronic back pain: A systematic review and meta-analysis of randomized controlled trials

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Abstract. The current study aimed to assess the efficacy of duloxetine in reducing pain and improving the quality of life of individuals with chronic low back pain (CLBP). An extensive literature search was conducted to identify relevant studies that examined the efficacy of duloxetine in CLBP management. The primary objective of the present study was to assess the role of duloxetine use on pain levels, as well as improvements in quality of life, using validated instruments. The results were synthesized using a random-effects model. A total of 8 studies were included in the analysis. Duloxetine demonstrated clear benefits in pain reduction, evidenced by improvements across multiple scales including the visual analogue scale, brief pain inventory-interference (BPI), BPI-severity, weekly worst pain over 24 hours and Roland-Morris Disability Questionnaire scores. Quality of life improved with duloxetine treatment, as indicated by the 36-item short form survey (SF-36). However, there was no significant impact on the physical function component of SF-36. The present study provides evidence to affirm the efficacy of duloxetine in treating CLBP. Further research is required to validate these findings and to establish whether combining duloxetine with other CLBP treatments yields superior outcomes.

Introduction

Chronic low back pain (CLBP) is a widespread public and occupational health issue, affecting ~23% of the population, with 11-12% experiencing disability (1,2). CLBP lasts 12 weeks or more and is influenced by various factors, including genetics, age, fitness level, weight and mental well-being (3,4). A number of studies have shown that the prevalence of CLBP steadily increases from the 3rd to the 6th decade of life, with a higher prevalence observed among women (3,4). In developed countries, 49-90% of individuals will experience at least one episode of low back pain in their lifetime, with the majority experiencing temporary relief within 2 weeks. However, 2-7% of people will go on to develop CLBP (3,4).

Duloxetine, a serotonin-noradrenaline reuptake inhibitor, increases dopamine levels in the prefrontal cortex and enhances the activity of noradrenergic and serotonergic neurons in the descending spinal pathway; thus, alleviates neuropathic and chronic pain (5,6). Clinical trials as well as systematic reviews, have demonstrated its effectiveness in treating CLBP, with significant improvements compared with placebo. A clinical trial conducted by Skljarevski *et al* (7), involving 404 patients with non-radicular CLBP over a 13-week period, demonstrated that the duloxetine group exhibited improvement in functional outcomes compared with the placebo group. Two previous systematic reviews by Weng *et al* (8) and Hirase *et al* (9) have been conducted to investigate the effect of duloxetine on CLBP. However, Weng *et al* (8) examined the impact of duloxetine on CLBP and osteoarthritis, while Hirase *et al* (9) performed a systematic review without a meta-analysis due to heterogeneity.

Considering the lack of comprehensive investigations into CLBP and the publication of recent clinical trials evaluating the use of duloxetine, the present systematic review was conducted to incorporate the most up-to-date evidence available as of the publication date of the present study. The current review aimed to not only assess the efficacy of duloxetine in managing CLBP but also explore its impact on the quality of life of the patients and the frequency of serious adverse effects.

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Abbreviations: CLBP, chronic low back pain; VAS, visual analogue scale; BPI, Brief Pain Inventory; SF-36, short form 36; PGI-I, patients' global impression of improvement

Key words: duloxetine, chronic back pain, pain management, pharmacotherapy, treatment efficacy, systematic review, meta-analysis

Materials and methods

The present systematic review and meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (10), ensuring methodological rigor and transparency throughout the research process.

Eligibility criteria. Randomized controlled trials (RCTs) that examined duloxetine across various dosage regimens in individuals suffering from chronic low back pain (CLBP) were included, compared with placebo. Observational studies, those with duplicated or overlapping populations, and those focusing solely on acute low back pain were excluded. Furthermore, studies that used accompanied treatment, such as exercise, electrotherapy or physiotherapy were excluded from this meta-analysis to maintain the integrity and relevance of the selected literature.

Search strategy. A comprehensive and systematic search strategy was developed based on four prominent electronic bibliographic databases: PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://0710oser8-1106-y-https-www-webofscience-com.mplbci.ekb.eg/wos/woscc/basic-search>), Cochrane Central (<https://www.cochranelibrary.com/advanced-search>) and Scopus (<https://07105sega-1106-y-https-www-scopus-com.mplbci.ekb.eg/search/form.uri?display=basic#basic>). The present study aimed to maximize the retrieval of relevant articles published from the inception of each database up to March 2024. The search strategy used was as follows: For PubMed, (duloxetine hydrochloride OR duloxetine OR Cymbalta) AND (low back pain OR back pain OR back pain OR backache); for Web of Science, (duloxetine OR Cymbalta) AND (low back pain OR back pain OR back pain OR backache); for Cochrane, (duloxetine OR Cymbalta) AND (low back pain OR back pain OR back pain OR backache); and for Scopus, (duloxetine OR Cymbalta) AND (low back pain OR back pain OR back pain OR backache).

Study selection. A total of 2 independent reviewers performed the study selection process. Initially, titles and abstracts were screened to identify potentially eligible studies, followed by full-text screening to confirm eligibility based on the predefined inclusion and exclusion criteria.

Data extraction. Data extraction was conducted using a structured electronic data extraction sheet. A total of 2 independent reviewers extracted the following data from the included studies: Study name, year of publication, study design, interventions, duration of duloxetine treatment, sample size, mean age, male percentage, weight, follow up duration and outcome measures.

Definition of outcomes parameters. The visual analogue scale (VAS) is a subjective, self-reported, pain rating scale. It is used to track pain regression. A handwritten mark placed at one point along the length of a 10 cm line that represents a continuum between the two ends of the scale; 'no pain' on the left end (0 cm) of the scale and 'worst pain' on the right (10 cm). Measurements from the zero point (left end) of the scale to the patients' marks are recorded in cm and are interpreted as their pain (11).

The Brief Pain Inventory (BPI) is a self-reported assessment. It provides information on the intensity of pain (sensory dimension or BPI-severity) and the degree to which pain interferes with function (reactive dimension or BPI-Interference). BPI-I is rated on a scale of 0 (no interference) to 10 (interferes completely). The average of 7 items or questions that the BPI-I scale addresses (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life) were reported (12). The Roland-Morris Disability Questionnaire-24 (RMDQ-24) measures physical disability due to CLBP on a scale ranging from 0 (no disability) to 24 (severe disability) (13).

The SF-36 includes 36 questions. In total, 8 different sub-scores (physical and social functioning, physical and emotional role limitations, mental health, energy, pain, and general health perceptions), and a mental and physical summary score can be obtained from these. A maximum score of 100 resembles the best possible health state (14). Patients' global impression of improvement (PGI-I) compares a participant's perception of improvement at the time of assessment with treatment initiation time. Score varies from 1 (very much better) to 7 (very much worse) (15).

Of the included studies, only Raskin *et al* (16) specifically addressed depression, defining it according to DSM-IV criteria (17). While this definition was referenced in the present study, none of the other 7 studies included a focus on depression. Depression was defined according to the criteria of DSM- IV (17). The included study by Raskin *et al* (16) also defined depression as in the DSM-IV. The diagnosis was confirmed by the Mini International Neuropsychiatric Interview, a standardized diagnostic interview based on DSM-IV criteria (17). Baseline disease severity was defined by patients' scores on the Hamilton Depression Rating Scale with 17 items (HAM-D) (18). Patients were required to have a HAM-D total score of ≥ 18 at visits 1 and 2; a Mini-Mental State Examination (MMSE) score of ≥ 20 with or without mild dementia; and at least one previous episode of major depression. Patients with an MMSE score of 20 to 23 were categorized as having mild dementia, while those with a score of ≥ 24 were categorized as having no dementia (18).

Quality assessment. The risk of bias in the included RCTs was assessed using the well-established Cochrane collaboration tool (19). This evaluation included sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. Each study's bias risk was categorized as 'Low', 'High', or 'Unclear' ensuring a comprehensive understanding of the methodological quality and robustness of the included studies.

Data analysis. For dichotomous data, risk ratios (RR) with 95% confidence intervals (CIs) were used. For continuous data, the mean differences (MD) with 95% CI were employed. Data synthesis was performed using the R software (meta-package; v.6.5-0; <https://www.r-project.org/>). Visual inspection of the forest plots and measurement of the Q and I^2 statistics were used to assess heterogeneity. Significant statistical heterogeneity was indicated by the Q statistic $P < 0.1$ or $I^2 > 50\%$. Random effect model was used in the meta-analysis.

Table I. Summary table of included studies; RCT, randomized controlled trial; NA, not available.

First author, year	Study design	Interventions	Duration of duloxetine treatment in weeks	Mean age (standard deviation) (Intervention/control)	Male n (%) (Intervention/control)	Weight (kg) (Intervention/control)	Follow up in weeks	Outcome parameters (Refs.)
Raskin <i>et al</i> , 2007	RCT	Duloxetine (60 mg) vs. placebo	8	72.6 (5.7)/73.3 (5.7)	82 (39.6%)/44 (42.3%)	80 (17.7)/79.7 (18.8)	8	VAS (16)
Skljarevski <i>et al</i> , 2009	RCT	Duloxetine 60-120mg vs. placebo	13	52.9 (12.8)/54.0 (13.5)	23 (39%)/53 (45.3%)	84.9 (14.2)/81.9 (17.4)	13	Weekly mean 24-h average pain, RMDQ-24, PGI-I, BPI (24)
Mazza <i>et al</i> , 2010	RCT	Duloxetine 60 mg vs. Escitalopram 20 mg	13	53.6 (13.5)/52 (12.4)	18 (43.1)/17 (43.6)	81.5 (18.6)/82.7 (16.9)	13	Weekly mean 24-h average pain, CGI-S, SF-36 (32)
Skljarevski <i>et al</i> , 2010a	RCT	Duloxetine 60-120 mg vs. placebo	13	51.8 (14.9)/51.2 (13.5)	44 (38.3)/48 (39.7)	76.2 (14.7)/75.9 (13.9)	13	BPI, RMDQ, PGI, CGI-S, BPI-S, BPI-I, weekly means of the 24-hour average pain (23)
Skljarevski <i>et al</i> , 2010b	RCT	Duloxetine 60 mg vs. placebo	12	54.9 (13.7)/53.4 (14.2)	80 (40.4)/75 (36.9)	78.3 (15.8)/79.4 (14.7)	12	BPI, PGI-I, RMDQ-24, BPI-S, BPI-I, SF-36 (7)
Konno <i>et al</i> , 2016	RCT	Duloxetine 60 mg vs. placebo	14	60.0 (13.2)/57.8 (13.7)	115 (50.0)/104 (46.0)	63.56 (12.75)/63.15 (13.42)	14	BPI, GGI-S, RMDQ (22)
Schukro <i>et al</i> , 2016	RCT	Duloxetine 120 mg vs. placebo	8	57.9 (13.4)	20 (49%)	80.5 (18.3)	8	VAS (20)
Samadi <i>et al</i> , 2021	RCT	Duloxetine 30 mg vs. placebo	6	45.13 (15.41)/52 (11.53)	7 (46.67%)/11 (68.75%)	NA	6	VAS, SF-36 (21)

RCT, randomized controlled trial; NA, not available; VAS, visual analogue scale; BPI, Brief Pain Inventory; RMDQ, Roland-Morris Disability Questionnaire; PGI, patient's global impressions; CGI-S, Clinical Global Impressions-Severity; BPI-I, Brief Pain Inventory-Interference; SF-36, 36-item short form survey.

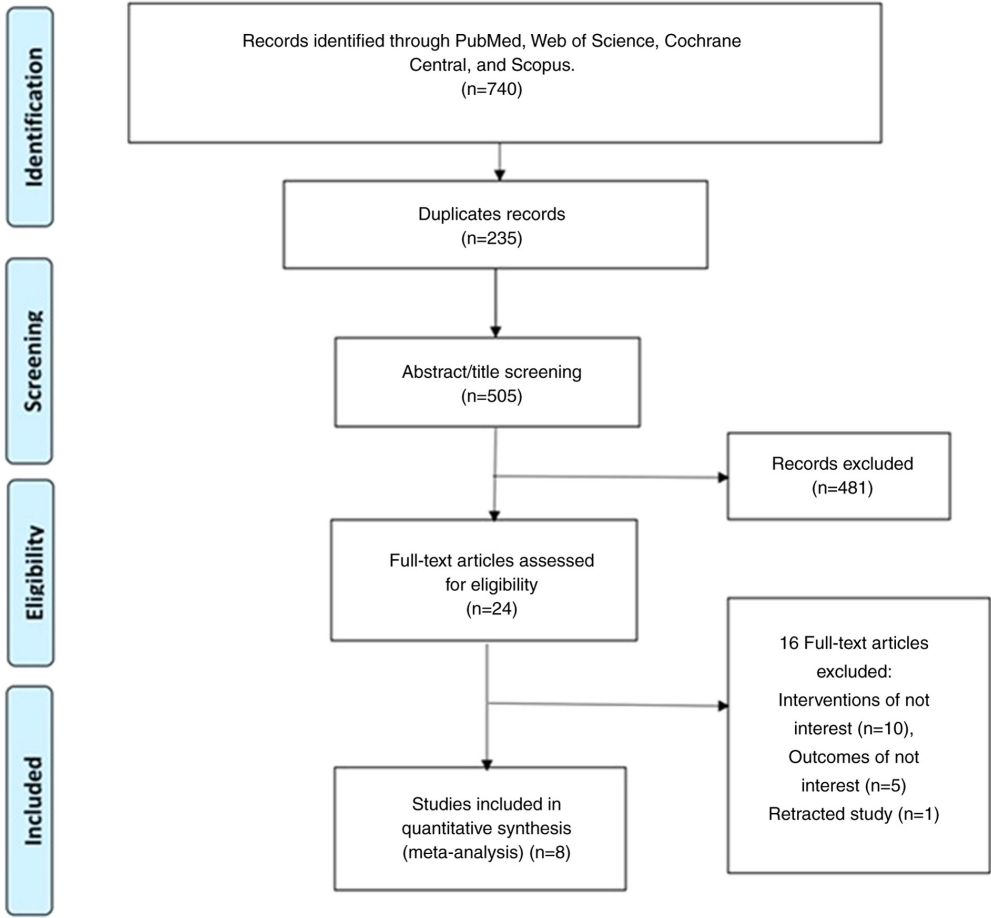


Figure 1. PRISMA flowchart.

Results

Search results. A total of 740 records were identified, 235 redundant entries were removed and 505 unique records were reviewed. After assessing the full-text articles, the pool was narrowed down to 24 relevant studies, and finally a total of 8 studies were included in the meta-analysis. Any discrepancies were resolved through discussion and consensus to ensure the robustness and integrity of the study selection process. The study selection process is shown in Fig. 1.

Study characteristics. The included studies collectively enrolled a total of 1,985 patients. These studies have exhibited diverse characteristics, as summarized in Table I. The methodological quality of each study was evaluated using the Cochrane collaboration tool, illuminating a spectrum ranging from moderate to high quality (Fig. 2).

Outcomes

Pain reduction and physical improvement. The results revealed that duloxetine was superior to placebo in reducing pain intensity, as demonstrated by significant improvements on both the VAS (20,21) [MD, -2.82; 95% CI, (-3.67 to -1.97); P<0.0001]. A subgroup analysis was conducted to differentiate patients with concomitant depression from those with only CLBP. The results of both groups (CLBP with and without depression) showed that duloxetine had significant

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Konno et al. 2016	+	+	+	+	+	+	+
Mazza et al. 2010	?	?	?	?	+	+	+
Raskin et al. 2007	+	?	+	?	+	+	+
Samadi et al. 2021	+	+	+	?	+	+	+
Schuckro et al. 2017	+	+	+	?	+	+	+
Skljarevski et al. 2009	+	+	+	+	+	+	?
Skljarevski et al. 2010a	+	+	+	+	+	+	?
Skljarevski et al. 2010b	+	+	+	+	+	+	

Figure 2. Risk of bias assessment of included studies.

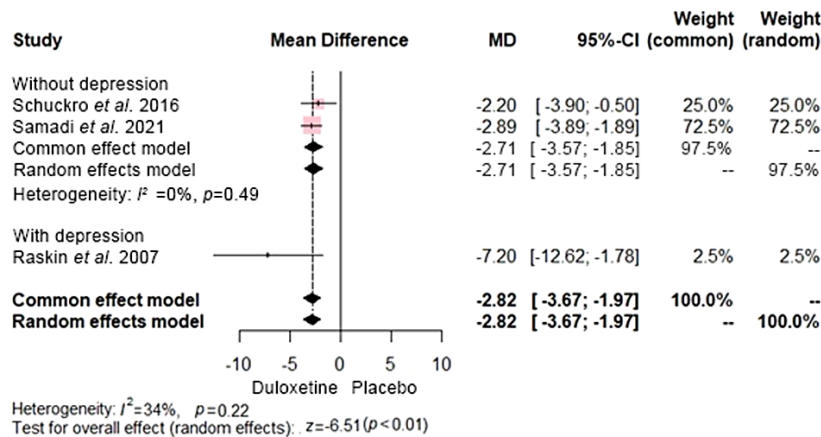


Figure 3. Forest plot of visual analogue scale comparing duloxetine vs. control. MD, mean difference; CI, confidence interval.

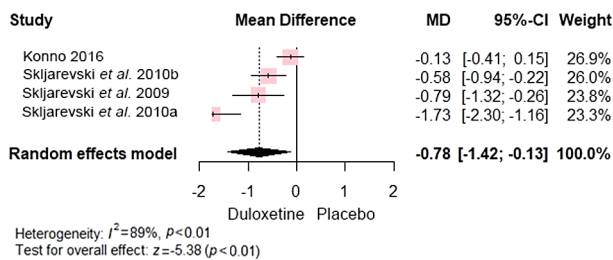


Figure 4. Forest plot of the brief pain inventory-interference score comparing duloxetine vs. control. MD, mean difference; CI, confidence interval.

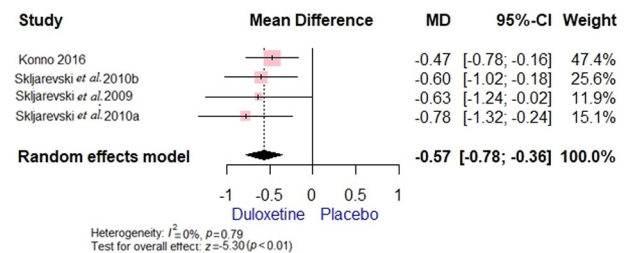


Figure 6. Forest plot of the brief pain inventory-interference-severity average pain comparing duloxetine vs. control. MD, mean difference; CI, confidence interval.

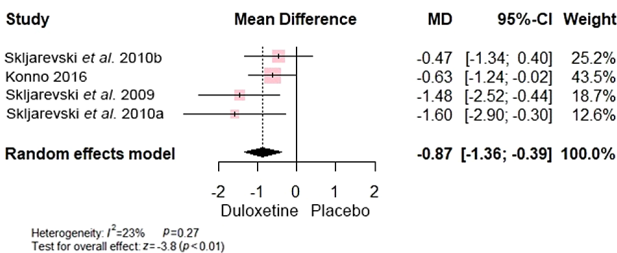


Figure 5. Forest plot of the Roland-Morris disability questionnaire-24 scale comparing duloxetine vs. control. MD, mean difference; CI, confidence interval.

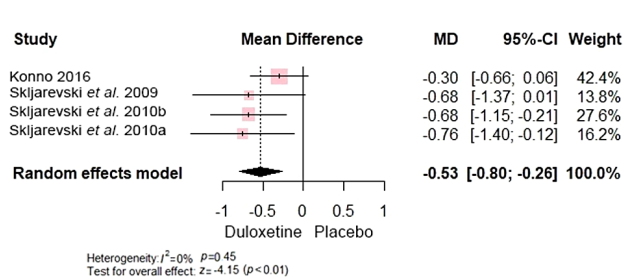


Figure 7. Forest plot of the worst pain scale comparing duloxetine vs. control. MD, mean difference; CI, confidence interval.

advantage over control [MD, -2.71; 95% CI, (-3.57 to -1.85) and MD, -7.20; 95% CI, (-12.62 to -1.78), respectively] (Fig. 3).

Furthermore, the overall mean difference favoured duloxetine over control in terms of the BPI score (7,22-24) [MD, -0.78; 95% CI, (-1.42 to -0.13); $P<0.0001$] (Fig. 4). In addition, the overall mean difference between favoured duloxetine over control regarding the RMDQ-24 scale [MD, -0.87; 95% CI, (-1.36 to -0.39), $P<0.0001$] (Fig. 5), BPI-S average pain [MD, -0.57; 95% CI, (-0.78 to -0.36); $P<0.00001$] (Fig. 6) and worst pain [MD, -0.53; 95% CI, (-0.80 to -0.26); $P<0.0001$] (Fig. 7).

Quality of life. One study (21) reported on impact of duloxetine on overall SF-36 scores, and showed no significant difference between the compared groups [MD, 4.30; 95% CI, (-3.59 to 12.19); $P>0.05$].

PGI-I. Assessment of PGI-I across the 4 studies (7,22-24) revealed significant advantages of duloxetine over placebo [MD, -0.33; 95% CI, (-0.46 to -0.21); $P<0.0001$], with no significant heterogeneity ($P=0.92$ and $I^2=0\%$) (Fig. 8).

Safety and tolerability. In total, 7 studies reported data on safety and tolerability while the study conducted by Samadi *et al.* (21) did not report any data on side effects. The analysis revealed no significant difference in the occurrence of serious adverse events (chest pain, vertigo, dyspnoea, perioral numbness, perioral numbness, myocardial infarction, toxic myopathy, asthma and alcohol poisoning) between the duloxetine and control groups [RR, 1.92; 95% CI, (0.80 to 4.60); $P=0.054$], with studies (7,22-24) demonstrating homogeneity ($P=0.36$ and $I^2=6\%$) (Fig. 9).

Compared with control, duloxetine exhibited more constipation [RR, 3.00; 95% CI, (1.86 to 4.84); $P<0.00001$] (Fig. 10),

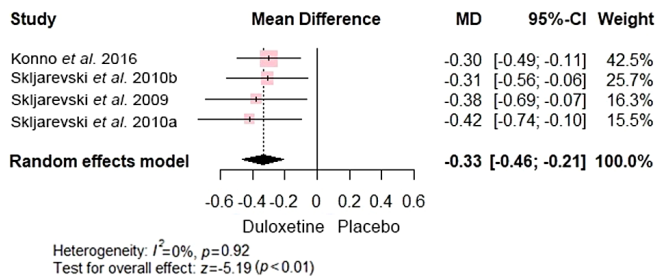


Figure 8. Forest plot of patients' global impression of improvement comparing duloxetine vs. control. MD, mean difference; CI, confidence interval.

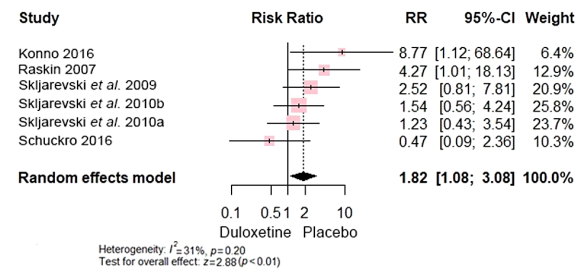


Figure 11. Forest plot of diarrhea comparing duloxetine vs. control. RR, risk ratio; CI, confidence interval.

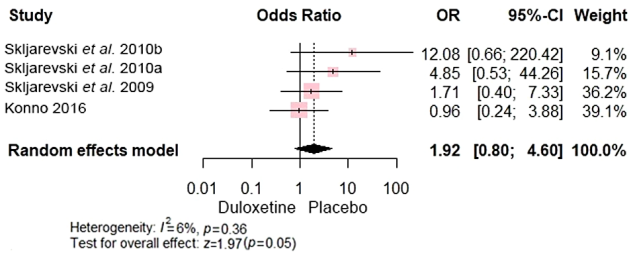


Figure 9. Forest plot of adverse events comparing duloxetine vs. control. OR, odds ratio; CI, confidence interval.

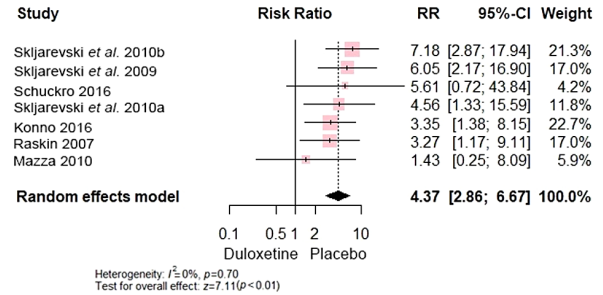


Figure 12. Forest plot of nausea comparing duloxetine vs. control. RR, risk ratio; CI, confidence interval.

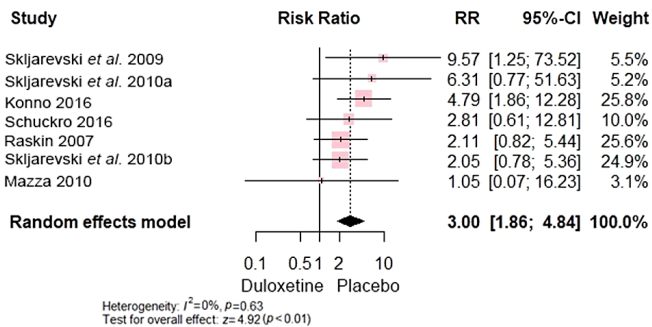


Figure 10. Forest plot of constipation comparing duloxetine vs. control. RR, risk ratio; CI, confidence interval.

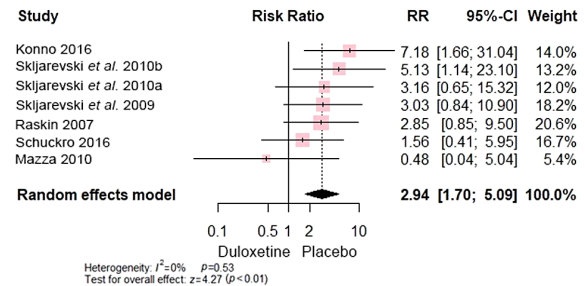


Figure 13. Forest plot of dizziness comparing duloxetine vs. control. RR, risk ratio; CI, confidence interval.

diarrhoea [RR, 1.82; 95% CI, (1.08 to 3.08); $P<0.0001$] (Fig. 11), nausea [RR, 4.37; 95% CI, (2.86 to 6.67); $P<0.00001$] (Fig. 12) and dizziness [RR, 2.94; 95% CI, (1.70 to 5.09); $P=0.0001$] (Fig. 13). In addition, no significant difference was found between both groups regarding insomnia [RR, 1.17; 95% CI, (0.65 to 2.10); $P=0.54$] (Fig. 14) and headache [RR, 1.08; 95% CI, (0.42 to 2.77); $P=0.82$] (Fig. 15).

Sensitivity analysis. A sensitivity analysis was performed to evaluate the impact of excluding the study by Samadi *et al* (21) that included post-surgical patients. The aforementioned study only reported on the VAS outcome. After removing it, the analysis did not show significant difference between duloxetine and placebo in terms of VAS outcome, as revealed in Fig. 16.

Discussion

The present study, including eight RCTs, provides robust evidence, supporting the efficacy of duloxetine in reducing

pain and enhancing quality of life of patients with CLBP. Duloxetine demonstrated superior outcomes over placebo in pain reduction measured by the VAS, BPI, BPI-S, RMDQ-24 scales and worse pain scales. In addition, duloxetine improved quality of life assessed by the SF-36. Clinically, these results favor the duloxetine group, indicating its efficacy in alleviating CLBP symptoms and enhancing patients' overall well-being (25,26).

Although the overall trend supports the effectiveness of duloxetine, individual study outcomes may vary. Variations in the study design, patient populations and methodological approaches contributed to the observed heterogeneity. Discrepancies in the findings can be attributed to factors such as differences in drug dosage, concomitant medication usage, and patient characteristics such as age and comorbidities. Methodological disparities, including study duration and outcome measures, also contribute to variability among studies (27).

The superiority of the duloxetine group over the placebo is scientifically grounded in its pharmacological mechanism

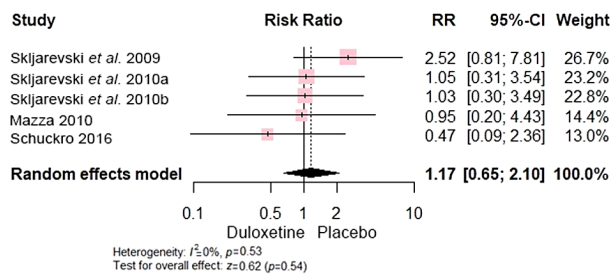


Figure 14. Forest plot of insomnia comparing duloxetine vs. control. RR, risk ratio; CI, confidence interval.

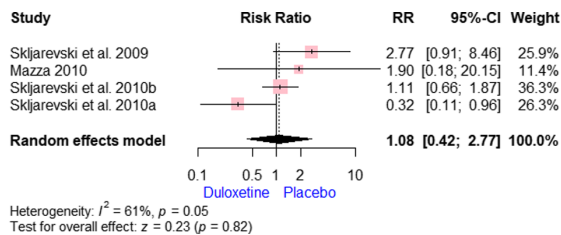


Figure 15. Forest plot of headache comparing duloxetine vs. control. RR, risk ratio; CI, confidence interval.

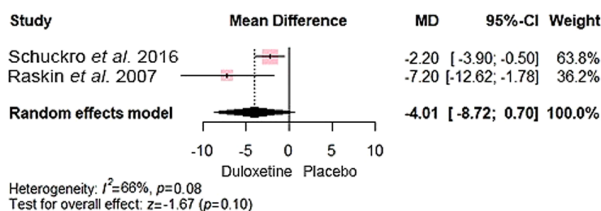


Figure 16. Forest plot of sensitivity analysis after excluding the study by Samadi et al (13). MD, mean difference; CI, confidence interval.

of action. As an antidepressant and serotonin-noradrenaline reuptake inhibitor, duloxetine modulates neurotransmitter levels in the central nervous system and attenuates pain-signaling pathways. This neurobiological mechanism, coupled with the demonstrated efficacy in clinical trials, elucidates why the duloxetine group exhibited superior outcomes in terms of pain reduction and quality of life improvement (28,29).

Previous studies have similarly highlighted the efficacy of duloxetine in the management of CLBP, corroborating the present findings (30,31). However, the present study advances the existing literature by incorporating the most up-to-date evidence through a comprehensive systematic review and meta-analysis. These findings align with those of previous studies that underscore the effectiveness of duloxetine in treating CLBP (9). Nevertheless, the present study provides additional insights and robust evidence, further strengthening the existing body of literature on this topic.

The strengths of the present study include a comprehensive methodology adhering to the PRISMA guidelines, meticulous selection and analysis of relevant studies, and robust assessment of study quality. However, limitations include the observed heterogeneity across studies, potential biases inherent in meta-analyses and limited number of

included studies, which may affect the generalizability of the findings.

Based on these results, future research should focus on specific subpopulations, such as patients with depression and CLBP, and explore the comparative efficacy of duloxetine in conjunction with conservative therapies. Additionally, further investigations into the efficacy of duloxetine across various types of back pain and its long-term effects are warranted. Future studies should also address the methodological inconsistencies and biases observed in previous research to strengthen the evidence base for the use of duloxetine in managing CLBP.

In conclusion, the present study has yielded promising outcomes concerning pain alleviation and improvements in the quality of life among individuals afflicted with CLBP. While acknowledging limitations such as study heterogeneity and the restricted number of included studies, the findings present compelling evidence for the efficacy of duloxetine in mitigating CLBP. These results highlight the potential of duloxetine as a valuable therapeutic intervention in CLBP management, particularly in individuals with comorbid depression. Further research is imperative to address the prevailing limitations and comprehensively validate these findings. Such efforts are crucial for refining treatment approaches and advancing CLBP management on a global scale.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MSAS, AZA and DB conceptualized and designed the study, contributed to data analysis and interpretation, and played a major role in writing the manuscript. HEM and ZB did the initial screening while ZB and DB contributed to full text screening and data interpretation. HEM and ZB curated and analyzed the data, created visualizations, and contributed to the interpretation of results. DB, HEM and ZB drafted the initial manuscript, synthesized study findings, and incorporated feedback from co-authors. All authors read and approved the final version of the manuscript. MSAS and HEM confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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