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REVIEW ARTICLE

EFFECT OF DULOXETINE ON PAIN RELIEF IN PATIENTS UNDERGOING ARTHROPLASTY SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

Duloxetine is a dual reuptake inhibitor of norepinephrine and serotonin. Serotonin or 5-hydroxytryptamine acts by affecting a wide range of receptors, including the 5-HT2A receptor, which plays a role in modulating neuropathic or inflammatory pain. This systematic review was aimed to consider the effect of duloxetine on reducing the pain in patients undergoing arthroplasty surgery. Articles with key words "Pain, Duloxetine, Postoperative pain, Total knee arthroplasty, Arthroplasty" were searched in four international databases *PubMed, Scopus, Science Direct, and Web of Science*. Nine articles which fulfilled the inclusion/exclusion criteria were selected of which 3 were conducted in *China*, 3 in *Korea*, 1 in *Netherlands*, and 2 in the USA. In three studies duloxetine was used in a dose of 30 mg, while in all other studies 60 mg was used. In all reviewed articles (except for the two), duloxetine reduced the pain of total knee arthroplasty patients. It is therefore recommended to prescribe this drug to reduce the pain in these patients, while recommending more studies in this field.

KEYWORDS: Duloxetine; Pain; Arthroplasty surgery; Total knee arthroplasty.

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INTRODUCTION

Duloxetine is a drug with molecular formula of *C18H-19NOS*, *PubChem CID* 60835, volume of distribution approximately 1640 liters, molecular weight approximately 297.4, elimination half-life approximately 10 to 12 hours, create time on 2005-06-24, with synonyms such as *(S)-Duloxetine, Yentreve, Cymbalta, LY 248686, UNII-O5TNM5N07U, Duloxetine (INN), Yentreve (TN), Duloxetine [INN: BAN] and (S)-Duloxetine; LY248686,* which are just a few examples of synonyms related to *Duloxetine*. The plasma concentration of approximately 47 to 110 ng/ml is obtained for about 6 hours after taking this drug.[1]

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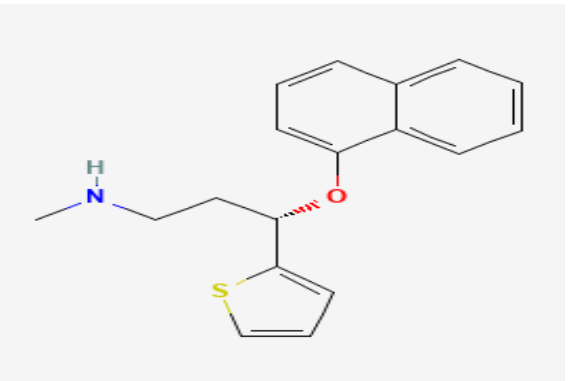

Figure 1: Chemical backbone of duloxetine.

Duloxetine is a dual reuptake inhibitor of norepinephrine (NE) and serotonin or 5 hydroxytryptamine (5-HT). Serotonin acts by affecting a wide range of receptors, including the 5-HT2A receptors, which play a role in modulating the neuropathic pain. NE and 5-HT are neurotransmitters that are effective in pain control. Inhibiting their reuptake results in reducing the pain signals in the spinal cord with resultant analgesia.[2-9] Duloxetine was discovered in 1993 and approved by the FDA in 2004 for the treatment of depression and is currently used to control

all types of pains including the diabetic neuropathy, knee osteoarthritis, chemotherapy, fibromyalgia, low back pain and orthopedic surgeries.[10-15]

The surgical processes whether diagnostic or therapeutic are associated with pain in many patients. Knee arthroscopy plays an important role in the diagnosis and intervention in a wide range of knee diseases. Total knee arthroplasty (TKP) is an invasive procedure and patients experience pain during or after the operation.[16] Management of the resulting pain with drug therapy is one of the most important measures.[17] Chronic diseases create different challenges for patients. Pain management in all patients, especially after surgery, is an important issue in order to improve the daily activities, patient comfort, & satisfaction and early discharge from the hospital. It has also been shown that the patients' pain is related to the state of self-efficacy and religious coping which has an impact on it.[18-23] Knee pain in the elderly has a high prevalence in the world and especially Iran will face major challenges in the field of aging and also the prevalence of chronic diseases in the coming years.[24-26] Various medicines can reduce the pain but which drug can reduce the pain to what extent requires research. Conducting interventional studies and review studies can be a guide in this matter.[27]

This systematic review was conducted to consider the effect of duloxetine on reducing the pain in patients undergoing arthroplasty surgery.

MATERIALS AND METHODS

This systematic review was carried out in five steps in 2022. The first step was preparation of research question (What is the effect of duloxetine on TKA pain?). The second step was to select suitable keywords from the MeSH and determine the search strategies. The key words selected were "Pain", "Duloxetine", "Postoperative pain", "Total knee arthroplasty", and "Arthroplasty." The third step was the inclusion and exclusion criteria. Articles being interventional, published in English and in the time frame of 2000 to 2022 were included. Repetitiveness, congress articles, letters to the editor, and reviews were the exclusion criteria. The fourth step was to conduct a search in the international medical databases *PubMed, Scopus, Science Direct and Web of Science*, which was carried out by two researchers familiar with the subject and the purpose of research (one week apart and individually). Finally, the last step of research was to select the articles and enter in the systematic review phase.

RESULTS

The titles and abstracts of 791 articles were reviewed. Based on inclusion/exclusion criteria only nine articles among these were included in the systematic review.

Among these nine studies, three were from *China*, three from *Korea*, one from *Netherlands*, and two from the USA.

All these studies were randomized controlled trials (RCTs) and placebo was used for control group except in the two by *Wang et al* (2020)[28] where the control group received celecoxib and Kim et al (2021)[31] where the control group received the opioid.

In two of these studies, *Kim et al* (2021)[29], and *Kim et al* (2021)[31], duloxetine was used at a dose of 30 mg, while in the rest of the studies a dose of 60 mg was used.

As per these RCTs duloxetine was effective in pain control in total knee arthroplasty patients except the two, *Rienstra et al* (2021)[32] from the *Netherlands* and *YaDeau et al* (2016)[33] from the USA.

Salient features of all these trials are given below. (Table 1)

Table 1: Specifications of studies of duloxetine included in the systematic review.

No.	Author	Country	Design	Number of patients	Duration	Intervention		Outcome
						Experimental	Control	
1	YaDeau et al (2022)[34]	USA	RCT	160	From the day of surgery to 14 days postoperatively.	Duloxetine 60 mg	Placebo	Duloxetine was noninferior to placebo for both primary outcomes and was superior to placebo for opioid consumption. Opioid consumption was 288±226 mg OME [94, 385] vs 432±374 [210, 540] (duloxetine vs placebo) P=.003. Pain scores on day-14 were 4.2±2.0 vs 4.8±2.2 P=0.01. Median satisfaction with pain management was 10 (8, 10) and 8 (7, 10) P=0.04. Duloxetine reduced interference by pain with walking, normal work, and sleep.

2	Li et al (2021)[35]	China	RCT	96	From 2 days preoperative to 14 days postoperatively	Duloxetine 60 mg	Placebo	Patients in the duloxetine group had significantly lower pain severity scores upon movement within 3 postoperative weeks ($p<0.05$) while none of the differences met the minimum clinically important difference. Moreover, patients in duloxetine group performed better in terms of resting pain (in 3 weeks after surgery), morphine requirements, and satisfaction level at discharge (all $p<0.05$). There was no difference between groups in the prevalence of adverse events.
3	Weng et al (2020)[28]	China	RCT	60	From the first day postoperative day for 4 weeks	Duloxetine 30 mg BD	Celecoxib 200 mg BD	There was no significant difference in VAS score between groups on postoperative day-3 but duloxetine was superior to celecoxib group at weeks 1, 2, and 4 ($p<0.05$). HAMD-17 scores in both groups decreased at week-4 compared to preoperative values ($p<0.05$), but duloxetine group's score was superior to celecoxib 4 weeks postoperatively ($P<0.05$). WOMAC pain scores of duloxetine group were superior to celecoxib ($P<0.05$) at weeks 1, 2 and 4. There was no significant difference in the incidence of adverse events.
4	YaDeau et al (2016)[33]	USA	RCT	106	From the day of surgery for 15 days	Duloxetine 60 mg	Placebo	On day 14, duloxetine had no effect on pain with ambulation; mean pain was 3.8 (SD, 2.3) for placebo versus 3.5 (SD, 2.1) for duloxetine (difference in means [95% CI], 0.4 [-0.5 to 1.2]; $P=0.38$). Symptoms potentially attributable to duloxetine discontinuation at study drug completion (nausea, anxiety) occurred among nine patients (duloxetine) and five patients (placebo); this was not statistically significant ($P=0.24$). Statistically significant secondary outcomes included opioid consumption (difference in mean mg oral morphine equivalents [95% CI], 8.7 [3.3 to 14.1], $P=0.002$ by generalized estimating equation) over the postoperative period and nausea on day 1 ($P=0.04$). There was no difference in other side effects or in anxiety and depression scores.

5	Yuan et al (2022)[36]	China	RCT	100	Two days before surgery to 14 days afterwards	Duloxetine 60 mg	Placebo	The rVAS in duloxetine group were significantly less than placebo group throughout the postoperative period: 4.7±2.3 vs 5.9±2.6 (P = 0.01) at 24 h postoperative; 2.1±1.6 vs 2.8±1.7 (P=0.03) at 7 days postoperative. In terms of aVAS, similarly, duloxetine group had less aVAS than placebo throughout postoperative period: 6.2±2.1 vs 7.1±2.2 (P=0.03) at 24 h postoperative; 3.3±1.7 vs 4.1±2.0 (P=0.03) at 7 days postoperative. Patients in duloxetine group consumed significantly less opioids per day than placebo group: 24.2±10.1 g vs 28.5±8.3 g (P=0.02) at 24 h postoperative; 2.7±2.5 g vs 4.1±2.6 g (P=0.007) at 7 days. aROM in duloxetine group were significantly better than placebo group until day 6, the aROM became comparable between the two groups: 110.2±9.9 in duloxetine group vs 107.5±11.5 in control group (P=0.21). In terms of pROM, duloxetine group had significantly better pROM until postoperative day 5, the pROM became comparable between two groups: 103.8±12.1 in duloxetine group vs 99.5±10.8 in control (P=0.06). No significant difference was found between two groups in the rates of dizziness, bleeding, sweating, fatigue and dryness of mouth. In placebo group, more patients got nausea/vomiting and constipation (P<0.05). However, in terms of drowsiness, duloxetine group was reported higher rate (P<0.05).
6	Kim et al (2021)[31]	Korea	RCT	944	6 weeks	Duloxetine 30 mg	Opioid	There was no significant difference in pain VAS score, WOMAC Pain and Function score, at each time point between before and after surgery (all p>0.05). Fifteen (9.8%) patients in opioid group and 6 (4.4%) in duloxetine group were prescribed additional medication after first 6 weeks, showing no significant (p>0.05) difference in proportion. The 30-day readmission rate and incidence of side effects were also similar (p>0.05). There was no difference in the incidence of side effects between the two groups (p>0.05).

7	Kim et al (2021)[29]	Korea	RCT	39	From 2 weeks to 8 weeks after surgery	Duloxetine 30 mg	Placebo	Duloxetine group reported significantly lower pain VAS scores during follow-up periods up to 6 weeks after surgery (all $p < 0.05$). BPI interference also showed significantly superior results in the duloxetine group ($p<0.05$). Although there was no difference in the rate of wound complications between the two groups ($p>0.05$), duloxetine group showed significantly lower wound temperature than placebo during follow-up period ($p<0.05$).
8	Koh et al (2019)[30]	Korea	RCT	80	One day before surgery to 7 weeks	Duloxetine 60 mg	Placebo	Patients in the duloxetine group had better performance across pain metrics during initial 2 to 12-week postoperative period ($p<0.05$). Duloxetine group also had a superior quality of recovery 2 weeks after TKA, as indicated by emotional & physical functioning ($p<0.05$). There was no difference between groups in the prevalence of adverse events.
9	Rienstra et al (2021)[32]	Netherlands	RCT	111	Seven weeks	Duloxetine 60 mg	Placebo	Mean improvement in the KOOS/HOOS pain subscale at 6 months postoperatively was 37 (SD 28.1) in intervention group and 43 (SD 26.5) in control group. No statistically significant difference was found in change score 6 months postoperatively between the two groups ($p=0.28$). 12 patients from intervention group (21%) discontinued duloxetine due to adverse effects.

DISCUSSION

Pain relief is the most important issue in arthroplasty surgery. Pain plays an important role in the quality of life.[37] In a study by Lian et al the prevalence of pain after surgery in TKA patients was 12.1% at rest and 37.7% at movement.[38] In a study by *George et al*[39] the rates of high impact pain (95% CI) was comparable for shoulder 7.6-16.3%, knee 9.8-13.3%, and hip 8.3-11.8%.[39]

Duloxetine has been used in various studies to reduce the pain. In the *Hatfi et al* review study on the effect of duloxetine on pain of spinal surgery patients, 6 interventional articles were included, which showed that duloxetine reduced the pain of these patients.[40] In a meta-analysis by *Lunn et al* (2014), duloxetine reduced diabetic neuropathy pain at 12 weeks and fibromyalgia pain at 12 and 28 weeks.[12] In the study by *Oliveira Filho et al* (2020), duloxetine reduced the pain caused by surgery at 24 and 48 hours after the operation.

Regarding the adverse effects duloxetine had no effect on headache, dizziness, itching and nausea after surgery.[41] In the meta-analysis by *Weng et al* (2020), duloxetine reduced the patient's 24-hour pain, improved performance and quality of life.[42]

Various drugs have been used to reduce TKA pain, such as dexamethasone[43], Celecoxib[44], and liposomal bupivacaine.[45] In a study by *Li et*

al, dexamethasone was used in TKA pain, with a volume of 496 patients and dexamethasone reduced patients' pain in 48 hours after the operation.[43] In a study by *Geng et al* (2022)[44] which examined 593 patients, celecoxib reduced the pain of TKA at 24 and 72 hours after the operation.[44] *Zhao et al* study (2019)[45] examined 12 articles and found that liposomal bupivacaine reduced the pain.[45]

CONCLUSION

In all reviewed articles (except for the two), duloxetine reduced the pain of total knee arthroplasty patients. It is therefore recommended to prescribe this drug to reduce the pain in these patients, while recommending more studies in this field.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	AK, HK
Acquisition, Analysis or Interpretation of Data:	AK, HK
Manuscript Writing & Approval:	AK, HK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.