# A meta-analysis on the use of gabapentinoids for the treatment of acute post-operative pain following total knee arthroplasty.


## Abstract

**Background:** Total knee arthroplasty (TKA) is a painful procedure with approximately one-half of patients reporting severe pain during the early post-operative period. Gabapentinoids are used as an adjunct for the management of acute pain in approximately one-half of Enhanced Recovery Programs (ERP). We performed a meta-analysis to assess the effectiveness and safety of gabapentinoids for the treatment of acute-post operative pain following TKA.

**Methods:** Randomized controlled trials (RCT) of patients undergoing elective primary TKA that compared the use of **the gabapentinoid class of drugs (gabapentin (Neurontin, Pfizer, New York) or pregabalin (Lyrica, Pfizer, New York))** to placebo were retrieved with 12 studies meeting inclusion criteria. The primary outcome was pain intensity with activity at 48-hours following surgery. Secondary outcomes included pain intensity at other time-points, opioid consumption, knee function, incidence of chronic pain and adverse events.

**Results:** No difference in pain score at 12, 24, 48 or 72-hours following surgery was seen between gabapentinoids and placebo. While subgroup analysis revealed that pregabalin was associated with reduced pain-scores at 24 and 48 hours this corresponded to 0.5 (95%CI 0 to 1.0) and 0.3-points (95%CI 0 to 0.6) reduction on an 11 point numeric rating scale respectively, which is not of clinical significance. Likewise, gabapentinoids were associated with a small, but not clinically significant, reduction in cumulative opioid consumption at 48-hours **(mean difference (MD) -23.2mg; 95%CI -40.9 to -5.4)**. There was no difference in knee flexion at 48-hours **(*p*=0.63)** or the incidence of chronic pain at 3 **(*p*=0.31)** or 6-months **(*p*=0.54)** associated with the use of gabapentinoids. While gabapentinoids were associated with a significant reduction in the incidence of nausea **(RR 0.7; 95%CI 0.6 to 0.9)** pregabalin was also associated

with a significant, clinically relevant, increase in the risk of sedation **(RR 1.4; 95%CI 1.1 to 1.9)**.

**Conclusion:** Based on this meta-analysis we found no evidence to support the use of gabapentinoids in the management of acute pain following TKA. This study does not support the routine use of gabapentinoids as part of an Enhanced Recovery P**rogram**.

## Introduction

**Approximately one-half of all total knee arthroplasty (TKA) patients experience severe postoperative pain, despite multimodal analgesia**[1]. Pain is the most common reason for delayed discharge as well as a common cause of readmission[2]. Improving a patient's peri-operative recovery through multi-modal Enhanced Recovery Programs (ERP) has significant benefits for the patient, surgeon and healthcare payer. ERPs have been demonstrated to reduce short and long term morbidity and mortality, improve functional outcomes and reduce length of stay[3-5]. While the literature supports the use of ERPs, which components of these programs are most important in optimising patient outcomes both in the short term and long term remain undefined.

**The** gabapentinoid **class of drugs which includes** gabapentin (Neurontin, Pfizer, New York) and pregabalin (Lyrica, Pfizer, New York), **has** an established role in the management of neuropathic pain[6]. While they are not **indicated** for the management of acute post-operative pain there is significant interest in their potential as opioid-sparing adjuncts and they are currently used in approximately one-half of TKA ERPs[7]. Gabapentin and pregabalin share a similar chemical structure[8]. They act by inhibiting central sensitization and, in addition, may inhibit nociceptive transmission in the descending noradrenergic system[9, 10]. While similarities in structure and mechanism exist, due to differences in pharmacokinetics pregabalin has an increased potency and as such is associated with an increased clinical efficacy as well as increased incidence of adverse effects including sedation and dizziness[11].

While previous meta-analyses support the use of gabapentinoids in reducing acute post-operative pain and limiting opioid use, in particular following abdominal hysterectomy and spinal surgery, the role of gabapentinoids following TKA has yet to be defined to our knowledge[12-15]. The objective of this meta-analysis was to determine if gabapentinoids are effective adjuncts in the

management of acute post-operative pain following TKA and, if so, whether any benefits seen outweigh the risk of harm posed by the risk of drug-related adverse effects.

## Materials and Methods

### Inclusion and Exclusion Criteria

Eligible studies included parallel-group, blinded, randomized controlled trials (RCTs) of patients aged 18 years or older undergoing elective primary TKA that **compared the use of oral gabapentin or pregabalin with placebo**. There was no restriction on studies that investigated single or multiple dosing schedules, pre- or pre and post-operative dosing or based on the type of anaesthesia.

### Information Sources and Search Strategy

Electronic databases (MEDLINE (Ovid), EMBASE (Ovid), Web of Science (ISI Web of Knowledge)) were searched from their inception until 8 September 2015 (Appendix 1). In addition, reference lists and registers of controlled clinical trials were searched. No restrictions were applied based on the publication status or language.

Studies were assessed, and data extracted, independently in duplicate (***** Blinded by JBJS *****). A risk of bias assessment was performed on included studies[16].

### Outcome measures assessed

The primary outcome was pain intensity with activity at 48 hours. Where pain with activity at 48-hours was not reported pain at rest was used if available.

Secondary outcomes included: pain scores at 12, 24 and 72 hours, cumulative opioid consumption (0 to 48 hours), active knee flexion at 48 hours, incidence of chronic pain and adverse events (sedation, dizziness, nausea and pruritus, 0 to 72 hours). If the incidence of

adverse events from 0 to 72 hours was not reported the incidence at 24 hours was used as the majority of adverse events occur following the initial loading dose.

**Statistical analysis**

Heterogeneity was assessed using the using the $I^2$ statistic. **Where** substantial heterogeneity ($I^2$>85%) **was identified** a meta-analysis was not be performed. As a degree of variability was expected a random-effects model was used. For continuous data the **standardized mean difference** (SMD) with 95% confidence-intervals (95%CI) was calculated using the inverse variance method. For opioid consumption the reported consumption was converted to oral opioid equivalent dose and the **mean difference** (MD) calculated. For dichotomous data the **risk ratio** (RR) was calculated using the Mantel-Haenszel method. Data analysis was performed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

**Protocol and registration**

***** Blinded by JBJS *****

**Source of Funding**

No external funding received.

**Results**

Twelve RCTs compared the use of gabapentin (5 studies) or pregabalin (7 studies) with placebo in patients undergoing elective primary TKA. Figure 1. The results from one study were presented in a manner that prevented their inclusion in the quantitative analysis[17]. A risk of bias assessment is outlined in Figure 2. Two studies, Lee *et al.* and **Brackel *et al.***, did not describe the use of placebos presenting a high risk of performance bias and an unclear risk of detection bias[17,18]. Singla *et al.* did not report information regarding allocation concealment, blinding of

participants and personnel and outcome assessors presenting an unclear risk of bias[19]. Additionally, only 69% of participants completed treatment giving a high risk of attrition bias. Three studies were funded by the manufacture of the trial drug presenting an unclear risk of other bias[19-21]. **A sensitivity analysis was performed based on the risk of bias and exclusion of studies at high risk of bias did not change the interpretation of results.**

The dose of gabapentin ranged from 300mg to 1300mg per day. The dose of pregabalin ranged from 100mg to 600mg per day. The mean age ranged from 57 to 68 years with 43% to 81% female participants. The primary indication for TKA was OA (96% to 100%). A summary of the trials, which included 1501 knees, is provided in Table 1.

**Pain intensity at 48-hours following surgery**

Pain intensity at 48-hours was reported in eight studies with a high heterogeneity seen ($I^2$=73%). Patient receiving gabapentinoids had lower pain scores at 48-hours compared to **placebo (SMD -0.15; 95%CI -0.28 to -0.02; *p*=0.03)**. Figure 3. Subgroup analysis revealed this effect was limited to those receiving pregabalin **(SMD -0.24; 95%CI -0.45 to -0.03; *p*=0.03)** with no difference seen with gabapentin **(SMD -0.09; 95%CI -0.26 to 0.08; *p*=0.29)**. The effect size associated with the use of gabapentinoids was small and interpreting SMD clinically is challenging. On the basis of the mean standard deviation from trials using an 11 point (0 to 10) NRS, the effect of gabapentinoids corresponds to a reduction of 0.3 points (95%CI 0 to 0.6 points).

These findings were supported by evidence from **Brackel *et al.*** who found no difference in pain intensity between those patients receiving gabapentin and those who did not[17]. Additionally, Buvanendran *et al*. found no differences in pain-scores from 0 to 32-hours and YaDeau *et al.* found no differences at both 24 and 72-hours in those patients receiving pregabalin[21, 22].

**Pain intensity at other time points following surgery**

At twelve-hours four studies (gabapentin one study, pregabalin three studies) reported pain-scores with activity. High heterogeneity ($I^2$=88%) limited statistical analysis. Clarke *et al.*, assessing gabapentin, found no difference in pain score at 12-hours[23]. Two studies found no significant difference associated with the use of pregabalin, and one small study, Lee *et al.* (41 knees), reported a positive effect[18, 19, 21].

At 24-hours pain scores were reported in ten studies. Subgroup analysis revealed that patients receiving pregabalin had lower 24-hour pain scores **(SMD -0.30; 95%CI -0.58 to -0.01; *p*=0.04)**; however overall, in patients receiving gabapentinoids no difference was seen **(SMD -0.17; 95%CI -0.40 to 0.06; *p*=0.14)**. Figure 4. On the basis of the mean standard deviation from trials using an 11 point NRS, the effect of pregabalin corresponded to a 0.5 point (95% CI 0 to 1.0 points) reduction at 24-hours.

At 72-hours no difference was seen between patients receiving gabapentinoids (four studies; **SMD 0.01; 95%CI -0.17 to 0.19; *p*=0.89)**, or on subgroup analysis, compared to placebo. Figure 5.

**Cumulative opioid consumption at 48-hours following surgery**

Patients receiving gabapentinoids had lower cumulative opioid consumption (six studies) compared with placebo **(MD -23.19mg; 95%CI -40.93mg to -5.44mg; *p*=0.01)**. Figure 6. Subgroup analysis revealed this effect was limited to pregabalin **(MD -33.14mg; 95%CI -53.98mg to -12.29mg; *p*=0.002)** with no difference seen with gabapentin **(MD -6.66mg; 95%CI -23.78mg to 10.47mg; *p*=0.45)**.

Whilst **Brackel *et* al.** found no difference in those receiving gabapentin Clarke *et al.* found a 10mg reduction in 24-hour cumulative opioid consumption associated with the use of Gabapentin[17, 24]. Buvanendran *et al.* and Jain *et al.* reported similar reductions in 24-hour opioid consumption associated with Pregabalin[20, 25]. The clinical relevance of these reductions was not

discussed in any studies but overall the reduction associated with Pregabalin was small, corresponding to a 15% reduction in opioid consumption.

**Functional Outcomes**

Active knee flexion at 48-hours was reported in five studies with no difference seen in patients receiving gabapentinoids **(MD 1.10°; 95%CI -3.41° to 5.62°; *p*=0.63)** or on subgroup analysis.

Three-studies investigated the incidence of chronic pain following peri-operative pregabalin. YaDeau and Buvanendran reported the incidence of neuropathic pain assessed using the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (LANSS)[20, 22,26]. Singla *et al.* reported the incidence of pain using a 11 point NRS where a score of 1 or greater was regarded as positive[19]. At both three-months **(RR 0.43; 95%CI 0.09 to 2.15; *p*=0.31)** and six-months **(RR 0.43; 95%CI 0.03 to 6.69; *p*=0.54)** no difference in the incidence of pain was seen between patients receiving pregabalin and placebo. Figure 7.

**Adverse effects**

No increase in the risk of sedation (five studies) was observed in those patient receiving gabapentinoids **(RR 1.19; 95%CI 0.90 to 1.56; *p*=0.22)**. Figure 8. Subgroup analysis revealed, that whilst in those studies assessing gabapentin no difference was seen **(RR 0.95; 95%CI 0.76 to 1.20; *p*=0.68)**, in those receiving pregabalin an increased incidence of sedation was observed **(RR 1.44; 95%CI 1.07 to 1.94; *p*=0.02)**. The Number Needed to Treat (NNT) with pregabalin to result in one case of sedation was 8.7.

This data was supported by evidence from Clarke *et al.* who found no difference in sedation associated with the use of gabapentin at any time points[24]. Additionally, whilst Lunn *et* al. found an increased incidence of sedation at 6-hours, following a loading dose of 900mg gabapentin there was no difference in sedation seen at any other time points[27].

No difference in the incidence of dizziness (six studies) was seen in patients receiving gabapentinoids **(RR 1.15; 95%CI 0.81 to 1.62; *p*=0.43)** or on subgroup analysis[19, 20, 24, 25, 28, 29].

There was a decreased risk of nausea (seven studies) associated with the use of gabapentinoids **(RR 0.74; 95%CI 0.63 to 0.88; *p*<0.001)**. Figure 9. Subgroup analysis revealed that this finding was seen in those studies assessing gabapentin **(RR 0.80; 95%CI 0.65 to 0.97; *p*=0.03)** but not in those receiving pregabalin **(RR 0.72; 95%CI 0.50 to 1.03; *p*=0.07)**, where no difference in the risk of nausea compared to placebo was seen. The NNT with Gabapentin to result in one less case of nausea was 9.7.

No difference in the incidence of pruritus (five studies) was seen in patients receiving gabapentinoids **(RR 0.69; 95%CI 0.39 to 1.22; *p*=0.20)** or on subgroup analysis[20, 23-25, 29].

**Effect of Dose**

**Subgroup analysis was performed to investigate the impact of dose. At 48-hours high dose gabapentin (≥900mg/day; three-trial arms, 206-participants) was associated with lower pain scores (SMD -0.30; 95%CI -0.54 to -0.05) compared to both control (*p*=0.02) and those receiving low dose gabapentin (<900mg/day; five trial arms, 153 participants; *p*=0.02) which was not associated with any difference in pain-scores (SMD 0.10; 95%CI -0.14 to 0.34). The effect of high dose gabapentin corresponds to a reduction of 0.4 points (95%CI 0 to 0.7-points) on an 11 point NRS and as such was not assessed as clinically relevant. No difference was seen between different doses on pain-score at other time points or cumulative opioid intake. No difference in pain outcome scores or opioid consumption was detected between pregabalin low dose (<300mg/day, eight-arms, 248-participants) and high dose (≥300mg/day, four arms, 277 participants). It was not possible to assess the impact of dose on the risk of adverse events for gabapentin or pregabalin.**

## Discussion

Our meta-analysis has demonstrated that the use of gabapentinoids is not associated with reduced pain-scores at 12, 24, 48 or 72-hours. While subgroup analysis revealed that pregabalin is associated with a reduction in pain scores, equivalent to 0.5 (95% CI 0 to 1.0) and 0.3 points (95%CI 0 to 0.6) on an 11 point NRS, at 24-hours and 48-hours respectively, this reduction is not of clinical significance. Gabapentinoids were associated with a reduction in cumulative opioid consumption, although this effect was found to be small, 15%, and likely not of clinical significance. There was no evidence that the use of gabapentinoids improved short or long-term function with no difference in knee flexion at 48-hours, or incidence of chronic pain at 3 or 6-months. Gabapentinoids were associated with a reduction in the incidence of nausea but pregabalin was associated with a clinically relevant increase in sedation. This is the first meta-analysis to assess the efficacy of gabapentinoids in the management of acute post-operative pain following TKA. We have found no evidence to support the routine use of gabapentinoids in the management of acute pain following TKA, and this study does not support the routine use of gabapentinoids as part of an ERP.

The results of this study are contradictory to previous meta-analysis assessing the use of gabapentinoids in the management of acute post-surgical pain which have found that their use was associated with significant reductions in pain following tonsillectomy, abdominal hysterectomy, thoracic and spinal surgery[30-35]. **Possible explanations for these differences include differences in the mechanism and response to pain at different surgical sites which may be due to disease factors, surgical factors or patient factors including patient selection and central sensitization.** A meta-analysis by Mishriky *et al.* found that the type of surgery was a significant predictor of post-operative pain scores, accounting for 32% of the variance at 24-hours[15]. Eipe *et al.* proposed that gabapentinoids are most likely to demonstrate efficacy in

conditions associated with chronic pain including spinal surgery, amputations and joint arthroplasty[36,14]. While chronic pain is seen in around 20% of patients following TKA this figure is lower than the 32% following discectomy and up to 85% seen following amputation[37-39]. If the mechanism proposed by Eipe *et al.* is correct then the lower incidence of chronic pain observed following TKA, compared to other surgeries, may explain why gabapentinoids failed to demonstrate efficacy in this population.

The use of pregabalin was associated with a 33mg (range 12 to 54mg), 15%, reduction in oral opioid equivalent dose over 48-hours following TKA with this finding unlikely to be of clinical relevance in this population due to baseline opioid consumption[12, 15]. While a reduction in the incidence of post operative nausea following TKA was associated with gabapentinoids this effect was limited to gabapentin (NNT=10), with no reduction seen with pregabalin. As such this anti-emetic effect is unlikely to be due to reduced opioid consumption, and is likely to be via alternative mechanisms[40]. Furthermore, no difference in other opioid-related adverse effects including pruritus or dizziness were seen providing further evidence that the reduction in opioid consumption may not be of clinical relevance. One adverse effect that was noted to increase following the administration of pregabalin, but not gabapentin, was the risk of sedation (Number Needed to Treat [NNT]=9). It has been reported previously that the risk of sedation increases with increasing dose, and the incidence is known to be higher following the first dose however it was not possible to evaluate these factors in the published studies. Whilst there is evidence that gabapentinoids improves sleep quality, and patient satisfaction, following TKA, sedation may prevent early mobilisation following surgery which has a strong evidence base in this population[21, 27, 41, 42].

It has previously been reported that the use of gabapentinoids may be associated with a reduction in the incidence of chronic pain[43]. This finding was not supported in this meta-analysis **which**

**found** no evidence of improved short-term knee function or reduction in knee pain at 3 or 6-months. Interesting, the only study which reported lower pain-scores at 3 and 6-months had a higher baseline incidence of chronic pain, 9%, compared to 4% seen in the other study using the same outcome measure (**Leeds Assessment of Neuropathic Signs and Symptoms;** LANSS)[20, 22]. Whilst the lack of data prevents formal analysis it is interesting to note that the baseline incidence of chronic pain in a meta-analysis reporting a reduction chronic pain associated with gabapentinoids was 25% (range 5% to 82%)[43]. Whilst the current evidence does not support the routine use of gabapentinoids to reduce chronic pain, further work is required to explore if gabapentinoids have a role in subgroups of TKA patients at high risk of this complication.

The limitations of this meta-analysis are that there were insufficient studies to permit evaluation of different doses, timings and frequency of gabapentinoids and that due to different anaesthetic and peri-operative analgesic regimes, as well as patient differences, significant heterogeneity was observed between studies. While the level of heterogeneity was below pre-specified levels to perform meta-analysis further studies would enhance the strength of the evidence presented. The strengths of this study are that it includes a large number of knees from high quality clinical trials at low risk of bias.

In summary, based on our meta-analysis, there was no evidence to support the analgesic efficacy of gabapentinoids in the management of acute post-operative pain following TKA and whilst opioid sparing effects were seen with the use of pregabalin these are unlikely to be of clinical significance. No beneficial effects in improving short term function or reducing the long term incidence of chronic pain were detected and whilst an anti-emetic effect was observed, a significant increase in the risk of sedation associated with the use of pregabalin was also detected. Further high quality randomized controlled trials, in particular investigating patients at

high risk of chronic pain, may yield positive results in subgroups of patients however the current evidence does not support the routine use of gabapentinoids as part of an ERP for TKA.

## References


1. Chan EY, Blyth FM, Cheow SL, Fransen M. Postoperative pain following hospital discharge after knee replacement surgery: a patient survey. Pain Manag. 2013 May;3(3):177-88. Epub 2014/03/25.

2. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop. 2011 Dec;82(6):679-84. Epub 2011/11/10.

3. Ibrahim MS, Khan MA, Nizam I, Haddad FS. Peri-operative interventions producing better functional outcomes and enhanced recovery following total hip and knee arthroplasty: an evidence-based review. BMC Med. 2013;11:37. Epub 2013/02/15.

4. Savaridas T, Serrano-Pedraza I, Khan SK, Martin K, Malviya A, Reed MR. Reduced medium-term mortality following primary total hip and knee arthroplasty with an enhanced recovery program. A study of 4,500 consecutive procedures. Acta Orthop. 2013 Feb;84(1):40-3. Epub 2013/02/02.

5. Paton F, Chambers D, Wilson P, Eastwood A, Craig D, Fox D, et al. Effectiveness and implementation of enhanced recovery after surgery programmes: a rapid evidence synthesis. BMJ Open. 2014;4(7):e005015. Epub 2014/07/24.

6. Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. Cochrane Database Syst Rev. 2005 (3):CD005452. Epub 2005/07/22.

7. Nagra N, Hamilton TW, Murray DW, Pandit HG. Inconsistencies in the Enhanced Recovery Programmes across the NHS. British Association for Surgery of the Knee; Telford, UK 2015.

8. 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 Oct;49(10):661-9.

9. Weinbroum AA. Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res. 2012 Apr;65(4):411-29.

10. Hayashida K, DeGoes S, Curry R, Eisenach JC. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. Anesthesiology. 2007 Mar;106(3):557-62.

11. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology. 2013 Nov;119(5):1215-21. Epub 2013/09/21.

12. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth. 2011 Apr;106(4):454-62. Epub 2011/03/02.

13. Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. Cochrane Database Syst Rev. 2010 (5):CD008183.

14. Eipe N, Penning J, Yazdi F, Mallick R, Turner L, Ahmadzai N, et al. Perioperative use of pregabalin for acute pain-a systematic review and meta-analysis. Pain. 2015 Jul;156(7):1284-300. Epub 2015/04/02.

15. 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 Jan;114(1):10-31. Epub 2014/09/12.

16. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. Epub 2011/10/20.

17. Brackel AML, Marting LN, Timmerman L. Comparison of local infiltration analgesia with epidural analgesia after total knee arthroplasty: a randomized clinical trial (NCT01489631). Dutch Society of Anesthesiology. Zeist, September 2014.

18. 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. Journal of Arthroplasty. 2015 Jan;30(1):38-42.

19. Singla NK, Chelly JE, Lionberger DR, Gimbel J, Sanin L, Sporn J, 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. Epub 2015/01/08.

20. 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 Jan 1;110(1):199-207. Epub 2009/11/17.

21. Buvanendran A, Kroin JS, Della Valle CJ, Moric M, Tuman KJ. Cerebrospinal fluid neurotransmitter changes during the perioperative period in patients undergoing total knee replacement: a randomized trial. Anesth Analg. 2012 Feb;114(2):434-41. Epub 2011/12/14.

22. YaDeau JT, Lin Y, Mayman DJ, Goytizolo EA, Alexiades MM, Padgett DE, et al. Pregabalin and pain after total knee arthroplasty: a double-blind, randomized, placebo-controlled, multidose trial. Br J Anaesth. 2015 Aug;115(2):285-93. Epub 2015/07/15.

23. Clarke H, Pereira S, Kennedy D, Gilron I, Katz J, Gollish J, et al. Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. Pain Res Manag. 2009 May-Jun;14(3):217-22.

24. Clarke HA, Katz J, McCartney CJ, Stratford P, Kennedy D, Page MG, 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 Nov;113(5):855-64.

25. Jain P, Jolly A, Bholla V, Adatia S, Sood J. Evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee arthroplasty. Indian J Orthop. 2012 Nov;46(6):646-52. Epub 2013/01/18.

26. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001 May;92(1-2):147-57. Epub 2001/04/27.

27. Lunn TH, Husted H, Laursen MB, Hansen LT, Kehlet H. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty A randomized, double-blind, placebo-controlled, dose-finding study. Pain. 2015 Jul 28.

28. Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J, et al. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. Acta Anaesthesiol Scand. 2009 Sep;53(8):1073-83.

29. Paul JE, Nantha-Aree M, Buckley N, Cheng J, Thabane L, Tidy A, et al. Gabapentin does not improve multimodal analgesia outcomes for total knee arthroplasty: a randomized controlled trial. Can J Anaesth. 2013 May;60(5):423-31.

30. Hwang SH, Park IJ, Cho YJ, Jeong YM, Kang JM. The efficacy of gabapentin/pregabalin in improving pain after tonsillectomy: A meta-analysis. Laryngoscope. 2015 Sep 25. Epub 2015/09/26.

31. Alayed N, Alghanaim N, Tan X, Tulandi T. Preemptive use of gabapentin in abdominal hysterectomy: a systematic review and meta-analysis. Obstet Gynecol. 2014 Jun;123(6):1221-9. Epub 2014/05/09.

32. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine (Phila Pa 1976). 2013 Oct 15;38(22):1947-52. Epub 2013/08/08.

33. Zakkar M, Frazer S, Hunt I. Is there a role for gabapentin in preventing or treating pain following thoracic surgery? Interact Cardiovasc Thorac Surg. 2013 Oct;17(4):716-9. Epub 2013/07/09.

34. Mathiesen O, Moiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol. 2007;7:6. Epub 2007/07/10.

35. Yao Z, Shen C, Zhong Y. Perioperative Pregabalin for Acute Pain After Gynecological Surgery: A Meta-analysis. Clin Ther. 2015 May 1;37(5):1128-35. Epub 2014/06/05.

36. Eipe N, Penning J, Ansari M, Yazdi F, Ahmadzai N. A protocol for a systematic review for perioperative pregabalin use. Syst Rev. 2012;1:40. Epub 2012/09/15.

37. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2(1):e000435.

38. Parker SL, Xu R, McGirt MJ, Witham TF, Long DM, Bydon A. Long-term back pain after a single-level discectomy for radiculopathy: incidence and health care cost analysis. J Neurosurg Spine. 2010 Feb;12(2):178-82. Epub 2010/02/04.

39. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res. 2013;6:121-36. Epub 2013/02/22.

40. Kong VK, Irwin MG. Gabapentin: a multimodal perioperative drug? Br J Anaesth. 2007 Dec;99(6):775-86. Epub 2007/11/17.

41. Gong L, Wang Z, Fan D. Sleep Quality Effects Recovery After Total Knee Arthroplasty (TKA) - A Randomized, Double-Blind, Controlled Study. J Arthroplasty. 2015 Feb 24. Epub 2015/09/08.

42. den Hertog A, Gliesche K, Timm J, Muhlbauer B, Zebrowski S. Pathway-controlled fast-track rehabilitation after total knee arthroplasty: a randomized prospective clinical study evaluating the recovery pattern, drug consumption, and length of stay. Arch Orthop Trauma Surg. 2012 Aug;132(8):1153-63. Epub 2012/05/31.

43. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. Anesth Analg. 2012 Aug;115(2):428-42. Epub 2012/03/15.

**Figure Legends**

Figure 1: PRISMA flow diagram of retrieved studies

Figure 2: Assessment of risk of bias of included studies

Figure 3: Pain intensity at 48 hours following surgery

Figure 4: Pain intensity at 24 hours following surgery

Figure 5: Pain intensity at 72 hours following surgery

Figure 6: Cumulative oral opioid equivalent 0 to 48 hours

Figure 7: Incidence of chronic pain associated with the use of Pregabalin at 3 and 6 months following surgery

Figure 8: Incidence of sedation

Figure 9: Incidence of nausea