General

Antineuropathic Pain Management After Orthopedic Surgery: A Systematic Review

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Background

The opioid crisis has become a present concern in the medical field. In an effort to address these complications, antineuropathic pain medications have been considered as alternatives to prescribed opioids.

Objective

This review focuses on the analgesic effects of neuromodulators, such as gabapentin, duloxetine, and pregabalin, that provide room for less dependence on narcotic analgesics following orthopedic surgery.

Methods

During the database searches, 1,033 records were identified as a preliminary result. After duplicates were removed, an initial screen of each article was completed which identified records to be removed due to absence of a full-text article. Articles were excluded if they were not either prospective or retrospective, showcased an irrelevant medication (such as tricyclic antidepressants) which are not pertinent to this review, or deemed to be unrelated to the topic.

Results

Ultimately, 19 articles were selected. Three different drugs, gabapentin, pregabalin, and duloxetine, were analyzed to compile data on the effectiveness of preventing opioid overuse and addiction following hand surgery. This review identifies potential evidence that peri-operative gabapentin, pregabalin, and duloxetine administration decreases post-operative pain and lowers opioid dependency.

Conclusion

Gabapentin, pregabalin, and duloxetine have potential to further decrease post-operative pain and lower opioid dependency. This review creates an opening for further research in hand surgery to assess an updated protocol for pain management to reduce opioid dependency.

INTRODUCTION

Surgeries involving the musculoskeletal system are some of the most painful, yet common procedures performed in the United States. According to a 2013 study, the 40 procedures with the highest pain scores included 22 orthopedic/trauma procedures on the extremities.[1] Thus, managing post-surgical pain is a critical part of orthopedic care and opioids have been a traditional tool used in the early post-operative period. Despite their efficacy in treating pain, opioids are known source of abuse, addiction, and overdose related death. In general, 21 to 29 percent of patients misuse the opioids that they are prescribed, and 8 to 12 percent of patients develop an opioid addiction.[2] Accordingly, overdose deaths involving opioids have continued to rise in the US, with 68,630 deaths reported in 2020.[3] Synthetic opioids other than methadone have been the dominant factor in deaths with rates increasing from 1.0 per 100,000 in 2013 to 11.4 per 100,000 in 2019.[3]

Orthopedic surgeons are the third highest prescribers of opioids in the US.[4] This is likely to do with the high level of pain associated with orthopedic procedures, however, a recent prospective evaluation of opioid use following upper-extremity procedures found that patients are being prescribed approximately three times more opioid medications than needed.[5] This is problematic as it has been

shown that patients initially prescribed more medication (30 tablets versus 10), used significantly more opioids, had significantly more leftover medication, and were three times more likely to still be taking opioids at their follow-up appointment.[6] Furthermore, increased opioid use has actually been correlated with less pain relief and greater pain intensity following orthopedic surgery.[7] Therefore, identifying alternative methods to manage postoperative pain has become an area of active research.[8]

With the current opioid epidemic, attention has shifted to a multimodal analgesic approach to minimize unnecessary opioid consumption. Multimodal analgesia is the use of multiple medications with different mechanisms of action, with the goal of improving pain relief with less side effects compared with a single class of medication.[9] Antineuropathic pain medications have become increasingly considered as part of a multimodal analgesic approach as they work by reducing the excitability of neurons in the peripheral nervous system and/or by modulating the activity of ion channels in the central nervous system.[10] This review focuses on the analgesic effects of three neuromodulators, gabapentin, duloxetine, and pregabalin, as these are commonly prescribed and have a wide oral availability. Gabapentin and pregabalin were chosen as they have been approved by the FDA for pain control. Additionally, duloxetine, an SNRI that is FDA approved for pain control, was chosen as an adjunct to the two above medications listed. Due to a lack of federal approval for pain management or a nonspecific mechanism of action, other medications such as venlafaxine and TCA's, respectively, were not compared within this study.

ANTINEUROPATHIC MEDICATION OVERVIEW

Gabapentin, a neuromodulator most commonly prescribed to treat neuropathic pain, was initially approved as an anticonvulsant in the mid 1990's.[9] Gabapentin works by blocking voltage-gated calcium channels by binding to the α2-δ subunit and reducing calcium influx.[9] By blocking calcium influx, gabapentin reduces the release of glutamate and substance P from primary nociceptive afferents, thereby modulating nociceptive transmission.[11] Common side effects of gabapentin include dizziness, somnolence, peripheral edema, and gait disturbance.[12]

Pregabalin is a newer gabapentinoid that also acts on voltage-gated calcium channels by binding to the α2-δ subunit and reducing calcium influx.[9] Of note, pregabalin may potentiate opioid-induced respiratory depression so caution should be taken, particularly in high-risk patients, such as those with obstructive sleep apnea and the elderly.[9]

While gabapentin and pregabalin are the most commonly used anticonvulsants used for pain control, there are slight differences between the two medications.[13] Both drugs display dose-response relationships, however gabapentin is absorbed at a slower rate than pregabalin.[14] Additionally, pregabalin possesses a much higher and more consistent bioavailability as found by Bockbrader.[14]

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, was originally intended as an antidepressant but has been further researched for the treatment of neuropathic pain.[15] Serotonin and norepinephrine are involved in the modulation of endogenous analgesic mechanisms via descending inhibitory pain pathways in the brain and spinal cord.[16] An increase in serotonin and norepinephrine may increase inhibition of nociceptive input and improve pain relief.[16] Thus, duloxetine has demonstrated efficacy in chronic pain conditions such as painful diabetic neuropathy and post-herpetic neuralgia.[17] Additionally, duloxetine has been shown to amplify the noradrenergic mechanisms recruited by gabapentin.[18] The most common side effects of this drug include nausea, dry mouth, dizziness, constipation, insomnia, asthenia, and hypertension.[19]

METHODS

ETHICAL CONSIDERATIONS

As this is a review article, no human subjects were in harm of data or confidentiality breaches and approval from the IRB, or an ethics committee were not required.

PubMed, Google Scholar and Elsevier databases were searched from inception to 10 October 2022 outlined in search terms Table 1. Additionally, pertinent keywords were utilized in independent searches to discover other articles unaccounted for in the primary string of keywords. The bibliography was reviewed once all articles were compiled.

The keyword "Nerve Block" was originally utilized for a more specific search but was eventually removed due to the limited number of articles that were generated with its addition. An example of the utilization of the keyword would be research concerning the analgesic effects of nerve block neuromodulation which takes the place of narcotic analgesics to decrease opioid dependency, addiction, and potential overdose.

During the database searches, 1,033 records were identified as a preliminary result. After duplicates were removed, authors completed an initial screen of each article. The initial screen identified records to be removed due to absence of a full-text article. Additionally, only randomized controlled trials and prospective and retrospective cohort studies were included for further review. After the initial screening process, authors carefully reviewed and selected articles that closely followed the study criteria. A detailed description of the study process is shown in Figure 1.

RESULTS

The utilized search techniques yielded 247 records from PubMed, 180 records from Google Scholar, and 19 records from the Elsevier search engine. After the initial search for records by one author (TH), 217 duplicates were removed. Following the elimination of duplicate articles, 62 records were excluded due to the absence of full-text articles for further analysis and unavailability for article access. Each of the remaining 167 full-text articles were assessed for eligibility. Articles were excluded if they exclusively showcased an irrelevant medication (such as Tricyclic Antide-

Table 1. Search Terms and Yield

Search Criteria
The PubMed search was performed using the string "(Orthoped* AND Surger*) OR (Upper extremit* AND Surger*) OR (Hand AND Surger*) OR Gabapentin OR Pregabalin OR Narcotic OR Addiction OR (Opi* AND Overdose) OR Duloxetine OR Cymbalta OR (Postoperat* AND Analgesia) AND ((Orthoped* AND Surger*) OR (Upper Extremity) OR (Nerve Block))." The Google Scholar search was performed using the string "(Orthoped* AND Surger*) OR (Upper extremit* AND Surger*) OR (Hand AND Surger*) OR Gabapentin OR Pregabalin OR Narcotic OR Addiction OR (Opi* AND Overdose) OR Duloxetine OR Cymbalta OR (Postoperat* AND Analgesia) AND ((Orthoped* AND Surger*) OR (Upper Extremity) OR (Nerve Block))." The Elsevier search was performed using the string "(Orthoped* AND Surger*) OR (Upper extremit* AND Surger*) OR (Hand AND Surger*) OR Gabapentin OR Pregabalin OR Narcotic OR Addiction OR (Opi* AND Overdose) OR Duloxetine OR Cymbalta OR (Postoperat* AND Analgesia) AND ((Orthoped* AND Surger*) OR (Upper Extremity) OR (Nerve Block))."
Search Yield = 1,033

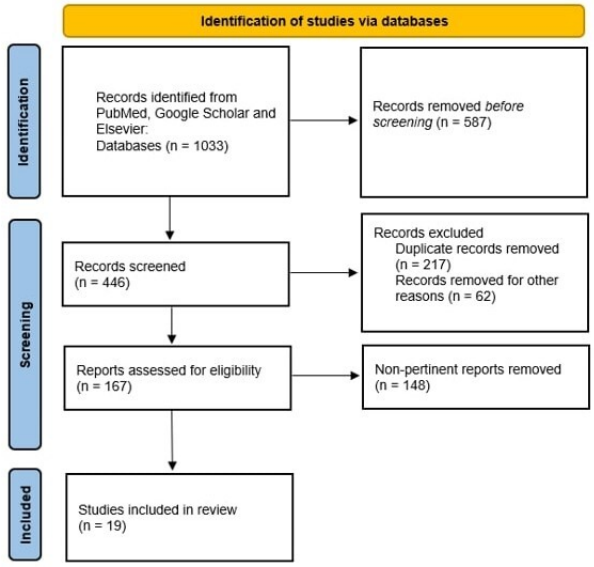

Figure 1. PRISMA flowchart for reviewed articles

pressants) which are not pertinent to this review or deemed to be unrelated to the topic. Ultimately, 19 articles were selected and are outlined in Table 2. Three different drugs, gabapentin, pregabalin, and duloxetine were analyzed on their effectiveness to provide analgesia and reduce opioid usage following various orthopedic surgeries.

PRE-OPERATIVE GABAPENTIN TREATMENT

Studies examining patient pain levels following various orthopedic procedures with pre-operative administration of gabapentin were included. In nearly all studies, the visual analog scale (VAS) was used to assess and quantify patient pain scores post-operatively.

In three different studies patients were given 300mg of gabapentin or placebo, 2 hours prior to surgery.[20-22] Bang et. al. reported that following arthroscopic rotator cuff surgery, VAS scores taken at 2, 6, and 12 hours post-operatively were significantly lower in patients that received gabapentin compared to placebo.[20] After open reduction and internal fixation surgery of the tibia, Panah Khahi et. al. found that VAS scores, measured 2 hours after surgery, were also significantly lower in the gabapentin group.[21]

In a clinical trial by Pandey et al., 100 patients were randomly divided into five groups to receive placebo or gabapentin 300, 600, 900, or 1200 mg, two hours before lumbar discectomy surgery.[23] They found that patients receiving 300 mg of gabapentin had significantly lower VAS pain scores at all time points compared to placebo and those receiving gabapentin 600, 900, and 1200 mg had lower VAS scores than the 300 mg group.[23] Increasing the dose from 600 to 1200 mg did not decrease the VAS score significantly, therefore the authors concluded that 600 mg is the optimal dose for post-operative pain relief following lumbar discectomy.[23]

In another study of 40 patients, Turan et al. found that 1200 mg gabapentin given daily before and for two days after lower extremity surgery decreased pain scores in the first 16 hours post-operatively and increased patient satisfaction with post-operative pain at 24 hours post-operatively.[24] Ménigaux et al. randomly assigned 40 patients to receive 1200 mg gabapentin or placebo one to two hours before arthroscopic anterior cruciate ligament (ACL) repair.[25] They found that VAS pain scores at rest and after mobilization were significantly reduced in the gabapentin group. Furthermore, pre-operative anxiety scores and early knee mobilization were improved in the gabapentin group.[25]

Wang et. al. assessed the efficacy of pre-operative gabapentin treatment to prevent phantom limb pain in pediatric patients undergoing amputation for malignant bone tumors.[26] Patients took one 300mg capsule a day for four days before surgery. Post-operatively patients took one capsule on day one (300 mg), one capsule twice a day on day two (600 mg), and then one capsule three times a day from day three until 30 days post-op (900 mg). They found that the rate of phantom limb pain and overall post-operative pain intensity were significantly lower in the gabapentin group than placebo at the last follow-up visit (60 days post-op).[26] This study additionally found that gabapentin may also help prevent development of phantom-limb pain if taken pre-emptively.

POST-OPERATIVE OPIOID CONSUMPTION WITH GABAPENTIN TREATMENT

With data that pre-operative gabapentin treatment can reduce early post-operative pain, it is consistent that less opioids would be required for analgesia. Hah et. al. reported

Table 2. Main findings from final quantitative synthesis studies

Authors, Year, Country	Study Design	Population, Injury Treated	Intervention, Dosage	Main Findings
Bang et al., 2010[18] USA	Randomized controlled trial	46 patients Arthroscopic rotator cuff repair	Gabapentin *(n=23) 300 mg 2 h before surgery*	VAS scores at 2, 6, and 12 h postoperatively were significantly lower in the gabapentin group than the placebo group (p=0.023, p=0.019, and p=0.022, respectively). Consumption of fentanyl over 24 h and the incidence of side effects was similar between the groups.
Panah Khahi et al., 2011[19] Singapore	Randomized controlled trial	64 patients Internal fixation of tibia	Gabapentin *(n=32) 300 mg 2 h before surgery*	Pain scores were significantly lower in the gabapentin group at 2 h post-surgery compared to placebo (p=0.004). However, scores at 12 and 24 h post-surgery were not significantly different between the two groups.
Pandey et al., 2005[20] India	Randomized controlled trial	100 patients Single-level lumbar discectomy	Gabapentin *(n=20) 300, 600, 900, or 1200 mg 2 h before surgery*	Patients who received gabapentin 300 mg had significantly lower VAS score at all time points. They consumed less fentanyl (987.5±129.6 µg) compared to placebo (1217.5±182.0 µg; p< 0.05). Those who received gabapentin 600, 900, and 1200 mg had lower VAS scores at all time points than those who received gabapentin 300 mg (p< 0.05). Increasing gabapentin dosage from 600 to 1200 mg did not decrease the VAS score, or significantly decrease fentanyl consumption (702.5, 635, and 626.5 µg).
Pandey et al., 2004[21] India	Randomized controlled trial	56 patients Lumbar discoidectomy	Gabapentin *(n=28) 300 mg 2 h before surgery*	Patients in the gabapentin group had significantly lower VAS scores at all time intervals of 0-6, 6-12, 12-18, and 18-24 h than those in the placebo group (3.5±2.3, 3.2±2.1, 1.8±1.7, 1.2±1.3 vs 6.1±1.7, 4.4±1.2, 3.3±1.1, 2.1±1.2; p< 0.05). The total fentanyl consumed after surgery in the first 24 h in the gabapentin group (233.5±141.9) was significantly less than in the placebo group (359.6±104.1; p<0.05).
Turan et al., 2006[22] Turkey	Prospective	40 patients Lower extremity surgery	Gabapentin *(n= 20) 1.2 g 1 day before and for 2 days after surgery*	Pain scores at 1, 4, 8, 12, and 16 h (p<0.001), PCEA bolus requirements at 24, 48, and 72 h (p<0.05), and paracetamol consumption (p<0.05), were significantly lower in the gabapentin group compared to the placebo group. Patient satisfaction with post-operative pain management at 24 h was also better in the gabapentin group (p<0.001). However, incidence of dizziness was higher in the gabapentin group (35% vs. 5%; p<0.05).
Ménigaux et al., 2005[23] France	Randomized controlled trial	40 patients Arthroscopic anterior cruciate ligament repair	Gabapentin *(n=20) 1200 mg 1-2 h before surgery*	Patients treated with gabapentin required less morphine than the control group (29±22 mg vs. 69±40 mg, respectively; p<0.001). VAS pain scores at rest and after mobilization were significantly reduced in the gabapentin group. Pre-medication with gabapentin also improved pre-operative anxiolysis and early knee mobilization at 24 and 48 h post-operatively.
Wang et al., 2018[24] China	Randomized controlled trial	45 pediatric patients Prevention of phantom limb pain (PLP) following lower limb amputation	Gabapentin *(n= 23) 300 mg on day 1, 600 mg on day 2, and 900 mg from day 3 to day 30 after surgery*	Acute post-operative pain intensity in gabapentin group was significantly lower than the placebo group p<0.05). The rate of PLP at the last follow-up was lower in the gabapentin group (43.48%) compared to placebo (77.27%, p=0.033).
Hah et al., 2018[25]	Randomized controlled	422 patients Mixed	Gabapentin *(n= 208)*	Patients treated with gabapentin had a 24% increase in the rate of opioid cessation after

	trial	Surgical Cohort	*1200 mg before surgery and 1800 mg for 72 hours after*	surgery (p=0.05). However, there were no significant differences in the number of adverse events.
Gordh et al., 2008[26] Sweden	Randomized controlled trial	98 patients Neuropathic pain caused by traumatic or post-surgical peripheral nerve injury	Gabapentin *(n=50) 300 mg increased stepwise until reaching total pain relief or a max. dose of 2400 mg*	Compared with placebo, gabapentin provided significantly better pain relief (p=0.015), more patients had at least a 30% pain reduction (p=0.040), and the pain interfered with patients sleep significantly less (p=0.0016).
Dolgun,[27] 2014 Turkey	Randomized controlled trial	54 patients Acute neuropathic pain after lumbar discoidectomy	Gabapentin *(n=27)* and Pregabalin *(n=27) 300 mg gabapentin on day 1, 600 mg on day 2, and 900 mg on day 3 with maintenance of 900-1800 mg TID 150 mg pregabalin increased to 300 mg after 1 week, up to 300 mg BID or 200 mg TID*	Both treatment groups pain improved according to the LANSS scale. Gabapentin scores decreased from 14 to 10 points 6 months after surgery and to 4 points at 1 year (p<0.001). Pregabalin scores decreased from 16 to 12 at 6 months post-op and further decreased to 5 at 1-year post-op (both p<0·001). Oswestry disability index (ODI) and VAS scores also significantly improved in both groups (p<0·001).
Khurana et al., 2014[28] India	Randomized controlled trial	90 patients Lumbar discectomy	Gabapentin and Pregabalin *(n= 30 each) 300 mg gabapentin or 75 mg pregabalin 1 hour before surgery and 8 hourly for 7 days thereafter*	Compared to placebo, patients receiving gabapentin and pregabalin had significantly reduced static and dynamic pain intensity and required significantly less doses of rescue drugs post-operatively. The pregabalin group had significantly improved Prolo scores and Oswestry Disability Index scores at all time intervals compared to placebo. Pregabalin had more pronounced clinical effect compared to gabapentin (not statistically significant until 21 days).
Kheirabadiet al., 2020[29] Iran	Randomized controlled trial	120 patients Lower extremity surgery	Pregabalin *(n=30)* and Gabapentin *(n=30) 300 mg gabapentin or 75 mg pregabalin 1 h before surgery*	There was a significant reduction in pain severity only at the first-time point between pregabalin and placebo treated patients (p=0.014). The pregabalin group required lower doses of opioids during admission. There was no significant difference in pain reduction, opioid administration, and side effects between the pregabalin, gabapentin, and celecoxib groups.
Altiparmak et al., 2018[30] USA	Randomized controlled trial	94 patients Spinal surgery	Duloxetine *(n=31)* and Pregabalin *(n=30) 60 mg duloxetine or 75 mg 1 h before surgery and 12 and 24 h after*	In all groups, there was a significant reduction in mean post-op Montreal Cognitive Assessment (MoCA) scores with the highest reduction in the pregabalin group (1.83±1.31 point), then the duloxetine group (1.16±0.82). The least decrease was in the control group (0.49±0.61). The mean VAS scores of the pregabalin and duloxetine groups were similar throughout the study and were significantly lower than the control group.
Attia and	Randomized	120 patients	Duloxetine	Duloxetine and etoricoxib alone did not affect pain

Monsour, 2017[31] Egypt	controlled trial	Lumbar laminectomy	*(n=30) 60 mg duloxetine or 60 mg duloxetine with etoricoxib 120 mg 1 h before surgery and 24 h after*	scores with movement, yet their combination allowed for a significant reduction over the post-operative period at rest and with movement. At rest, Etoricoxib showed a significant decrease in pain at all times when compared to placebo, and at 0, 2 and 4 h when compared with the Duloxetine group. Duloxetine alone only showed a significant decrease in pain at 24 h and 48 h when compared with placebo. Morphine requirement after 24 h were significantly lower in the combination group but both Duloxetine and etoricoxib alone showed a significant decrease.
Kim et al., 2021[32]	Retrospective	239 patients Total knee arthroplasty	Duloxetine *(n=137) 30 mg for 6 weeks after surgery*	There was no significant difference in pain VAS score, WOMAC Pain and Function score between the duloxetine and opioid treated groups at each time point between before and after surgery (all $p>0.05$).
Li et al., 2021[33] USA	Randomized controlled trial	96 patients Total Hip Arthroplasty	Duloxetine *(n=48) 60 mg daily from 2 days before surgery to 14 days after*	Patients administered duloxetine had significantly lower pain severity scores upon movement and performed better in terms of resting pain (3 weeks after surgery), morphine requirements, and satisfaction level at discharge compared to placebo (all $p<0.05$).
Ho et al., 2010[34]	Randomized controlled trial	47 patients Total knee arthroplasty	Duloxetine *(n=23) 60 mg 2 h before and one day after surgery*	In the duloxetine group, morphine requirements were significantly lower throughout the first 48 h following surgery compared to placebo ($p=0.017$). However, there were no statistically significant differences in pain score or adverse effects between the groups.
YaDeau et al., 2016[35] USA	Randomized controlled trial	106 patients Total knee arthroplasty	Duloxetine *(n=53) 60 mg 30 min before surgery until 14 days after*	Total opioid use was significantly reduced in the duloxetine group from the day of surgery through three months post-op ($p=0.002$). Nausea severity was also significantly reduced in the duloxetine group on the first day post-op. Fourteen days post-op, duloxetine did not reduce pain scores at rest, with ambulation, and with flexion compared to placebo.
Bedin et al., 2016[36] Brazil	Randomized controlled trial	57 Patients Lumbar spinal fusion	Duloxetine *(n=28) 60 mg 1 h before surgery and once the following morning*	At 24 and 48 hours post-operatively, fentanyl consumption was significantly lower in the duloxetine group compared to placebo ($p<0.001$ and $p<0.000$, respectively). Pain scores did not significantly differ between groups during this time.

that in a randomized clinical trial of 410 patients undergoing a variety of surgeries (294 of which were orthopedic surgeries), patients given 1200 mg gabapentin preoperatively and 600 mg three times daily postoperatively for three days, demonstrated a 24% increase in the rate of opioid cessation after surgery.[27] Menigaux et al. reported that 1200mg of gabapentin given one to two hours before arthroscopic ACL repair also reduced morphine requirements compared to patients receiving placebo.[25] An alternative study found that 1200 mg gabapentin given before and for two days after lower extremity surgery decreased patient-controlled epidural analgesia and paracetamol requirements post-operatively.[24] Two studies by Pandey et al. demonstrated support for a decreased opioid consumption following spinal surgery.[22,23] A single dose of 300 mg of gabapentin, two hours before surgery reduced the amount of Fentanyl, a synthetic opioid, consumed during the first 24 hours after lumbar discoidectomy.[23] In the second study, 300, 600, 900, or 1200 mg of gabapentin reduced the amount of Fentanyl consumed compared to placebo, however, increasing the dose of gabapentin from 600 to 1200 mg did not significantly decrease fentanyl consumption.[22] It was also reported that 1200mg gabapentin given one hour before spinal surgery decreased post-operative morphine consumption while also decreasing some morphine-associated side effects.[24]

POST-OPERATIVE GABAPENTIN TREATMENT FOR NEUROPATHIC PAIN

One article described the effects of gabapentin on traumatic nerve injury or post-surgery nerve pain and found that gabapentin provided significantly better pain relief when compared to placebo, with more patients having at least a 30% pain reduction and less sleep interference due to pain.[28] Dolgun et. al. assessed the acute neuropathic pain levels of their patients following lumbar discectomy utilizing the Leeds Assessment of Neuropathic Symptoms

and Signs (LANSS) scale (LANSS score ⩾ 12 suggests the presence of neuropathic pain). The authors demonstrated decreased pain scores (14 to 10) following six months of gabapentin treatment, and after one year of treatment the score further decreased to a four.[37]

PRE AND POST OPERATIVE PAIN RELIEF FOLLOWING PREGABALIN TREATMENT

Pregabalin (Lyrica™) is another commonly prescribed neuromodulator that has proven effective in pain management. There are two studies comparing the effects of pregabalin with gabapentin. Khurana et. al. compared three groups receiving either 300 mg of gabapentin daily, 75 mg of pregabalin daily, or placebo, one dose one hour before lumbar discectomy surgery and eight hourly for seven days, thereafter.[29] The authors found that pregabalin treated patients reliably showed reduced static and dynamic pain intensity and required fewer rescue drugs throughout the post-operative period. Pregabalin had significantly improved Prolo and Oswestry Disability Index (ODI) scores (semi-quantitative scale of 2-20 and quantitative scale of 0-20, respectively) at all time intervals compared to placebo.[33] Pregabalin also had more pronounced clinical effect compared to gabapentin but there was not a statistically significant difference until 21 days.[29] Similarly, an alternative study treated patients with either pregabalin or gabapentin to control acute neuropathic pain following lumbar discectomy.[37] In the pregabalin group, the LANSS scores decreased from 16 to 12 at six months post-op and further decreased to five at one-year post-op. At all times points, these scores were higher than the gabapentin group, however, both medications prevented the conversion of acute to chronic neuropathic pain at one-year follow-up. Additionally, ODI and VAS scores significantly improved in both groups.[37] Kheirabadi et. al. observed a significant reduction of pain severity or attenuation of postoperative pain following administration of 75mg of pregabalin before lower extremity orthopedic surgery.[30]

One article compared pain scores between three treatment groups undergoing spinal surgery.[31] This included treatment with 75 mg of pregabalin at one hour prior to surgery and at 12 and 24 post-operatively; 60 mg of duloxetine one hour prior to surgery, placebo at 12 hours post-op and duloxetine 60 mg again at 24 hours; or placebo at all three time-points.[31] Throughout the study, the mean VAS scores of the pregabalin and duloxetine groups were similar to each other, and were both lower than that of the control group.[31]

PAIN RELIEF FOLLOWING DULOXETINE TREATMENT

Two studies compared pain scores with duloxetine to other analgesic medications or placebo.[32,34] Altiparmak et al. provided evidence that duloxetine may perform similarly to pregabalin in terms of pain relief through findings of similar VAS scores in patient treated with pregabalin or duloxetine post spinal surgery.[32] Attia and Mansour treated 120 patients with either duloxetine 60 mg, etoricoxib 120 mg, placebo, or duloxetine 60 mg and etoricoxib 120 mg together, one hour before lumbar laminectomy and 24 hours after.[34] They found that neither drug individually influenced pain with movement, while the combination resulted in a significant reduction in pain scores with rest and movement over the entire post-operative period.[34] Etoricoxib, a non-steroidal anti-inflammatory, alone showed a significant decrease in pain at rest compared to placebo at all time points, and at zero, two, and four hours compared to duloxetine.[34] While duloxetine alone showed a significant decrease in pain at rest at only 24 and 48 hours compared to placebo.[34] Additionally, Kim et. al. identified that duloxetine can act as an alternative to opioids for post-operative pain control following total knee arthroplasty (TKA).[35] Of the 118 patients treated with duloxetine and 121 treated with opioids for 6 weeks post-operatively, there was a non-significant difference in VAS scores and Western Ontario and McMaster Universities OA Index (WOMAC) scores at each time point before and after surgery.[35] There was also no significant difference in the number of patients prescribed additional medication after the first six weeks and the incidence of side effects between the two groups.[35]

Li et al. also investigated the post-operative pain intensity of patients treated with duloxetine in the pre- and early post-operative period.[31] Duloxetine 60mg was administered daily starting two days prior to total hip arthroplasty surgery and continued this dose until 14 days post-op.[31] Patients in this treatments group had significantly lower pain severity scores upon movement within three postoperative weeks compared to placebo.[31] Furthermore, the duloxetine treated patients performed better in terms of resting pain, morphine requirements, and satisfaction level at discharge.[31]

POST-OPERATIVE OPIOID CONSUMPTION WITH DULOXETINE TREATMENT

Ho et. al. demonstrated significantly lower post-operative morphine usage following TKA with dosage of duloxetine two hours pre-operatively and the morning of the first post-operative day, compared to placebo.[36] Additionally, YaDeau et al. found that there was a statistically significant decrease in opioid consumption, compared to placebo, when patients received duloxetine for 15 days, starting from the day of TKA.[38] Another author demonstrated a significant decrease in fentanyl consumption during the first 48 hours post-operatively compared to placebo following dosage with 60mg duloxetine one hour prior to lumbar spinal fusion surgery and again the following morning.[39] Attia and Mansour reported that patients treated with duloxetine or etoricoxib 120mg in the pre-operative and early post-operative period had significantly decreased morphine requirements compared to placebo when undergoing lumbar laminectomy.[34] The combination treated group had the lowest requirements.[34]

DISCUSSION

With the current opioid epidemic, alternative and multimodal pain management strategies need to be well studied

in order to identify the best solution or substitute. The United States, which only consists of 4.25% of the world's population, consumes 80% of the global opioid supply and 99% of the global hydrocodone supply.[40] Among this, orthopedic surgeons are the third highest prescribers.[40] Although recommendations exist among specialties, there are currently no standardized prescriber education or postoperative opioid prescription guidelines.[41] Thus, many prescribing physicians have little training in pain management, despite evolving education, and tend to overprescribe opioids.[42] For example, 59% to 76% of hand surgery patients are prescribed opioids and on average receive two to five time more opioids than needed.[43] Therefore, the current atmosphere of prescription opioids, particularly in orthopedic surgery, puts patients at risk for abuse and addiction.

Pain after surgery is reported mainly during the first week.[44] The greatest consumption of opioids happens on day zero and postoperative day one, and the median for total days of consumption is two to five days.[43] Thus, pain management should be tailored to maintain low pain levels for the first five days post-operatively as the probability of long-term opioid use increases most sharply in this time frame. Antineuropathic pain medications, such as gabapentin, pregabalin, and duloxetine are well established in the management of neuropathic pain and may offer a solution to avert the use and detrimental effects of opioids. This data suggests that although duloxetine has variable outcomes in terms of pain relief outcomes, it may have similar effects as Pregabalin or opioids while potentially avoiding the side effects and dependency that accompanies those therapies.

Twelve studies identified show that gabapentin treatment resulted in decreased pain and/or opioid consumption following orthopedic surgery.[20,29,30] Thus, as reported in our results, the administration of gabapentin, even with one 300 mg pre-operative dose, may effectively aid physicians in decreasing patients' post-operative pain and opioid dependence following various orthopedic surgeries.

These studies suggest that pregabalin can reduce postoperative and neuropathic pain, with similar efficacy to gabapentin or duloxetine. However, pregabalin does have frequent reported side effects such as euphoria and a potential of abuse which should be taken into consideration when while deciding on a treatment plan.[45] The majority of case reports concerning abuse of pregabalin involved patients with a history of substance abuse and, similarly, epidemiological studies found evidence of abuse, especially among opiate abusers.[45] Thus, prescribing pregabalin should be approached with caution; however, if a patient is allergic to gabapentin, pregabalin may also act as an effective postoperative analgesic.

The aforementioned studies additionally suggest that pre-operative and early post-operative administration of 60mg duloxetine can significantly reduce the consumption of opioid analgesics post-operatively. Multiple studies have also shown that the addition of a daily maintenance dose of duloxetine to a pre-existing pain management regimen significantly lowers post-operative pain and opioid consumption.[15,31,32,34,36,38,39] The results of this review further support the effectiveness of duloxetine as a possible post-operative analgesic tool.

Patient counseling performed by the physician is an extra measure that can be taken to increase the effectiveness of neuromodulator therapy, improve patient pain satisfaction, and avoid opioid dependence. A recent study on patients undergoing upper extremity surgery found that those receiving pre-operative counseling consumed significantly fewer opioids post-operatively. Patients receiving counseling consumed 93.7 Morphine Equivalent Units (MEU) to 143.2 MEU in the control group.[46] This reduced opioid consumption did not reflect increased pain scores between the two groups. Stepan et. al. found that prescriber education and post-operative opioid guideline dissemination led to significant decreases in the number of opioid pills prescribed after ambulatory hand surgery.[41] Another study found that patients who were pre-operatively educated on opioid use were less likely to become opioid dependent at two-year follow-up.[47] The average intensity of expected post-operative pain reported during the pre-operative period was the only variable associated with the development of moderate to severe acute pain after surgery showing that there may be a psychosocial element to post-operative pain.[48] Pre-operative counseling may add to the effectiveness of a transition to primary neuromodulator therapy and decreased opioid dependence. Therefore, pre-operative counseling may be implemented to help improve the transition to primary neuromodulator therapy while increasing pain management satisfaction and decreasing opioid use.

Overall, the data obtained in these studies suggest that pre-operative and early post-operative administration of gabapentin, pregabalin, and duloxetine can greatly reduce the consumption of opioid analgesics, such as Morphine and Fentanyl.

CONCLUSION

This review demonstrates that pre-operative and early post-operative 300 mg of gabapentin administration decreases post-operative pain and lowers opioid dependency. 75 mg of pregabalin before surgery, followed by an increase to 300 mg after one week, is a validated alternative to gabapentin and may exhibit varying effectiveness in managing postoperative pain due to its quicker onset of action. However, pregabalin requires extra monitoring for side effects and dependency. As an adjunct, 60 mg duloxetine preoperatively and postoperatively can further reduce postoperative pain and lower opioid dependency by inhibiting noradrenergic reuptake, which is additive to gabapentin's mechanisms of pain reduction. Sodium levels do, however, need to be monitored if gabapentin and duloxetine are prescribed together.[49] Pre-operative counseling is also an additional intervention that can be employed to help decrease post-operative pain by lowering expectations of pain levels.

POTENTIAL CLINICAL APPLICATION

This review establishes the foundation for possible further research to assess an updated protocol for pain manage-

ment to reduce opioid dependency. This research would include a randomized, controlled, single blind trial with use of gabapentin 300mg and duloxetine 60mg nightly four days prior to surgery, gabapentin 300mg twice daily and duloxetine 60mg once daily for 14 days following index procedure. The VAS pain surveys from these trial patients would be used to compare to a control of patients following current narcotic post-operative pain management protocol. If substituted for gabapentin, pregabalin would be prescribed as pregabalin 75 mg and duloxetine 60 mg at night 4 days prior to surgery, pregabalin 75 mg twice daily and duloxetine 60 mg once daily for 14 days following procedure.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Gerbershagen HJ, Aduckathil S, Wijck AJM, Peelen LM, Kalkman CJ, Meissner W. Pain Intensity on the First Day after Surgery: A Prospective Cohort Study Comparing 179 Surgical Procedures. *Anesthesiology*. 2013;118:934-944.

2. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156(4):569-576. doi:10.1097/01.j.pain.0000460357.01998.f1

3. Hedegaard H, Miniño AM, Warner M. *Drug Overdose Deaths in the United States, 1999–2019. NCHS Data Brief, No 394*. National Center for Health Statistics; 2020.

4. Volkow ND. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011;305(13):1299. doi:10.1001/jama.2011.401

5. Kim N, Matzon JL, Abboudi J, et al. A Prospective Evaluation of Opioid Utilization After Upper-Extremity Surgical Procedures: Identifying Consumption Patterns and Determining Prescribing Guidelines. *J Bone Joint Surg Am*. 2016;98(20):e89. doi:10.2106/jbjs.15.00614

6. Gaddis A, Dowlati E, Apel PJ, et al. Effect of Prescription Size on Opioid Use and Patient Satisfaction After Minor Hand Surgery: A Randomized Clinical Trial. *Ann Surg*. 2019;270(6):976-982. doi:10.1097/sla.0000000000003127

7. Trasolini NA, McKnight BM, Dorr LD. The Opioid Crisis and the Orthopedic Surgeon. *J Arthroplasty*. 2018;33(11):3379-3382.e1. doi:10.1016/j.arth.2018.07.002

8. Moura SP, Nicholson S, Hoftiezer YAJ, Lans J, Chen NC, Eberlin KR. Prolonged Opioid Use following Hand Surgery: A Systematic Review and Proposed Criteria. *Plastic and Reconstructive Surgery - Global Open*. 2022;10(4):e4235. doi:10.1097/gox.0000000000004235

9. Pitchon DN, Dayan AC, Schwenk ES, Baratta JL, Viscusi ER. Updates on Multimodal Analgesia for Orthopedic Surgery. *Anesthesiol Clin*. 2018;36(3):361-373. doi:10.1016/j.anclin.2018.05.001

10. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database of Systematic Reviews*. 2012;18;1(1):CD008921. doi:10.1002/14651858.cd008921.pub2

11. Gropper MA, Miller RD. *Miller's Anesthesia*. Elsevier; 2020.

12. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;2020(2). doi:10.1002/14651858.cd007938.pub4

13. Robertson K, Marshman LAG, Plummer D, Downs E. Effect of Gabapentin vs Pregabalin on Pain Intensity in Adults With Chronic Sciatica: A Randomized Clinical Trial. *JAMA Neurol*. 2019;76(1):28. doi:10.1001/jamaneurol.2018.3077

14. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;49(10):661-669. doi:10.2165/11536200-000000000-00000

15. Saoud A, Elkabarity RH. Effect of Perioperative Duloxetine on Postoperative pain relief following Anterior Cervical Microdiscectomy and fusion. A Pilot Study. Published online 2014.

16. Onuţu AH. Duloxetine, an antidepressant with analgesic properties - a preliminary analysis. *Rom J Anaesth Intensive Care*. 2015;22(2):123-128.

17. Branton MW, Hopkins TJ, Nemec EC. Duloxetine for the reduction of opioid use in elective orthopedic surgery: a systematic review and meta-analysis. *Int J Clin Pharm*. 2021;43(2):394-403. doi:10.1007/s11096-020-01216-9

18. Hayashida KI, Eisenach JC. Multiplicative interactions to enhance gabapentin to treat neuropathic pain. *European Journal of Pharmacology*. 2008;598(1-3):21-26. doi:10.1016/j.ejphar.2008.09.004

19. Shelton RC. Serotonin and Norepinephrine Reuptake Inhibitors. *Handb Exp Pharmacol*. 2019;250:145-180. doi:10.1007/164_2018_164

20. Bang SR, Yu SK, Kim TH. Can gabapentin help reduce postoperative pain in arthroscopic rotator cuff repair? A prospective, randomized, double-blind study. *Arthroscopy*. 2010;26(9):S106-S111. doi:10.1016/j.arthro.2009.11.010

21. Panah Khahi M, Yaghooti AA, Marashi SH, Nadjafi A. Effect of pre-emptive gabapentin on postoperative pain following lower extremity orthopaedic surgery under spinal anaesthesia. *Singapore Med J*. 2011;52(12):879-882.

22. Pandey CK, Navkar DV, Giri PJ, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. *J Neurosurg Anesthesiol*. 2005;17(2):65-68. doi:10.1097/01.ana.0000151407.62650.51

23. Pandey CK, Sahay S, Gupta D, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. *Can J Anesth*. 2004;51(10):986-989. doi:10.1007/bf03018484

24. Turan A, Kaya G, Karamanlioğlu B, Pamukçu Z, Apfel CC. Effect of oral gabapentin on postoperative epidural analgesia. *Br J Anaesth*. 2006;96(2):242-246. doi:10.1093/bja/aei294

25. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. *Anesth Analg*. 2005;100(5):1394-1399. doi:10.1213/01.ane.0000152010.74739.b8

26. Wang X, Yi Y, Tang D, et al. Gabapentin as an Adjuvant Therapy for Prevention of Acute Phantom-Limb Pain in Pediatric Patients Undergoing Amputation for Malignant Bone Tumors: A Prospective Double-Blind Randomized Controlled Trial. *J Pain Symptom Manage*. 2018;55(3):721-727. doi:10.1016/j.jpainsymman.2017.11.029

27. Hah J, Mackey SC, Schmidt P, et al. Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort. *JAMA Surg*. 2018;153(4):303. doi:10.1001/jamasurg.2017.4915

28. Gordh TE, Stubhaug A, Jensen TS, et al. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study. *Pain*. 2008;138(2):255-266. doi:10.1016/j.pain.2007.12.011

29. Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. *Spine*. 2014;39(6):E363-E368. doi:10.1097/brs.0000000000000185

30. Kheirabadi D, Safavi M, Taghvaei M, Habibzadeh M, Honarmand A. Comparing the prophylactic effects of oral gabapentin, pregabalin, and celecoxib on postoperative pain management in orthopedic surgery of the lower extremity: A double-blind randomized controlled trial. *J Res Med Sci*. 2020;25(1):9. doi:10.4103/jrms.jrms_140_19

31. 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). doi:10.1186/s12891-021-04377-4

32. Altiparmak B, Güzel Ç, Gümüş Demirbilek S. 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):1114-1120. doi:10.1097/ajp.0000000000000640

33. Vanti C, Prosperi D, Boschi M. The Prolo Scale: history, evolution and psychometric properties. *J Orthopaed Traumatol*. 2013;14(4):235-245. doi:10.1007/s10195-013-0243-1

34. Attia JZ, Mansour HS. Perioperative Duloxetine and Etoricoxibto improve postoperative pain after lumbar Laminectomy: a randomized, double-blind, controlled study. *BMC Anesthesiol*. 2017;17(1). doi:10.1186/s12871-017-0450-z

35. Kim MS, Koh IJ, Choi KY, Yang SC, In Y. Efficacy of duloxetine compared with opioid for postoperative pain control following total knee arthroplasty. *PLoS ONE*. 2021;16(7):e0253641. doi:10.1371/journal.pone.0253641

36. Ho KY, Tay W, Yeo MC, et al. Duloxetine reduces morphine requirements after knee replacement surgery. *Br J Anaesth*. 2010;105(3):371-376. doi:10.1093/bja/aeq158

37. Dolgun H, Turkoglu E, Kertmen H, et al. Gabapentin versus pregabalin in relieving early post-surgical neuropathic pain in patients after lumbar disc herniation surgery: a prospective clinical trial. *Neurological Research*. 2014;36(12):1080-1085. doi:10.1179/1743132814y.0000000404

38. YaDeau JT, Brummett CM, Mayman DJ, et al. Duloxetine and Subacute Pain after Knee Arthroplasty when Added to a Multimodal Analgesic Regimen: A Randomized, Placebo-controlled, Triple-blinded Trial. *Anesthesiology*. 2016;125(3):561-572. doi:10.1097/aln.0000000000001228

39. 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):865-869. doi:10.1097/ajp.0000000000000471

40. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. *J Am Acad Orthop Surg*. 2015;23(5):267-271. doi:10.5435/jaaos-d-14-00163

41. Stepan JG, Sacks HA, Lovecchio FC, et al. Opioid Prescriber Education and Guidelines for Ambulatory Upper-Extremity Surgery: Evaluation of an Institutional Protocol. *J Hand Surg Am*. 2019;44(2):129-136. doi:10.1016/j.jhsa.2018.06.014

42. Jamison RN, Scanlan E, Matthews ML, Jurcik DC, Ross EL. Attitudes of Primary Care Practitioners in Managing Chronic Pain Patients Prescribed Opioids for Pain: A Prospective Longitudinal Controlled Trial. *Pain Med*. 2016;17(1):99-113.

43. Sraj S. Narcotic-Free, Over-the-Counter Pain Management After Wide-Awake Hand Surgery. *J Am Acad Orthop Surg Glob Res Rev*. 2019;3(11):e19.00137. doi:10.5435/jaaosglobal-d-19-00137

44. Rosén HI, Bergh IH, Odén A, Mårtensson LB. Patients' experiences of pain following day surgery - at 48 hours, seven days and three months. *Open Nurs J*. 2011;5:52-59. doi:10.2174/1874434601105010052

45. Schjerning O, Rosenzweig M, Pottegård A, Damkier P, Nielsen J. Abuse Potential of Pregabalin: A Systematic Review. *CNS Drugs*. 2016;30(1):9-25. doi:10.1007/s40263-015-0303-6

46. Vincent S, Paskey T, Critchlow E, et al. Prospective Randomized Study Examining Preoperative Opioid Counseling on Postoperative Opioid Consumption after Upper Extremity Surgery. *Hand (New York, N,Y)*. 2020;17(2):200-205. doi:10.1177/1558944720919936

47. Cheesman Q, DeFrance M, Stenson J, et al. The effect of preoperative education on opioid consumption in patients undergoing arthroscopic rotator cuff repair: a prospective, randomized clinical trial—2-year follow-up. *J Shoulder Elbow Surg*. 2020;29(9):1743-1750. doi:10.1016/j.jse.2020.04.036

48. Bayman EO, Parekh KR, Keech J, Larson N, Vander Weg M, Brennan TJ. Preoperative Patient Expectations of Postoperative Pain Are Associated with Moderate to Severe Acute Pain After VATS. *Pain Med*. 2019;20(3):543-554. doi:10.1093/pm/pny096

49. Fourlanos S, Greenberg P. Managing drug-induced hyponatraemia in adults. *Aust Prescr*. 2003;26(5):114-117. doi:10.18773/austprescr.2003.083