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The efficacy of peri-operative duloxetine on reducing post-operative pain and opioid doses – literature review

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Abstract

Introduction and Objective. Surgery and anaesthesia are crucial components of healthcare services which significantly reduce the risk of mortality and disability for millions of people worldwide each year. The most common problem occurring after inpatient and outpatient procedures continues to be post-operative pain. One possible way to prevent pain may be the use of co-analgesics such as duloxetine.

Review Methods. The PubMed database was searched to gather studies examining the utilization and efficacy of duloxetine in the treatment of post-operative pain. Three search formulations were employed to broaden the scope of results: 'duloxetine and pain and post-operative', 'duloxetine and pain and peri-operative', and 'duloxetine and pain and pre-operative'.

Brief description of the state of knowledge. Currently, duloxetine, together with other coanalgesics, is a first-line drug in the treatment of neuropathic pain. The use of peri-operative duloxetine has also been investigated in systemic reviews and meta-analyses. According to current knowledge, duloxetine may have measurable effects in the treatment of pain and reduction of opioid use, but the decision to undertake such treatment should be specific to the patient.

Summary. The efficacy of duloxetine administration during the peri-operative period in reducing post-operative pain is contingent upon the nature of the surgical intervention and the therapeutic protocol employed. The documented benefits underscore the importance of pursuing additional research efforts.

Key words

pain, analgesics, perioperative, duloxetine, surgery

INTRODUCTION

Surgery and anaesthesia are crucial components of healthcare services which significantly reduce the risk of mortality and disability for millions of people worldwide each year. However, the most common problem occurring after inpatient and outpatient procedures continues to be post-operative pain [1, 2]. Despite progress in understanding pain mechanisms and advances in new pain management strategies, post-operative pain remains a prevalent issue frequently addressed with inadequate treatments [2, 3].

Historically, opioids have been the primary standard of care for post-operative pain. Although opioid medications are undeniably effective, they are also associated with a significant risk of adverse effects and addictive potential. Subsequent investigations have revealed that peri-operative (the period from the evaluation of the patient's health condition to 30 days after the procedure) opioid administration may cause nausea, constipation, pruritus, altered mental status, urinary retention, opioid-induced respiratory depression, and prolonged hospitalization [4, 5].

Since the 1990s, considerable research has been devoted to multimodal analgesia, a pain control approach that combines medications with various mechanisms of action to synergistically manage pain. This approach aims to reduce total analgesia requirements, mitigate adverse effects, and prevent misuse potentially associated with single-agent therapies such as opioids [5, 6].

Recently, in clinical trials, scientists have considered duloxetine, a serotonin and noradrenaline reuptake inhibitor, as an adjuvant in multimodal analgesia for acute post-operative pain [7]. Duloxetine is commonly prescribed for the treatment of post-traumatic depression, major depression, and generalized anxiety disorder. It is also approved for the treatment of various chronic pain syndromes, including neuropathic pain associated with diabetes, musculoskeletal pain, and fibromyalgia [8, 9].

The analgesic efficacy of duloxetine is ascribed to its capacity to enhance serotonin and norepinephrine neurotransmission in descending inhibitory pain pathways in the brain and spinal cord [10, 11]. Therefore, the favourable effects of duloxetine on pain and emotions have prompted researchers to explore its application during the peri-operative period. The aim of this literature review was to assess the evidence on the ability of peri-operative duloxetine administraton to reduce post-operative pain, and the potential to reduce opioid doses in patients undergoing elective orthopaedic, gynaecological or general surgery.

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MATERIALS AND METHOD

The PubMed database was searched to identify studies examining the utilization and efficacy of duloxetine for the treatment of post-operative pain. Three search formulations were used to broaden the scope of the results: 'duloxetine and pain and post-operative', 'duloxetine and pain and peri-operative', and 'duloxetine and pain and preoperative'. Given the objective of this study, available filters on PubMed were applied, limiting the search to a combined pool of 58 studies, utilizing the filters 'Clinical Trial' and 'Randomized Controlled Trial'. The inclusion criteria for studies in the review included patients aged 18 years and older, the use of duloxetine peri-operatively in the experimental group, and a statistical analysis comparing the efficacy of duloxetine versus placebo. An additional non-mandatory criterion was the examination of the impact of duloxetine on reducing the intake of other analgesic pharmacotherapies, with particular emphasis on opioids.

RESULTS

Based on the above methods and criteria, 17 studies were included in the analysis, with full access obtained for all. Among them, duloxetine was examined pre-operatively in four studies and peri-operatively in 13 studies. The intervention protocols varied significantly in terms of the administered dose and duration of duloxetine intake. The studies included in this review can be divided into three groups based on surgical specializations: orthopaedic operations (nine studies), general surgery (six studies), and gynaecology (two studies). Accordingly, this section will be divided into three parts, each describing one specialization. A detailed characterization of the selected studies, including the doses and efficacy of administered duloxetine, is presented in Table 1.

Orthopaedic surgeries. Five studies focused on total knee replacement surgery. In all but one of them, 60 mg of duloxetine was administered orally for two weeks post-surgery [12–15]. In the remaining study, 30 mg was used for six weeks [16]. Pain reduction was statistically significant in two studies [12, 16], non-inferior in one [13], and not statistically significant in the remaining studies [14,15]. Opioid administration was significantly reduced in four of these studies [12–15]. The average age of the participants ranged from 63 – 69 years. In studies where duloxetine alleviated pain, the gender ratio was skewed toward females, while in other studies, the gender distribution was even. Notably, opioid administration was not reduced in the study with the largest gender discrepancy [16] (1:7, favouring females). This may be associated with females being more prone to pain and more willing to admit suffering. Combining celecoxib with duloxetine resulted in significant pain reduction [12]. Acetaminophen had similar effects in one study [16] but not in another in which it was used [14]. The study that used lower doses of both duloxetine and acetaminophen showed significant pain alleviation, but did not reduce opioid intake, suggesting that opioids might be responsible for pain reduction. When meloxicam was used as part of the basic analgesia, duloxetine was ineffective [15]. These discrepancies might have been caused by the differing strengths and interactions of these substances with duloxetine. Pain scales also varied; studies with significant findings regarding pain alleviation used the Visual Analog Scale (VAS) [12, 16], while others used the Numerical Rating Scale (NRS) [13–15], which might have affected the results due to differences between the scales. In the surgical treatment of disc herniation, both studies showed that duloxetine alleviates post-operative pain and reduces the need for additional analgesics [17, 18]. In the study with three doses of 60 mg of duloxetine, pain alleviation was recorded on the first and second days post-operation, whereas in the study with two doses, pain alleviation was recorded only on the second day. This difference might be due to dosage variations and the basic pain treatment medications used; the three-dose study used tramadol and paracetamol, while the two-dose study used only paracetamol. The average age in the three-dose study was 53–54 years, while in the two-dose study, it was 46–48 years. The gender ratio in the three-dose study favoured females, while in the two-dose study, it favoured males. The three-dose study used VAS scores, and the two-dose study used NRS scores.

One study focused on total hip arthroplasty [19], where 60 mg of duloxetine was administered orally once daily from two days before surgery to two weeks after surgery. The basic pain treatment used was celecoxib, which resulted in significant pain alleviation and reduced opioid consumption, similar to the findings of knee arthroplasty studies. The gender ratio was even, and the average age was approximately 50 years. Pain severity was measured using the VAS.

A study on patients after opening-wedge high tibial osteotomy showed significant pain reduction and reduced NSAID consumption among patients receiving duloxetine [20]. Duloxetine was administered at the lowest dosage among all studies, at 20 mg per day, with loxoprofen as the basic pain relief treatment. The average age of the patients was approximately 65 years, and males were the more prevalent gender. Pain severity was measured using the NRS.

Gynaecological surgery. Among gynaecological procedures, the peri-operative use of duloxetine has been studied in hysterectomy and hysterectomy with oophrectomy. In each of the studies, patients underwent surgery for reasons other than malignancies. Observations on these surgeries vary from study to study. The use of 60 mg of duloxetine 2 h before surgery and 24h after surgery in patients who underwent hysterectomy along with oophrectomy based on the QoR-40, had no positive effect on post-operative pain perception, in addition, no analysis of the reduction in opioid intake was performed [21]. The same intervention was implemented in another study in which patients underwent only abdominal hysterectomy. In this case, the researchers showed a slight decrease in pain level in the experimental group using the NRS and QoR-40; however, this decrease occurred only 24 hours after surgery. Importantly, from the perspective of opoid use, patients taking duloxetine were significantly less likely to insist on additional morphine administration 24h after surgery due to worsening pain [22]. The mean ages of the patients in both studies were similar. The baseline analgesic treatment, that did not show a positive effect of duloxetine consisted of 1 g of paracetamol, 50 mg of metamizole, and 1 mg of morphine administered intravenously at appropriate intervals, while the other study used 100 mg of ketoprofen and 50 mg of metamizole intravenously at appropriate intervals.

Table 1. Characteristics of selected works including research results

Study and year	Type of study performed	Characteristics of patients included in the analysis	Inclusion criteria and main disease	Type of surgery performed	Basic pain relief treatment	Characteristics of the intervention	Pain assesment	Additional pain treatment
Otsuki et al. 2022	Prospective clinical trial	35 patients in duloxetine group (20 M, 15 F; mean age 66.5 ± 10.9) and 33 in control group (19 M, 14 F; mean age 64.8 ± 8.7)	Patients with knee osteoarthritis, aged >18	Opening-wedge high tibial osteotomy	60 mg loxoprofen sodium hydrate maximum 3 tablets per day	One 20-mg capsule once daily for 1 week at 3 weeks before surgery, and two 20-mg capsules once daily for 2 weeks before surgery	Knee pain evaluated by NRS measured at 1, 3, 7, 14 and 90 days after operation. Significantly lower NRS pain score in duloxetine group at 1, 7 i 14 days after surgery.	Acetaminophen 200mg, tramadol hydrochloride 37.5 mg. Significantly rarer consumption of NSAID among duloxetine patients (14.1 ± 9.8 vs (29.3 ± 8.8 tablets)
Attia et al. 2017	Prospective double-blind, randomized, controlled study	30 patients in duoxetine group (18 M, 12 F; mean age 48.36 ±) and 30 patients in placebo group (15 M, 15 F; mean age 46.5 ±)	Patients of both genders aged between 18-70 years; ASA physical status I, II and III, who were scheduled for single level lumbar spinal disc prolapse surgery	Single level lumbar spinal disc prolapse surgery (laminectomy)	1g of paracetamol iv every 6h for 48h after surgery.	60 mg capsule of duloxetine given 1h before surgery and repeated after 24h	NRS pain scores recorded at 30min after the end of anaesthesia and at the end of 2, 4, 6, 12, 24 and 48h post-operatively. Duloxetine group had significantly lower NRS pain scores at 24 and 48h after surgery (mean difference in NRS: 0.5 at 24h and 1 at 48h)	Morphine 2mg iv bolus. Patients in duloxetine group, on average, had to take morphine half an hour later, compared to placebo (62 min vs 91.7 min); they also required smaller doses of morphine at 24h after surgery (mean doses of morphine 22.6 mg vs 31.9 mg) and at 48h (mean doses of morphine 14.8 vs 20.2 mg)
Takmaz et al. 2020	Randomized placebo-controlled trial	40 patients in duloxetine group (mean age 45 ± 42.3–51.3) and 37 patients in placebo group (mean age 43 ± 36.7–45.9)	Patients undergoing LH owing to benign gynecologic conditions (myomas, chronic pelvic pain, or uterine prolapse), and older than 18 years.	Laparoscopic hysterectomy and oophorectomy for patients aged ≥50 years.	1g of paracetamol iv every 8h, metamizole 50 mg iv every 12 h. 1 mg of morphine every 15min iv	60 mg oral duloxetine 2h before surgery and 24h after surgery	Quality of Recovery-40 questionnaire completed 48h after surgery. No positive effect in duloxetine group according to pain part of questionnaire.	-/-
Li et al. 2021	Randomized double-blinded, placebo-controlled study	48 patients in duloxetine group (22 M, 26 F; mean age 52.7 ± 12.0) and 48 patients in placebo group (24 M, 24 F; mean age 50.2 ± 13.2)	Patients over 18 years of age; classified under ASA status I, II, or III; and scheduled to undergo primary THA for end-stage hip joint diseases, were screened using the Hamilton Depression Scale (HAMD) and the Hamilton Anxiety Scale (HAMA). Subjects whose HAMD and HAMA scores were both <7 were included.	Total hip arthroplasty	Oral administration of celecoxib 200 mg twice daily, started 1 day after surgery	60 mg of oral duloxetine administrated every day from 2 days before surgery to 14 days after surgery	VAS pain score evaluation upon movement and at rest (3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 1w, 3w, and 3 m following surgery). In duloxetine group, from 3h to 3 weeks VAS scores were significantly lower than in placebo, but not after 3 months post-operatively	Morphine 5 mg iv when pain became unbearable or VAS score > 6. Patients in duloxetine group significantly rarer used morphine at 1, 3 and 7 days after surgery (11 vs 14.2; 16.8 vs 20.4; 18.7 vs 23.3 mg)

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Erdmann et al. 2022	Prospective, double-blinded, randomized, controlled trial	30 patients in duoxetine group (15 M, 15 F; mean age 62.73 ± 11.56) and 29 patients in placebo group (16 M, 13 F; mean age 56.93 ± 14.55)	Patients with tumours (26 in both groups) and benign (4 in duloxetine and 3 in placebo group) diseases aged 18-85 of both genders, ASA physical status I through III, scheduled for elective open colectomy (including any part of the colon) under general anesthesia in a University Hospital tertiary surgery centre	Elective open major colonic surgeries	Ketoprofen 100 mg i.v. every 12h and dipyrone 1 g i.v. every 6h for 48h after surgery	Duloxetine 60 mg orally 2h before surgery and 24h after surgery	VAS pain score evaluation upon movement and at rest (on arrival, 6, 24 and 48h after surgery). No significant differences observed between groups	Morphine 1 mg iv bolus when VAS score >5 or in insufficient anaesthesia. Patients in duloxetine group cumulative morphine consumption was lower than in placebo group, but this result was not statistically significant at 24 and 48h after surgery
Hetta et al. 2020	Parallel, randomized, placebo-controlled trial	30, 60 and 90 mg duloxetine groups, resptectevily, 20, 21 and 20 patients (mean age: 47.9 ± 148, 47.7 ± 10.8 and 41.2 ± 14.2) and 20 patients in placebo group (mean age 48.15 ± 10.9)	Adult females scheduled for unilateral MRM with axillary evacuation for breast cancer, ASA class I and II and aged 20- 70 years.	Modified radical mastectomy	1g of paracetamol iv every 8h	Duloxetine 30, 60 or 90 mg orally 2 h before surgery	VAS pain score evaluation upon movement and at rest (0, 2, 4, 8, 12, 16 and 24h after surgery), and QoR-40 questionnaire. Significant VAS pain score difference between 60mg and 90mg group in comaprison to placebo group was observed up to 8h after surgery. Significatnly better results were observed in 60 and 90 mg duloxetine, compared to placebo in QoR-40 score.	Morphine 2 mg iv bolus on-demand. Significantly lower median consumption of morphine at 24h post-operatively in 60 and 90 mg duloxetine group, compared to placebo (0 vs 0 vs 10 mg, respectively)
Yuan et al. 2022	Prospective randomized, double-blind, placebo-controlled trial	50 patients in duloxetine (20 M, 30 F; mean age 67.8 ± 10.12) group and 50 patients in placebo group (23 M, 27 F; mean age 66.2 ± 9.83)	Patients were diagnosed with knee osteoarthritis and scheduled to undergo primary unilateral TKA were eligible for study enrollment.	Unilateral total knee arthroplasty	From pre-operative day 2 to the day before surgery 200 mg of celecoxib twice a day. Since post-operative day 1, the protocol of oral celecoxib restarted until 3 weeks post-operative	Duloxetine 60 mg since pre-operative day 2 until post-operative day 14 (17days altogether) .	VAS pain score evaluated before surgery and at 2, 4, 6, 24, 36, 48h after surgery, and in days 2-7, 3 weeks and 3 months post-operative. Significant difference between duloxetine and placebo group in VAS pain score observed after 24h and 7 days post-operative (4.7 vs 5.9 and 2.1 vs 2.8, respectively)	Oral oxycodone or subcutaneous morphine if VAS> 6 or resistant pain occured. Patients in duloxetine group consumed signifcantly less opioids (24.2 vs 28.5 and 2.7 vs 4.1 mg after 24h and 7 days post-operative)

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Ho et al. 2010	Parallel group, double-blind, randomized, placebo-controlled trial	23 patients in doluxetine group (7 M, 16 F; mean age 65.2 ± 50-80) and 24 patients in placebo group (7 M, 17 F; mean age 65.7 ± (51-79)	Patients between the ages of 18-70 and of ASA physical status I – III	Knee replacement surgery	Acetaminophen 1 g every 6h	Duloxetine 60 mg 2 days before surgery and in the first post-operative day.	NRS pain score evaluated at 0.5, 1, 2, 6, 12, 24, and 48h after surgery. No significant differences observed between both groups.	Morphine 1 mg iv bolus. In duloxetine group consumed signifcantly less opioids (12.9 vs 19.8 and 19.5 vs 30.3 mg after 24 and 48h post-operative)
Castro-Alves et al. 2016	Prospective, randomized, placebo-controlled, double-blinded trial.	Patients with benign diseases. 31 patients in duloxetine group (mean age 42.4 ± 5,8) and 32 patients in placebo group (mean age 42.1 ± 4,6)	Female patients 18-64 years old, undergoing abdominal hysterectomy for benign (non-cancerous) diseases, ASA physical class I-III.	Abdominal hysterectomy	Ketoprofen 100 mg iv every 8h and metamizol 50 mg iv every 6h	Duloxetine 60 mg orally 2h before the surgery and at 24h after the surgical procedure	NRS pain score evaluated at rest and after asking patients to cough every 15 min. QoR-40 questionnaire pain section at 24 and 48h after surgery. Significant difference between duloxetine and placebo group in NRS score at rest and coughing was observed only at 24h after surgery (3 vs 5). Small difference also shown in QoR-40 questionnaire pain section (34 vs 31) after 24h post-operative	Morphine 1-2 mg IV to maintain NRS <4. In duloxetine group consumed signifcantly less opioids (1 vs 5.5 mg after 24h pos-toperative)
YaDeau et al. 2016	Randomizedplacebo-controlled, Ttiple-blinded trial	53 patients in duloxetine group (25 M, 28 F; mean age 67 ± 61-71) and 53 patients in placebo group (27 M, 26 F; mean age 63 ± (57–67)	Patients with osteoarthritis, English speakers, age 25-75, who were judged able to follow the protocol and who planned to have regional anaesthesia and to be discharged either to home or to a participating rehabilitation centre	Total knee arthroplasty	Meloxicam 7.5- 15 mg orally daily	Duloxetine 60 mg 30min before transfer to the operating theatre, and every next day up to and Including day 14 post-operative.	NRS score for pain with ambulation. No significant differences between duloxetine and placebo group in NRS pain score.	Oxycodone/ acetaminophen 5/325mg; 1-2 orally. Total opioid use was significantly reduced in the duloxetine group during the day of surgery through 3 months post-operatively (difference in means 8.7 mg oral morphine equivalents)
Koh et al. 2019	Prospective, randomized controlled study	40 aptients in duloxetine group (5 M, 35 F; mean age 69.1 ± 5.8) and 40 patients in placebo group (6M, 34 F; mean age 68.6 ± 9.5)	Patients >18 years old, assigned an ASA class of I, II, or III and were scheduled to undergo primary unilateral TKA for primary osteoarthritis of the knee.	Primary unilateral total knee arthroplasty	Celecoxib 200 mg and pregabalin 150 mg pre-operatively. 650 mg of acetaminophen every 12h for 6 weeks after the operation.	Duloxetine 30 mg 1 on the night before surgery, and every day for 6 weeks after surgery.	VAS pain score at rest, while walking, and at night was evaluated on post-operative days 1, 3, and 5, and at post-operative weeks 1, 2, 6, and 12. Patients in duloxetine group had significatnly lower results in VAS pain scores in all dimensions from 2-12 weeks after surgery.	Fentanyl iv pump 1 mL of a 100-mL mixture containing 2,000 µg of substance on demand. Once patients resumed oral intake: 1 mg of oxycodone every 12h for 7 days and 200 mg of celecoxib, 37.5 mg of tramadol, and 650 mg of acetaminophen every 12h for 6 weeks after surgery. There were no differences in analgesics intake between groups.

Study and year	Type of study performed	Characteristics of patients included in the analysis	Inclusion criteria and main disease	Type of surgery performed	Basic pain relief treatment	Characteristics of the intervention	Pain assesment	Additional pain treatment
JaDeau et al. 2022	Triple-blinded randomized controlled trial	For NRS analysis: 75 patients in duloxetine group and 73 in placebo group. For cumulative opioid use analysis: 80 patients in duloxetine group and 77 in placebo group. Characteristic after allocation: 40 M, 40 F; mean age 63 ± 11.0 in interevention group and 45M, 35 F; mean age 64 ± 7 in placebo group.	Patients with knee pain, English-speaking, age 25-75 years, scheduled to receive regional anaesthesia for primary TKA who were planning to be discharged home or to a participating rehabilitation facility.	Total Knee Arthroplasty	10 mg sustained-release oxycodone, and 15 mg meloxicam pre-operatively.	Duloxetine 60 mg the day before surgery and next 14 days.	NRS pain score at rest and movement evaluated pre-operatively and at 1, 2 and 14 days after surgery. Patients in duloxetine group showed non-inferiority in NRS pain scores compared to placebo.	For 14 days: 4 doses of 1,000 mg IV acetaminophen every 6h followed by 1,000 mg oral acetaminophen every 8h; 4 doses of 15 mg IV ketorolac followed by 15 mg meloxicam every 24h. 5-10 mg oral oxycodone when needed. There was significantly less opioid consumption in the duloxetine group compared to placebo (288 vs 432 mg of oral morphine equivalents).
Gerber et al. 2022	Prospective, randomized, double-blind placebo-controlled trial	25 patients in duloxetine group (14M, 11 F; mean age 46.08 ± 11.07) and 27 patients in placebo group (15 M, 12 F; mean age 50.41 ± 8.56).	Patients aged 18–65 years with symptomatic grades II through IV hemorrhoidal disease, scheduled for elective hemorrhoidectomy under subarachnoid anaesthesia.	Elective hemorrhoidectomy	Ketoprofen 100mg pre-operatively, ketoprofen 100mg at 12h intervals and dipyrone 2 g at 6h intervals for 48h post-operatively.	Duloxetine 60 mg, 2h before and 24h after surgery.	VAS pain score evaluated before surgery and after 12, 24, and 48 h post-operatively. VAS pain scores did not differ between duloxetine and placebo groups at 12, 24, and 48h after surgery.	Morphine 1 mg bolus iv on demand. Dipyrone 500mg for 7 days, nimesulide 100mg for 6 days and tramadol 100 mg. There was no between-group difference in cumulative morphine consumption at 12, 24 and 48h after surgery.
Altiparmak et al. 2018	Prospective double-blind randomized clinical trial with placebo	31 patients in duloxetine age (11 M, 20 F; mean age 53 ± 11) and 33 patients in placebo group (12 M, 21 F; mean age 54 ± 11)	Patients aged 18-65 years old, scheduled for an elective repair of lumbar disc herniation and with ASA status I-II	Unspecified elective surgery for lumbar intervertebral disc herniation	At the end of the surgery, administered intravenously tramadol at a dose of 1 mg/kg, and intravenous paracetamol at a dose of 1 g every 8h during the first day after surgery.	Duloxetine 60 mg 1h before the procedure. At 12h after surgery, administration of a placebo capsule, and at 24h another dose of duloxetine 60 mg.	Assessment of pain in the VAS at the following time points: first min, 30 min, 1h, and 12, 24, and 48h after urgery. Duloxetine intake resulted in a similar statistically significant reduction in pain at all time points compared to placebo.	If VAS is greater than or equal to 4, diclofenac intramuscularly at a dose of 75 mg. The time to administration of analgesics upon patient request was longer in the duloxetine group compared to placebo.
Hetta et al. 2021	Prospective double-blind randomized clinical trial with placebo	30 patients in duloxetine group (gender not provided; mean age 51.2 ± 10.4) and 30 patients in placebo group (gender not provided; mean age 52 ± 12.4)	Unspecified malignant tumour located in the abdominal cavity. Patients aged20-70, subjected to major abdominal cancer surgery and with American Society of Anesthesiologists (ASA) score I to II.	One of the following: Whipple's procedure, radical cholecystectomy, gastrectomy, unspecified major colorectal surgery, nephrectomy, hysterectomy or cystectomy	During surgery intravenously administered 50 µg of fentanyl as a bolus.	Experimental group: Oral administration of 60 mg duloxetine 2h before the procedure.	Assessment of pain intensity in VAS immediately after surgery and at 2, 4, 8, 12, 16, 24, 36, and 48h post-operatively. In duloxetine group, a reduction in post-operative pain intensity, as well as improved QoR-40 results	2 mg of morphine intravenously as a bolus. In duloxetine group decreased cumulative morphine requirement in the first 48h after surgery and extended time to the first patient request for morphine

Study and year	Type of study performed	Characteristics of patients included in the analysis	Inclusion criteria and main disease	Type of surgery performed	Basic pain relief treatment	Characteristics of the intervention	Pain assesment	Additional pain treatment
Nath et al. 2022	Prospective double-blind randomized clinical trial with placebo	30 patients (3 M, 27 F; mean age 32.3 ± 8.5) and 30 patients in placebo group (3 M, 27 F; mean age 35.1 ± 8.6)	Unspecified disease of gallbladder. Patients aged 18-50. Laparoscopic Cholecystectomy of American Society of Anesthesiologists (ASA) I or II, scheduled for general anaesthesia.	Radical laparoscopic cholecystectomy with the possibility of intraoperative conversion to open technique	1g of intravenously administered paracetamol 30min before the end of surgery.	Experimental group: Oral administration of 60 mg duloxetine 2h before the procedure.	Assessment of pain intensity in VAS immediately after surgery and at 15, 30 min, and 4, 8, and 12h post-operatively. A statistically significant reduction in pain intensity in duloxetine group immediately after surgery, as well as at 15, 30 min, 4, 8, and 12h post-operatively compared to placebo.	After surgery, 1g of intravenously administered paracetamol if VAS is greater than or equal to 4, up to a maximum dose of 4 grams per day. Alternatively, 50 mg of tramadol intravenously administered as a bolus. 3 mg of morphine administered intravenously. The requirement for the first and second doses of rescue analgesia was lower in the experimental group
Hetta et al. 2023	Prospective double-blind randomized clinical trial with placebo	30 patients in doluxetine group (13 M, 17 F; mean age 45.83 ± 10.4) and 30 patients in placebo group gender (10 M, 20 F; mean age 43.83 ± 6.4)	Patients aged 8-85 with ASA I-III, and, scheduled for laparoscopic colorectal surgery for cancer colon.	Laparoscopic resection of the large intestine	During surgery, r 25 µg of fentanyl administered intravenously as a bolus. At the end of surgery, 1g of intravenously administered paracetamol. After surgery, 1g of intravenously administered paracetamol every 8h	Experimental group: Oral administration of duloxetine at a dose of 60 mg 1h and 12h before surgery, as well as 24h after surgery	Assessment of pain intensity in VAS within the following time frames: 0-2h, 2-4h, 4-8h, 8-12h, 12–24h, 24-36h, and 36-48h after surgery. In the duloxetine group, lower VAS scores were demonstrated during the first 48h post-operatively, compared to the placebo group in all time intervals. Duloxetine group had statistically better post-operative recovery quality expressed in the QoR-40 scale than in the placebo group	3 mg of morphine administered intravenously. In the duloxetine group the requirement for intra-operatively administered fentanyl and proposed morphine for 48h after surgery was reduced.

Abdominal surgery and others. In the studies listed, the use of duloxetine has been investigated most frequently in cancerous colon resections. Among the two studies treating only this type of surgery, a positive effect of 60 mg of duloxetine given peri-operatively on pain reduction and morphine supply was observed in a group of patients with a mean age of 45.38, and baseline analgesic treatment containing initially a bolus of fentanyl and later 1 g of intravenous paracetamol [23]. In contrast, a positive effect, both in terms of pain and opioid supply, was not observed in a group of patients with a mean age of 62.73 years, and who received basic analgesic treatment based on 100 mg ketoprofen and 1 g dipyrone intravenously [24].

A study analyzing the effect of a single dose of 60 mg of duloxetine pre-operatively in a variety of abdominal surgeries (Whipple's procedure, radical cholecystectomy, colorectal surgery, gastrectomy, nephrectomy, cystectomy, and hysterectomy) showed its positive effect in terms of pain reduction and a lower supply of cumulative morphine [25]. However, in this case, the manner of the analysis performed and the fact that only a bolus of 50 μg of fentanyl was used as the primary analgesic treatment means that the results are not comparable with those of other works, and it is not possible to distinguish a specific group benefitting from the intervention used. The same intervention, also with positive results according to the analysis, was applied in the case of a radical cholecystectomy procedure, and in this instance, the primary pain treatment involved the administration of only a single medication in the form of 1 g of paracetamol intravenously just before the end of surgery [26].

Other procedures in which duloxetine has been used include hemorrhoidectomy and modified radical mastectomy. In the case of hemorrhoidectomy, 60 mg of duloxetine administered peri-operatively had no positive effect on pain reduction or additional opioid treatment; notably, the primary post-operative analgesia consisted of two drugs – 100 mg of ketoprofen and 2 g of dipyrone, at appropriate intervals [27]. Single administration of 60 mg and 90 mg duloxetine prior to mastectomy surgery may have a positive effect on reducing pain as measured by the VAS score, but at no more than 8h after surgery, with baseline pharmacotherapy based on 1 g of intravenous paracetamol. In addition, duloxetine significantly reduced the morphine supply in the group receiving duloxetine [28].

Based on the above results, the effectiveness of duloxetine depends on the type of surgery performed and the baseline pain treatment. With the multitude of options for selecting baseline pharmacotherapy, it is difficult to determine with which drug groups duloxetine can produce the most beneficial effects for patients, as noting that the weaker the baseline treatment, the stronger the effect of the intervention. In addition, the observed pain reduction usually persists for a maximum of the first 2 days after treatment, with minor exceptions in which the analgesic effect lasts longer. Importantly, from the point of view of physicians and the rest of the medical staff taking care of the patient, fewer doses of opioids are used, whose side-effects and interactions with other medications could affect the recovery process after surgery.

DISCUSSION

Duloxetine, together with venlafaxine, SSRIs, tricyclic antidepressants, pregabalin, and gabapentin (enacarbil or extended-release), is a first-line drug for the treatment of neuropathic pain [29]. Since, in addition to the somatic and visceral components, the neuropathic component is also an important element of pos-operative pain, multimodal analgesia using drugs with mechanisms of action other than classic analgesics is the optimal management strategy for patients after surgery [30]. Therefore, it is not surprising that there is increasing interest in duloxetine, whose potential as a component of post-operative analgesia has become the subject of numerous studies, systematic reviews, and meta-analyses.

A meta-analysis conducted by Branton et al. revealed a significant reduction in opioid consumption in the post-operative period (24 and 48h after surgery) in patients undergoing elective orthopaedic surgery in whom 60 mg of duloxetine was added peri-operatively. This resulted in a reduction in the incidence of nausea and vomiting, i.e. side-effects of opioids in this population, with an increase in the incidence of insomnia, another side-effect of duloxetine.

Although not all studies included in the analysis showed a statistically significant effect of the drug on reducing pain in the period in question, there was no increase in its intensity. The choice of orthopaedic procedures as the basis for conducting the review was not accidental, the authors draw attention to the dynamic increase in their number and the particularly frequent occurrence of severe post-operative pain in patients undergoing them. Among the limitations of their work, the authors mention the significant heterogeneity of the results, the low number of study participants, and the extensive scope of the analyzed operations [31].

The effectiveness of duloxetine was also assessed in patients who underwent total knee arthroplasty, one of the most common orthopedic procedures. Metaanalyses describing this topic indicate a significant reduction in opioid consumption in the first 24h after the procedure, and a favourable safety profile of the drug. Data on the analgesic effectiveness of duloxetine differ among the studies discussed: Yang et al. reported a significant reduction in pain in the range from three days to eight weeks after the procedure, while Zhou et al. noted the above effect only within the first 24h after surgery. In all the mentioned works, the authors pointed to the small amount of material available for analysis, and therefore reported the need to conduct further, large, well-designed RCTs [32–34]. In another meta-analysis assessing the effectiveness of duloxetine for post-operative pain control after total knee or hip arthroplasty, Jones et al. reported a reduction in opoid consumption 48 and 72h after surgery in patients taking the drug. In this group, a significant reduction in pain was also observed, lasting until the sixth week after surgery for pain assessed at rest and up to three months for pain assessed at movement. The main limitations of this work, according to the authors themselves, were the variable drug administration and placebo regimens used in the included studies [35].

A systematic review conducted by Harder et al., focusing on the treatment of neuropathic pain after orthopaedic surgery, also highlighted the beneficial effect of duloxetine used in the peri-operative period on reducing opioid consumption after the procedure. The authors suggest administering duloxetine

as an adjuvant drug at a dose of 60 mg, alongside gabapentin or pregabalin, to more effectively reduce pain and the need for opiates [36].

Two further meta-analyses assessing the effectiveness of duloxetine/SSNRIs in the treatment of post-operative pain in adult patients, confirmed the effect of these substances on pain reduction 24–48h after surgery. However, although the difference was statistically significant, the effect size was not clinically significant. Moreover, duloxetine increased the risk of dizziness and did not affect the incidence of PONV in the study population. In conclusion, the authors do not recommend the use of duloxetine for the treatment of post-operative pain or indicate that it can be used only for individual patients. The significant heterogeneity of the obtained results is among the limitations mentioned in both works [37, 38].

Regarding gynaecological procedures, a meta-analysis conducted by Baradwan et al. covering a wide range of gynecological laparoscopic procedures, favourably assessed the safety and effectiveness of duloxetine in patients undergoing these procedures. The limitations include the previously mentioned multitude of analyzed treatments [39]. Another study in this field, focusing on laparoscopic or open hysterectomy, did not reach any decisive conclusions about the routine use of the drug in this group of patients. Once again, the authors emphasized the need for further research, emphasizing the small amount of material available for analysis, the short duration of follow-up, and variable results as the most serious limitations of their work [40].

This literature review has both strengths and limitations. The adopted methodology and broad presentation of the problem are among the strengths of this work. Its most serious limitations are the restriction of the search for included studies to only one database, and the multitude of material that does not allow us to delve deeper into the presented issues.

CONCLUSIONS

The efficacy of duloxetine administration during the peri-operative period, aimed at alleviating post-operative pain, is contingent upon the nature of the surgical intervention and the therapeutic protocol employed. Given the findings of previous studies, definitive conclusions regarding the optimal duloxetine administration regimen for post-operative pain management remain elusive. Nonetheless, the documented benefits underscore the importance of pursuing additional research efforts, concentrated on determining its effectiveness across specific surgical procedures.

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