Gabapentoids in knee replacement surgery: contemporary, multi-modal, peri-operative analgesia

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ABSTRACT

Pain remains a significant barrier to rapid patient recovery and rehabilitation post-surgery, particularly after joint replacement surgery. Historically, protocols used for peri-operative pain management have been largely reactive and dependent on opioid use, with adjunctive non-steroidal and other simple analgesia. This review explores the evidence supporting the use of gabapentoids (eg. Lyrica®) in surgical fields, then in orthopaedics more specifically, and finally in the targeted domain of total knee replacement (TKR) surgery. The concept of 'pre-emptive' analgesia is also explored. Gabapentoids have shown clinical value in reducing the patient-reported pain experience and also decreasing concurrent opioid requirements in the post-surgical period in a number of surgical areas, however there remains no consensus for their optimal use in patients undergoing knee arthroplasty. Reported adverse effects including sedation and potential respiratory depression should herald some caution, and monitored use in 'at risk' patient groups. There have been a small number of clinical trials conducted around the use of gabapentoids in TKR, however the validity and generalisability of these results have been limited by small sample sizes, and cross-study analysis is confounded by adoption of inconsistent analgesic protocols, non-comparable dosing regimes, poor (or absent) control selection, and cohort heterogeneity. High-quality trials are needed to allow the role of gabapentoids in multi-modal peri-operative analgesic pathways to be better defined, to permit wider endorsement for main-stream or standardised care.

1. Introduction

Pain remains one of the most limiting factors of a patient's recovery post-orthopaedic surgery. In particular, in those undergoing total knee replacements (TKRs), poorly-controlled pain often prevents full engagement with post-operative rehabilitation programs and can markedly delay return-to-function. Pain endured after surgery is, in most instances, predictable and self-limiting, and adequate early control leads to reduced morbidity and fewer complications - such as respiratory depression, hypertension, tachycardia and provoked acute coronary events.¹ Most hospital protocols for post-operation pain management include the combination of two or more classes of analgesic (i.e. multi-modal care), with an aim of reducing pain experienced by the patient in the peri-operative period. The goal of reducing the consumption of opioid-based analgesics remains a key focus in the current clinical climate. Morphine (and other opioid analgesics) have been shown to be effective in reducing pain experienced in most patient groups, however such agents are associated with a wide range of recognised adverse effects relating to nausea and vomiting, constipation

and bowel dysfunction, sedation and respiratory depression, the latter of which is of particular importance to the vulnerable group of older patients undergoing TKR.^{2,3} In more recent years, large professional bodies such as the American Orthopaedic Association have suggested integrating pre-emptive and multi-modal analgesia approaches to reduce opioid requirements and their associated adverse effects.⁴ Gabapentoids such as gabapentin and pregabalin (Lyrica®) have been suggested in preliminary research, as reviewed in this paper, as a leading change in multi-agent analgesia to potentially address these issues. In this review, the evidence available for the use of pregabalin and gabapentin in the peri-operative surgical patient, and particularly of its use in patients undergoing a TKR, are examined.

1.1. Pregabalin and its role in pain perception

Post-operative pain is not only caused by direct tissue injury, but also resulting inflammation, neuropathic and visceral stimulation, and is the complex result of the release of a cascade of neurotransmitters, mediators, peptides and gated-ions. Structurally, pregabalin is an

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analogue of the intrinsic neurotransmitter gamma-aminobutyric acid (GABA), however it does not act as GABA functionally. Pregabalin interferes with the α -2 subunit of presynaptic voltage-gated calcium channels to reduce the release of calcium into the synaptic cleft. As a result, there is suppressed release of the neurotransmitters glutamate, noradrenaline, dopamine and serotonin,⁵ and a decrease in relative neural hyperexcitability, resulting in blockade of hyperalgesia and central sensitisation pathways.⁶ These same mechanisms also likely explain the secondary anxiolytic and anti-seizure effects observed with this class of medications. The principal gabapentoid anti-nociceptive effect has been suggested to be the result of specific activation of noradrenergic descending inhibitory pathways,^{7,8} which have been demonstrated in animal models via the coined ‘spinal noradrenergic mechanism’.⁹ The early work of Kissin¹⁰ suggested that preoperative administration of pregabalin worked through the concept of pre-emptive analgesia; which is that “anti-nociceptive treatment given before incision is more effective than that given after”, and is now recognised to be strongly based on the prevention of establishment of central pain sensitisation. The exact physiologic mechanism-of-action through which pregabalin exerts its overall pain-preventing effects however, remains contentious.

Pregabalin is accepted to be more potent, and with fewer adverse effects, than its class counterpart gabapentin. It has fast gastrointestinal absorption, a high bioavailability, and its serum representation is dose-proportional leading to a predictable and near-linear pharmacokinetic profile.⁶ The maximum plasma concentration is reached at 1 h after oral administration, and its elimination half-life at steady state is approximately 6 h.¹¹ Additional benefits in the peri-operative setting include that it can be taken on an empty stomach and has not been associated with gastrointestinal irritation or bleeding, and it is generally well tolerated.¹² The recognised adverse effects of pregabalin include sedation, dizziness, visual disturbances, speech difficulties, tremor, vertigo or urticaria,¹³ although these have not all been reported in arthroplasty populations. Treatment doses usually range between 75 and 300 mg/day for adults, with a maximum recommended dose of 600 mg/day.¹¹

1.2. Peri-operative pregabalin use

Pregabalin has a strong evidence base in improving pain associated with diabetic neuropathy¹⁴ and herpetic neuralgia.^{15,16} Pregabalin has been approved by the Therapeutic Goods Administration (TGA) as an adjunctive therapy in adults with partial seizures, with or without secondary generalisation, also now with an established literature base.¹⁷ Other indications which have been studied include management of generalised anxiety and social anxiety disorders,¹⁸ and pain and sleep disturbance in fibromyalgia.¹⁹ Within the broad realm of surgery, there have been positive studies for use as a peri-operative adjunctive medication to reduce post-operative pain and opioid requirements. Specific applications for which the controlled use of pregabalin has been studied include general intra-abdominal gynaecological surgery,^{20,21} laparoscopic cholecystectomy,^{22,23} third molar surgery,²⁴ laparoscopic sleeve gastrectomy,²⁵ septoplasty,²⁶ dacryocystorhinostomy²⁷ and transperitoneal nephrectomy.²⁸ A systematic review of pregabalin use in cervicofacial surgery²⁹ showed that peri-operative oral pregabalin use resulted in clinically-significant pain reduction and post-operative analgesic requirements without major adverse effects. There was no clear evidence supporting the ideal dose or effective administration regimen, however. Several smaller meta-analyses have shown that use of oral pregabalin reduces post-operative analgesic requirements,^{30–32} within the areas studied. Mirshriky et al., in 2015³³ showed in their meta-analysis that pregabalin given both pre- and post-surgery reduced pain scores and opioid consumption, but they too could not confidently establish recommendations for ideal doses or delivery regimens. Mathiesen et al.³⁴ demonstrated that pre-operative oral pregabalin reduced subsequent opioid use, but not pain scores or opioid-related adverse effects. A similar meta-analysis by Zhang, Ho

and Wang³¹ showed that peri-operative multiple administration of pregabalin reduced post-operative morphine consumption, although did not reduce the intensity of the patient-reported pain experience. Of note however, the majority of the eleven studies included in this review reported outcomes from ‘minimally invasive’ surgery and therefore the pain generation drivers and pain experiences may not be directly comparable to that of open major surgery (i.e. TKR). Furthermore, no standardised measure of pain was adopted across the analysed studies, potentially limiting the utility of comparative drug-effect determination. Further review by Canihuate et al., in 2017³⁵ concluded that there was ‘probably’ no clear evidence that peri-operative pregabalin could contribute to a clinically-important reduction in pain experienced by patients after major surgery, although arthroplasty patients were poorly represented in the meta-analysed cohort. The oral pregabalin in this study was however, associated with a clear decrease in post-surgical nausea, vomiting and overall opioid requirements. The authors also commented that there was an apparent increase in observed sedation scores among patients receiving oral pregabalin – this may prove a cautionary insight for orthopaedic patients, especially in older patient cohorts. Similarly, Jokela et al.³⁶ reported that the sedation effect of oral pregabalin in 75 mg and 150 mg doses was of a similar clinical effect to that of 5 mg of diazepam.

1.3. Uses in orthopaedic surgery

The evidence-supported use of pregabalin in orthopaedics has largely been confined to spinal surgery due to the high association with established (chronic) pain in these patients. Single administration of pregabalin was demonstrated to have benefit in opioid consumption reduction following both lumbar laminectomy^{32,37} and discectomy.³⁸ Liu and colleagues³⁹ compared the use of gabapentoids and placebo in management of pain post spinal surgery, concluding that the use of such medications was associated with meaningful analgesic effects and reduction in the use of post-operative opioids. These findings largely mirrored that of an earlier study of 60 patients undergoing lower limb orthopaedic surgery by Akhavankbari et al.,⁴⁰ who found the peri-operative administration of pregabalin had significant opioid-sparing effects and a reduction in post-operation pain in the first 24 h after surgery. They also found a notable reduction in nausea and vomiting. Similar to previous findings, gabapentoids had a decrease in the adverse effects of nausea, vomiting, and pruritus.³⁹

Fujita et al.⁴¹ compared the use of single dose pregabalin pre-operatively compared to a diazepam control and found reduced post-operative pain intensity and opioid consumption. Fujita's paper also commented there was an improved reduction in the pain experience at 150 mg dose, when compared to a 75 mg dose, and suggested the 150 mg single dose might be the ‘ideal’ amount for maximum safe effect. Gonano et al.⁴² in their small study did not find a significant difference in pain scores between pregabalin and placebo in reviewing 40 patients, however they did note there was a significant anxiolytic effect of a 300 mg pregabalin dose for patients undergoing minor orthopaedic surgery. Ménigaux et al.⁴³ had similar findings of reduced anxiety in their study of using 1200 mg doses of gabapentin prior to anterior cruciate ligament reconstructions. Ménigaux also found the gabapentin group had half the opioid consumption at 48 h post-surgery. The later work of Lam and colleagues⁴⁴ reinforced the suggestion of a reduction in opioid consumption, however they also identified a significant increase in sedation scores, for patients taking pregabalin, which again raised concerns of the risks in elderly patient groups. Sebastian et al.⁴⁵ had similar findings in their paper suggesting a decrease in overall opioid consumption, but increased frequencies of dizziness, hypotension and sedation. The paper noted that pregabalin lead to higher patient satisfaction levels in patients undergoing lower limb orthopaedic surgery, and did not alter intra-operative patient haemodynamics. The stabilisation of intra-operative haemodynamics was also reported in the recent work by Dahmardeh et al.,⁴⁶ likely reflecting a stable

background analgesic effect. Exploring the peri-operative pain experience more broadly, Khetarpal et al.⁴⁷ concluded that the use of pre-operative pregabalin (300 mg) had clinically-significant effects in reducing analgesic requirements, the re-administration of an epidural during operation, and increased the duration of the epidural anaesthetic effects post-operation.

In other specific areas of orthopaedic surgery there have been similar results. In a double-blinded, randomised controlled trial (RCT), Montazeri and colleagues⁴⁸ found patients who received a 300 mg dose of gabapentin had significantly lower pain scores, and less morphine consumption within the first 24 h post-surgery. In contrast, the later work of YaDeau and colleagues⁴⁹ found no clinical benefit with peri-operative administration of 100 mg pregabalin followed by 12 hourly intervals of 50 mg in their 66 patients undergoing foot and ankle surgery. It is noted the confounding effect of the concurrent administration of pre-operative regional anaesthetic blockade, which may have ameliorated much of the potential block to pain sensitisation benefit of the pregabalin. Equally, YaDeau and colleagues measured the duration of the analgesic gap from moderate to severe pain, as opposed to patient-reported pain scores which have largely been used as primary outcome measures in most other investigations. Clarke et al.⁵⁰ examined the role of pregabalin in hip arthroplasty and found that peri-operative pregabalin was successful in decreasing the opioid consumption and pain scores of their patients at one-week post-surgery but had no impact on the pain of physical function at six weeks and three months post-surgery. Post and colleagues⁵¹ examined two pain control protocols after total hip arthroplasties, comparing a fentanyl-based patient controlled analgesia (PCA) and a non-opioid based protocol including 75 mg pregabalin. These authors found that the group treated with pregabalin had lower pain scores, less breakthrough opioid use and fewer reported adverse effects, suggesting peri-operative benefit over traditional PCA use.

1.4. Pregabalin in total knee replacement

Clarke and colleagues⁵² reported one of the first studies to examine the role of gabapentoids in TKR in a small study of 36 patients. The small sample size may have left the work underpowered to demonstrate meaningful clinical benefit. Participants were divided into five smaller subgroups and given pre- and post-operative gabapentin with different regimes. While they found no statistical difference in pain scores between gabapentin and placebo, the former group did however demonstrate significantly better early post-operative knee flexion. A follow up study published by Clarke et al., in 2014⁵³ found that there was lower pain experienced in both 600 mg gabapentin and 200 mg gabapentin groups, compared to placebo, in the first 24 h post TKR, with all other considerations otherwise standardised. A RCT by Buvanendran et al., in 2010⁵⁴ found that for their 240 patients undergoing TKR, the half who received 300 mg pregabalin pre- and for 14 days post-surgery had reduced post-operative opioid consumption and improved mobility during rehabilitation, with decreased pain scores on passive range-of-motion at discharge. The primary outcome of this study was incidence of neuropathic pain at six months, which was found to decrease from 8.7% to 0%. YaDeau et al.⁵⁵ failed to demonstrate an analgesic benefit on knee flexion at post-op day 14 of pregabalin doses ranging from 100 to 300 mg pre-operatively, with half doses given post-surgery. Interestingly, they also commented on reduced patient satisfaction and increased drowsiness with the pregabalin groups. However, in contrast to the earlier Buvanendran study, YaDeau's treatment regime favoured bupivacaine peripheral nerve blocks, again making direct comparison of the study findings difficult. In a patient cohort of 300 who were randomised to receive 150 mg or 300 mg of pregabalin, or a placebo, research conducted by Singla et al.⁵⁶ failed to show a significant difference in pain levels experienced at 48 h post-surgery but noted improved range-of-motion and an opioid-sparing effect of the pregabalin groups. The study's election to record the patient's individual

recollection of the 'worst pain' in the previous 24 h also makes validation and wider generalisability of the method difficult to establish. Furthermore, the choice of post-operative analgesic regime was determined by the individual treating surgeons, with great between-patient variability. Another 2015 prospective, randomised, controlled single-centre trial in 2015 by Lee, Chung and Choi⁵⁷ had 52 patients split between 150 mg pregabalin and non-active placebo as a single dose prior to surgery and found the pregabalin groups had less pain during mobilisation at 48 h but not less stationary pain scores at the earlier 12 h mark. Hamilton, Strickland & Pandit⁵⁸ performed the first noted meta-analysis of the 12 RCTs available for gabapentoids (five gabapentin, seven pregabalin) and TKR in 2016. They concluded from their review that while there was no statistical reduction in overall pain scores associated with gabapentoid use, there was a clinically-significant reduction in overall opioid consumption. From the review, it was also noted that there existed little evidence confirming an improvement of function during rehabilitation or a reduction in pain during active knee flexion. The side effect profile of pregabalin was noted to have less nausea than opioids but at the expense of an increase in sedation. The authors noted there were insufficient studies available to evaluate the dosages and dosing regimens of gabapentoids and their optimal efficacy. Several of the findings of this recent review are in contrast to comparable reviews noted in other areas of surgery, the authors proposing that this was potentially due to differing nociceptive responses at different surgical sites. This notion was explored independently by Mishriky et al.³³ who found that the type of surgical procedure was a significant predictor of post-operative pain, accounting for 32% of the observed variance at 24 h. Eipe et al.⁵⁹ commented that gabapentoids are likely most efficacious in conditions associated with chronic pain, such as spinal surgical procedures – true chronic pain conditions are estimated to occur in less than 20% of patients following TKR. Dong, Li and Wang⁶⁰ concluded in their meta-analysis in 2016 that pregabalin has valuable independent analgesic action while concurrently reducing opioid consumption, although cautioning the previously heralded concern that it may increase dizziness and/or sedation. In a review of seven RCTs examining pregabalin in TKR, Han et al.⁶¹ found that pregabalin was effective at reducing opioid consumption and permitted better passive flexion range at 48 h post-surgery. Lubis, Rawung and Tantri⁶² were unable to replicate this result in their 2018 study and found that, although pregabalin was effective at decreasing pain scores for a stationary patient, it was ineffective for motion pain scores. Equally, they did not find a demonstrable analgesic benefit between their two study groups of single dose 150 mg and twice daily repeated 75 mg doses for three days. In retrospect, their study was limited by small sample sizes (only 10 patients per group, 30 total), potentially undermining any meaningful potential value of the sub-group analyses reported.

2. Conclusion

Robust evidence in the contemporary literature regarding the use of pregabalin in surgery remains limited, and within the domain of orthopaedics even more so, however initial studies do suggest a potential benefit for peri-operative pregabalin use in the reduction of opioid requirements post-surgery. The evidence-based accepted body-of-understanding for gabapentoid use in peri-operative management of lower limb arthroplasty populations is even more scant. Less opioid-based analgesic use post-arthroplasty is of appreciable benefit in reducing a suite of known drug-related adverse effects, not the least of which is respiratory depression and global sedation – both particularly concerning in older patient cohorts undergoing joint replacement. There remains no current consensus on the exact mechanism of analgesic effect of pregabalin in patients undergoing a TKR, nor objective definition of its value in recovering post-operative knee function. The ideal dosage and dose frequency of pregabalin has also not been well established in this setting, limiting broader recommendations for standardised use.

While it may not prove the panacea for analgesic control post-arthroplasty surgery, there certainly appears a role for these medications in optimized multi-modal patient-centric care. Further high-quality randomised controlled trials are indicated to better elucidate the optimized role of pregabalin and other gabapentinoids for the peri-operative management of patients undergoing elective TKR surgery.

Conflicts of interest

The authors have no conflict of interests to declare.

References

1. Apfelbaum JL, Gan TJ, Chen C. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97:534–540.
2. Pavlin DJ, Chen C, Penaloza DA, Poilsar NL, Buckley FP. Pain as a factor complicating recovery and discharge after ambulatory surgery. *Anesth Analg*. 2002;95:627–634.
3. Kates SL. Geriatric orthopaedic surgery & rehabilitation: the imminent silver tsunami and the need for a new journal. *Geriatr Orthop Surg Rehabil*. 2010;1–5.
4. Herkowitz HN, Dirschl DR, Sohn DH. Pain management: the orthopaedic surgeon's perspective. *J Bone Jt Surg*. 2007;89A:2532–2535.
5. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia*. 2004;45(6):13–18.
6. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother*. 2005;39:2029–2037.
7. Tanabe M, Takasu K, Takeuchi Y, Ono H. Pain relief by gabapentin and pregabalin via supraspinal mechanisms after peripheral nerve injury. *J Neurosci Res*. 2008;86:3258–3264.
8. Hayashida K, Obata H, Nakajima K, Eisenach J. Gabapentin acts within the locus coeruleus to alleviate neuropathic pain. *Anesthesiology*. 2008;109:1077–1084.
9. Hayashida K, DeGoes S, Curry R, Eisenach J. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. *Anesthesiology*. 2007;106:557–562.
10. Kissin I. Preemptive analgesia. Why its effect is not always obvious. *Anesthesiology*. 1996;84:1015–1019.
11. Bockbrader HN, Radulovic LL, Posvar EL, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. *J Clin Pharmacol*. 2010;50:941–950.
12. Hindmarch I, Trick L, Ridout F. A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. *Psychopharmacology*. 2005;183:133–143.
13. Kavoussi R. Pregabalin: from molecule to medicine. *Eur Neuropsychopharmacol*. 2006;16(2):S128–S133.
14. LaMoreaux L. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110:628–638.
15. Dworkin RHP, Corbin AEM, Young JPJ, et al. Pregabalin for the treatment of post-herpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*. 2003;60:1274–1283.
16. Sabatowski R, Gálvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain*. 2004;109:26–35.
17. French JA, Kugler AR, Robins JL, Knapp LE, Garofalo EA. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. *Neurology*. 2003;60:1631–1637.
18. Feltner DE, Crockatt JG, Dubovsky SJ. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol*. 2003;23:240–249.
19. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52:1264–1273.
20. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. *Anesth Analg*. 2007;105:1449–1453.
21. Ittichaikulthol W, Virankabutra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S. Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salpingo-oophorectomy: a randomized, double-blind trial. *J Med Assoc Thai*. 2009;92:1318–1323.
22. Peng PWH, Li C, Farcas E, et al. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. *Br J Anaesth*. 2010;105:155–161.
23. Balaban F, Yağar S, Özgök A, Koç M, Güllapoğlu H. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. *J Clin Anesth*. 2012;24:175–178.
24. Cheung CW, Choi WS, Leung YY, et al. A double-blind randomized crossover study to evaluate the timing of pregabalin for third molar surgery under local anaesthesia. *J Oral Maxillofac Surg*. 2012;70:25–30.
25. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. *Obes Surg*. 2010;20:1678–1681.
26. Demirhan A, Akkaya A, Tekelioglu UY, et al. Effect of pregabalin and dexamethasone on postoperative analgesia after septoplasty. *Pain Res Treat*. 2014;2:850794.
27. Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. *Reg Anesth Pain Med*. 2012;2:72–76.
28. Bornemann-Cimenti H, Lederer AJ, Wejbor M, et al. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. *Br J Anaesth*. 2012;108:845–849.
29. Liébana-Hermoso S, Manzano-Moreno FJ, Vallecillo-Capilla MF, Olmedo-Gaya MV. Oral pregabalin for acute pain relief after cervicofacial surgery: a systematic review. *Clin Oral Investig*. 2018;22(1):119–129.
30. Engelman E, Cateloy F. Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized controlled trials. *Acta Anaesthesiol Scand*. 2011;55:927–943.
31. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. *Br J Anaesth*. 2011;106:454–462.
32. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of post-operative pain after lumbar spinal surgery: a systematic review and meta-analysis. *Spine*. 2013;38:1947–1952.
33. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Br J Anaesth*. 2015;114:10–31.
34. Mathiesen O, Jacobsen LS, Holm HE, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. *Br J Anaesth*. 2008;101(4):535–541.
35. Canihuante J, Molina I, Altermatt F. Is perioperative pregabalin effective for reducing postoperative pain in major surgery? *Medwave*. 2017;17(9):e7115.
36. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth*. 2008;100:834–840.
37. Kumar KP, Kulkarni DK, Gurajala I. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blind, placebo-controlled study. *J Pain Res*. 2013;6:471–478.
38. Spreng UJ, Dahl V, Raeder J. Effect of a single dose of pregabalin on post-operative pain and pre-operative anxiety in patients undergoing discectomy. *Acta Anaesthesiol Scand*. 2011;55:571–576.
39. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. *Medicine*. 2017;96(37):e8031.
40. Akhavanakbari G, Entezariasl M, Isazadehfah K, Mirzarahimi T. The effects of oral pregabalin on post-operative pain of lower limb orthopedic surgery: a double-blind, placebo-controlled trial. *Perspect Clin Res*. 2013;4(3):165–168.
41. Fujita N, Tobe M, Tsukamoto N, Saito S, Obata H. A randomized placebo-controlled study of preoperative pregabalin for postoperative analgesia in patients with spinal surgery. *J Clin Anesth*. 2016;31:149–153.
42. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. *J Psychopharmacol*. 2011;25(2):249–253.
43. 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;100:1394–1399.
44. Lam D, Choi SW, Wong S, Irwin M, Cheung C. Efficacy of pregabalin in acute post-operative pain under different surgical categories: a meta-analysis. *Medicine*. 2015;94(46):e1944.
45. Sebastian B, Talkikoti AT, Nelamangala K, Krishnamurthy D. Effect of oral pregabalin as preemptive analgesic in patients undergoing lower limb orthopedic surgeries under spinal anaesthesia. *J Clin Diagn Res*. 2016;10(7):UC01–UC04.
46. Dahmardeh AR, Moosavi A, Tabatabaei SM, Ordoni Avval J, Sistanizad M. The effect of a single dose oral pregabalin on hemodynamic changes and duration of analgesia after spinal anesthesia in orthopedic surgeries of tibial fractures. *Iran J Pharm Res (IJPR)*. 2018;17:2–7.
47. Khetarpal R, Kataria AP, Bajaj S, Kaur H, Singh S. Gabapentin vs pregabalin as a premedication in lower limb orthopaedics surgery under combined spinal epidural technique. *Anesth Essays Res*. 2016;10(2):262–267.
48. Montazeri K, Kashefi P, Honarmand A. Pre-emptive gabapentin significantly reduces postoperative pain and morphine demand following lower extremity orthopaedic surgery. *Singap Med J*. 2007;48:748–751.
49. YaDeau JT, Paroli LP, Kahn RL, et al. Addition of pregabalin to multimodal analgesic therapy following ankle surgery: a randomized double-blind, placebo-controlled trial. *Reg Anesth Pain Med*. 2012;37:302–307.
50. Clarke HA, Pagé GM, McCartney CJL, et al. Pregabalin reduces postoperative opioid consumption and pain for 1 week after hospital discharge, but does not affect function at 6 weeks or 3 months after total hip arthroplasty. *Br J Anaesth*. 2015;115(6):903–911.
51. Post ZD, Restrepo C, Kahl LK, van de Leur T, Purtill JJ, Hozack WJ. A prospective evaluation of 2 different pain management protocols for total hip arthroplasty. *J Arthroplast*. 2010;25:410–415.
52. Clarke HA, Pereira S, Kennedy D, et al. Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. *Pain Res Manag*. 2009;14:217–222.
53. Clarke HA, Katz J, McCartney CJ, et al. Perioperative gabapentin reduces 24 h opioid consumption and improves in-hospital rehabilitation but not post-discharge outcomes after total knee arthroplasty with peripheral nerve block. *Br J Anaesth*. 2014;113:855–864.
54. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg*. 2010;110:199–207.
55. YaDeau JT, Lin Y, Mayman DJ, et al. Pregabalin and pain after total knee arthroplasty: a double-blind, randomized, placebo-controlled, multidose trial. *Br J*

- Anaesth.* 2015;115(2):285–293.
56. Singla NK, Chelly JE, Lionberger DR, et al. Pregabalin for the treatment of postoperative pain: results from three controlled trials using different surgical models. *J Pain Res.* 2015;8:9–20.
 57. Lee JK, Chung KS, Choi CH. The effect of a single dose of preemptive pregabalin administered with COX-2 inhibitor: a trial in total knee arthroplasty. *J Arthroplast.* 2015;30(1):38–42.
 58. Hamilton TW, Strickland LH, Pandi HG. A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. *J Bone Jt. Surg.* 2016;98:1340–1350.
 59. Eipe N, Penning J, Yazdi F, et al. Perioperative use of pregabalin for acute pain-a systematic review and meta-analysis. *Pain.* 2015;156(7):1284–1300.
 60. Dong J, Li W, Wang Y. The effect of pregabalin on acute postoperative pain in patients undergoing total knee arthroplasty: a meta-analysis. *Int J Surg.* 2016;34:148–160.
 61. Han C, Kuang MJ, Ma JX, Ma XL. Is pregabalin effective and safe in total knee arthroplasty? A PRISMA-compliant meta-analysis of randomized-controlled trials. *Medicine.* 2017;96(26):e6947.
 62. Lubis AMT, Rawung RBV, Tantri AR. Preemptive analgesia in total knee arthroplasty: comparing the effects of single dose combining celecoxib with pregabalin and repetition dose combining celecoxib with pregabalin: double-blind controlled clinical trial. *Pain Res. Treat.* 2018;3:1–6.