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Review Article

Duloxetine for Postoperative Pain in Orthopedic Surgeries: A Review Article

Alireza Nankali[1], Maryam Sabouri[2], Hediye Gholamshahi[3,*]

[1] Resident, Orthopedic Subspeciality Research Center (OSRC), Tehran University of Medical Sciences, Tehran, Iran
[2] Surgical Technologist, Surgical Research Society (SRS), Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3] Medical Student, Orthopedic Subspeciality Research Center (OSRC), Tehran University of Medical Sciences, Tehran, Iran

[*]Corresponding author: Hediye Gholamshahi; Orthopedic Subspeciality Research Center (OSRC), Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-21-66348500
Email: hediye.gholamshahi@gmail.com

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Abstract

Postoperative pain plays a key role in patients' satisfaction. Since opioids may cause dependence and have a high abuse rate, non-opioid drugs such as duloxetine are being investigated for their effect in this matter. This review investigated the pharmacokinetics and the effects of duloxetine on postoperative pain after orthopedic surgeries. Duloxetine is a dual serotonin and norepinephrine reuptake inhibitor that causes a synergistic effect and can help manage postoperative pain. For this cause, it is prescribed as 60 mg per day. There have been studies in recent years proving its effectiveness both in total hip and knee arthroplasties and elective surgeries. The collective data show that duloxetine can be used for postoperative pain management, and with minimal side effects, it can lower opioid usage and dependence. However, considering duloxetine side effects including gastrointestinal (GI) disturbances (nausea, constipation), dry mouth, and loss of appetite, and the limitations of current literature, further studies need to be conducted.

Keywords: Duloxetine Hydrochloride; Orthopedics; Pain Management

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Background

Orthopedic surgeries cover a wide array of procedures from arthroplasties to fracture fixations, which all entail significant changes in the quality of life. Inadequate pain control has a major impact on patient satisfaction and translates to prolonged recovery time, lower functional outcomes, as well as less overall satisfied patients. Opioid medications have traditionally been the standard for the management of postoperative pain based on their effectiveness. Yet, the opioid crisis has forced people to consider other ways of managing pain –an important factor in strategies that reduce dependence and abuse.

In recent times, this has changed as non-opioid analgesics have been identified and introduced for postoperative pain management that not only alleviate the unbearable agony of patients but also decrease the chances of unintended side effects and addiction (1). Multiple studies have investigated the effectiveness of non-opioid medications including nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, and antidepressants for postoperative pain management (2). Magni has shown that gabapentin reduces opioid use after surgery (3). Hah also showed that perioperative administration of gabapentin had no effect on postoperative pain resolution, but it had a modest effect on promoting opioid cessation after surgery (4).

Duloxetine has now garnered significant interest as a potential addition to our non-opioid options, reflecting dual reuptake inhibition in both serotonin and norepinephrine (5). Being one of the few options that has been shown to have an analgesic effect on neuropathic pain, as opposed to just mood and anxiety disorders for which it is traditionally used, duloxetine may thus be ideal in postoperative pain control. This is in line with previous studies including Noshahr et al., who showed that duloxetine might decrease the need for opioids when included as part of multimodal pain management (6).

The current study explores the pharmacokinetics and targeted effects of duloxetine on postoperative pain series following orthopedic surgeries. Our focus differs from previous work on chronic pain conditions or the overall surgical population. The reasons for this are clear, given that orthopedic surgery often involves significant local tissue trauma, and post-op pain management is essential to ensure an uneventful recovery (7). As such, examination of duloxetine in this context may be beneficial to elucidate its potential advantages for reducing opioid requirements and improving pain control or other aspects related to patient recovery within an orthopedic framework.

Duloxetine's Mechanism of Action and Drug Interactions

Duloxetine is a dual serotonin and norepinephrine reuptake inhibitor, and it first received approval from the United States (US) Food and Drug Administration (FDA) in August 2004 (Figure 1).

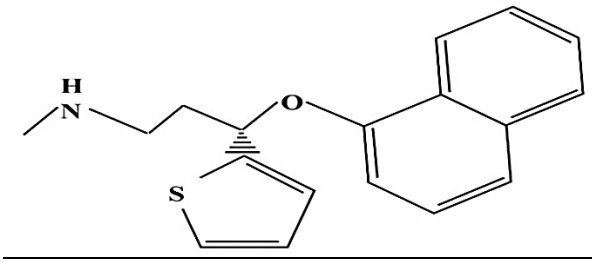

Figure 1. The biochemical structure of duloxetine

It is widely prescribed for three indications, including major depressive disorder (MDD), peripheral diabetic neuropathy pain, and female stress urinary incontinence. Norepinephrine and serotonin are proven to have a

synergistic effect on reducing pain in both acute and chronic conditions (8, 9). In terms of pharmacokinetics, duloxetine reaches the monoamine receptors 2 hours after ingestion. This drug's protein binding is more than 90%, and its metabolism is mainly hepatic by multiple oxidative pathways, conjugation, and methylation. Duloxetine's half-life is about 12 hours, after which it is excreted from both the kidneys (70%) and the gastrointestinal (GI) system (20%) (10).

Since duloxetine has a high protein binding rate, administrating it with other drugs that share this trait will result in decreased effects due to the competition for binding sites. Due to the hepatic pathway of metabolism, duloxetine should not be prescribed with CYP1A2 inhibitors (theophylline, cimetidine, clozapine, etc.) or nonselective, irreversible monoamine oxidase inhibitors (phenelzine, tranylcypromine, etc.).

Dosing and Side Effects

Duloxetine capsules are available in four different dosages, including 20, 30, 60, and 120 mg. The 60 mg capsules are mostly used once a day for pain relief (11). While duloxetine is generally well-tolerated, it is associated with several adverse effects, including GI disturbances (nausea, constipation), dry mouth, and loss of appetite.

These side effects are generally dose-dependent, increasing in frequency with higher doses such as 60 mg to 120 mg per day, which are typical in pain management. Patients often report GI issues, including nausea, which is one of the most common complaints, along with mild somnolence and headaches. Although serious adverse effects are rare, approximately 12% of patients discontinue duloxetine due to these side effects, which underscores the need for careful patient monitoring during its use. Some patients experience elevated blood pressure, fatigue, or sweating, which may complicate postoperative recovery in orthopedic settings (12, 13).

Pain Control in Total Joint Arthroplasty

In a study conducted by YaDeau et al. in 2022 on 160 patients undergoing total knee arthroplasty (TKA), 60 mg of duloxetine was administered daily from the surgery date till 14 days after surgery. Opioid use was 29% lower compared with the placebo group (which in numbers means 17 fewer 5mg oxycodone pills were used), and no increase in pain scores occurred (14).

A study by Koh et al. also assessed the effect of duloxetine on post-TKA pain and found that 30 mg capsules once a day for six weeks caused significantly better patient performance and a higher recovery rate (15).

In addition, Li et al. conducted a study on 96 patients undergoing total hip arthroplasty (THA) surgery (16). Patients were divided into two groups, including duloxetine receivers and placebo receivers. The duloxetine group received 60 mg of duloxetine daily from two days before the operation to 14 days after the operation. This intervention reduced the postoperative pain of the patients for three weeks after the operation and the need for narcotics in the first 48 hours.

Interestingly, in 2021, Rienstra et al. conducted a randomized controlled trial (RCT) and found that 60 mg of duloxetine for six months had no significant effect on the patients' outcomes (17).

Finally, a 2023 systematic review and meta-analysis by Jones et al. found that duloxetine reduced postoperative opioid use in hours 48 and 72 and reduced the visual analog scale (VAS) for pain at rest score in days 3, 7, and 6 weeks post-surgery (18).

Pain Control in Elective Surgeries

A study in 2017 on spine fusion patients concluded that the use of 60 mg of duloxetine one hour before surgery and 24 hours after the surgery was effective in reducing the need for fentanyl in the first 48 hours after surgery (19).

In a study conducted by Su et al. in 2022 on patients undergoing arthroscopic rotator cuff repair surgery (20), patients were divided into two groups: one group received duloxetine, and the other group received placebo. Pain at 48 hours postoperatively was significantly lower in the duloxetine group but did not result in a reduction in opioid use.

In 2018, Altiparmak et al. conducted a study on patients with lumbar disc herniation and concluded that the use of 60 mg of duloxetine one hour before surgery and 24 hours after surgery was as effective as pregabalin in reducing postoperative pain (21).

In another clinical trial conducted by Otsuki et al., 35 patients undergoing high tibial osteotomy surgery in Japan were analyzed. They determined that daily consumption of 40 mg of duloxetine two weeks before and after the surgery was effective in reducing postoperative pain and the need for NSAIDs (22). A summary of the included studies is presented in table 1.

Limitations of Current Literature and Future Prospects

Despite the promising results associated with duloxetine, limitations in the current literature must be acknowledged. Many studies have small sample sizes, varying methodologies, and differing dosages, which complicate the interpretation of results. Furthermore, the long-term effects of duloxetine on postoperative pain management remain inadequately explored. Future research should focus on larger, multicenter trials to establish standardized dosing regimens and assess the long-term efficacy and safety of duloxetine in diverse surgical populations.

Conclusion

Duloxetine presents a viable option for postoperative pain management in orthopedic surgeries, demonstrating the potential to reduce opioid consumption and improve patient outcomes. However, the associated side effects and limitations in the current literature necessitate a cautious approach to its use. Further studies are essential to elucidate duloxetine's role in postoperative pain management and to establish comprehensive guidelines for its application in clinical practice.

Conflict of Interest

The authors declare no conflict of interest in this study.

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Table 1. Summary of included studies

Study	Year	Sample size	Intervention	Outcome measures	Key findings
YaDeau et al. (14)	2022	160	60 mg duloxetine	Opioid use, pain scores	29% reduction in opioid use
Koh et al. (15)	2019	N/A	30 mg duloxetine	Recovery rate	Improved recovery
Rienstra et al. (17)	2021	N/A	60 mg duloxetine	Patient outcomes	No significant effect
Bedin et al. (19)	2017	N/A	60 mg duloxetine	Fentanyl use	Reduced fentanyl requirements
Su et al. (20)	2022	N/A	Duloxetine vs. placebo	Pain scores	Lower pain but no opioid reduction

N/A: Not available

References

1. Martinez V, Beloeil H, Marret E, Fletcher D, Ravaud P, Trinquart L. Non-opioid analgesics in adults after major surgery: Systematic review with network meta-analysis of randomized trials. *Br J Anaesth*. 2017;118(1):22-31. doi: 10.1093/bja/aew391. [PubMed: 28039239].
2. Eckhard L, Jones T, Collins JE, Shrestha S, Fitz W. Increased postoperative dexamethasone and gabapentin reduces opioid consumption after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2019;27(7):2167-72. doi: 10.1007/s00167-019-05449-8. [PubMed: 30826856].
3. Magni G. The use of antidepressants in the treatment of chronic pain. A review of the current evidence. *Drugs*. 1991;42(5):730-48. doi: 10.2165/00003495-199142050-00002. [PubMed: 1723371].
4. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J, et al. Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort: A Randomized Clinical Trial. *JAMA Surg*. 2018;153(4):303-311. doi: 10.1001/jamasurg.2017.4915. Erratum in: *JAMA Surg*. 2018;153(4):396. doi: 10.1001/jamasurg.2018.0004. Erratum in: *JAMA Surg*. 2022;157(6):553. doi: 10.1001/jamasurg.2022.1392. [PubMed: 29238824]. [PubMed Central: PMC5933381].
5. Carter NJ, McCormack PL. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. *CNS Drugs*. 2009;23(6):523-41. doi: 10.2165/00023210-200923060-00006. [PubMed: 19480470].
6. Noshahr RM, Kouhestani E, Dibamehr M, Alshohaib M. The effect of duloxetine on postoperative pain and opium consumption in spine surgery: A systematic review. *N Am Spine Soc J*. 2024;17:100303. doi: 10.1016/j.xnsj.2023.100303. [PubMed: 38235484]. [PubMed Central: PMC10793159].
7. Gessner DM, Horn JL, Lowenberg DW. Pain management in the orthopaedic trauma patient: Non-opioid solutions. *Injury*. 2020;51(Suppl 2):S28-S36. doi: 10.1016/j.injury.2019.04.008. [PubMed: 31079833].
8. Briley M, Moret C. Treatment of comorbid pain with serotonin norepinephrine reuptake inhibitors. *CNS Spectr* . 2008;13(7 Suppl 11):22-6. doi: 10.1017/s1092852900028285. [PubMed: 18622371].
9. Rosenberg MB, Carroll FI, Negus SS. Effects of monoamine reuptake inhibitors in assays of acute pain-stimulated and pain-depressed behavior in rats. *J Pain*. 2013;14(3):246-59. doi: 10.1016/j.jpain.2012.11.006. [PubMed: 23332494]. [PubMed Central: PMC3743421].
10. Jost W, Marsalek P. Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus. *Clin Auton Res*. 2004;14(4):220-7. doi: 10.1007/s10286-004-0197-8. [PubMed: 15316838].
11. Pergolizzi JV, Raffa RB, Taylor, Rodriguez G, Nalamachu S, Langley P. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract*. 2013;13(3):239-52. doi: 10.1111/j.1533-2500.2012.00578.x. [PubMed: 22716295].
12. Wernicke JF, Gahimer J, Yalcin I, Wulster-Radcliffe M, Viktrup L. Safety and adverse event profile of duloxetine. *Expert Opin Drug Saf*. 2005;4(6):987-93. doi: 10.1517/14740338.4.6.987. [PubMed: 16255658].
13. Polychroniou PE, Mayberg HS, Craighead WE, Rakofsky JJ, Aponte R, V, Haroon E, et al. Temporal profiles and dose-responsiveness of side effects with escitalopram and duloxetine in treatment-naive depressed adults. *Behav Sci (Basel)*. 2018;8(7). doi: 10.3390/bs8070064. [PubMed: 30018196]. [PubMed Central: PMC6071033].
14. YaDeau JT, Mayman DJ, Jules-Elysee KM, Lin Y, Padgett DE, DeMeo DA, et al. Effect of Duloxetine on Opioid Use and Pain After Total Knee Arthroplasty: A Triple-Blinded Randomized Controlled Trial. *J Arthroplasty*. 2022;37(6S):S147-S154. doi: 10.1016/j.arth.2022.02.022. [PubMed: 35346549].
15. Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, In Y. Duloxetine reduces pain and improves quality of recovery following total knee arthroplasty in centrally sensitized patients: A prospective, randomized controlled study. *J Bone Joint Surg Am*. 2019;101(1):64-73. doi: 10.2106/JBJS.18.00347. [PubMed: 30601417].
16. Li H, Zeng WN, Ding ZC, Yuan MC, Cai YR, Zhou ZK. Duloxetine reduces pain after Total hip arthroplasty: a prospective, randomized controlled study. *BMC Musculoskelet Disord*. 2021;22(1):492. doi: 10.1186/s12891-021-04377-4. [PubMed: 34049519]. [PubMed Central: PMC8161627].
17. Rienstra W, Blikman T, Dijkstra B, Stewart R, Zijlstra W, van Raaij T, et al. Effect of preoperative duloxetine treatment on postoperative chronic residual pain after total hip or knee arthroplasty: a randomized controlled trial. *BMJ Open*. 2021;11(11):e052944. doi: 10.1136/bmjopen-2021-052944. [PubMed: 34732491]. [PubMed Central: PMC8572398].
18. Jones IA, Talehakimi A, Murphy LS, Wang JC, Piple AS, Christ AB, et al. Duloxetine for postoperative pain control following knee or hip replacement: A systematic review and meta-analysis. *Arthroplast Today*. 2023;20:101097. doi: 10.1016/j.artd.2023.101097. [PubMed: 36852213]. [PubMed Central: PMC9957748].
19. Bedin A, Caldart Bedin RA, Vieira JE, Ashmawi HA. Duloxetine as an analgesic reduces opioid consumption after spine surgery: A randomized, double-blind, controlled study. *Clin J Pain*. 2017;33(10):865-9. doi: 10.1097/AJP.0000000000000471. [PubMed: 28002096].
20. Su P, Pang L, Li S, Sun W, Zhao Y, Fu W, et al. Evaluation of analgesic efficacy and opioid-sparing effect of duloxetine after arthroscopic rotator cuff repair: A randomized clinical trial. *Clin J Pain*. 2022;38(5):328-33. doi: 10.1097/AJP.0000000000001032. [PubMed: 35413023].
21. Altiparmak B, Guzel C, Gumus DS. Comparison of preoperative administration of pregabalin and duloxetine on cognitive functions and pain management after spinal surgery: A randomized, double-blind, placebo-controlled Study. *Clin J Pain*. 2018;34(12):1114-20. doi: 10.1097/AJP.0000000000000640. [PubMed: 30020088].
22. Otsuki S, Okamoto Y, Ikeda K, Wakama H, Okayoshi T, Neo M. Perioperative duloxetine administration reduces pain after high tibial osteotomy and non-steroidal anti-inflammatory administration: A prospective, controlled study. *Knee*. 2022;38:42-9. doi: 10.1016/j.knee.2022.07.006. [PubMed: 35908360].