

Pregabalin does not decrease acute pain or postoperative nausea and vomiting after hysterectomy: a meta-analysis

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Abstract

Objective: Hysterectomy is associated with severe postoperative pain. The relative efficacy of pregabalin compared with other treatments for post-hysterectomy pain is unclear.

Methods: We searched the PubMed, Cochrane Library, and Web of Science databases for studies that compared the use of pregabalin and placebo for reducing pain in patients undergoing hysterectomy.

Results: This meta-analysis showed that pregabalin had limited pain-relieving effects at 2, 6, 24, and 48 hours after hysterectomy compared with placebo. Pregabalin significantly reduced postoperative nausea and vomiting. However, there was no significant difference in postoperative sedation or visual disturbances between patients treated with pregabalin and placebo.

Conclusions: Pregabalin is not clinically superior to placebo in terms of reducing pain intensity and morphine consumption in patients undergoing hysterectomy. However, the limitations of this meta-analysis mean that more high-quality randomized controlled trials are necessary to verify our pooled results.

Keywords

Pregabalin, hysterectomy, acute pain, meta-analysis, morphine consumption, postoperative pain

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Introduction

Hysterectomy causes significant postoperative pain, characterized by a combination of somatic and predominantly visceral pain.¹ Poorly managed acute postoperative pain may increase pain-related complications,

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delay out-of-bed activity, and affect quality of life.²⁻⁴ Enhanced recovery after surgery protocols have recently undergone rapid developments and have been widely applied in orthopedic, general, and cardiothoracic surgery.^{5,6} Numerous kinds of analgesics with different pharmacological mechanisms have been used to reduce postoperative pain.

Pregabalin is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid and the main treatment for neuropathic pain. Its analgesic effect differs from that of other analgesics, including morphine,⁷ nonsteroidal anti-inflammatory drugs,⁸ and morphine-like drugs.⁹ Previous studies showed that pregabalin could downregulate visceral hyperalgesia, in addition to reducing the severity of basic pain.¹⁰

A previous meta-analysis indicated that pregabalin could decrease postoperative pain after spinal cord injury,¹¹ diabetic neuralgia,¹² and neuropathic pain;¹⁰ however, the role of pregabalin following hysterectomy has yet to be defined. Asgari et al.¹³ found that pregabalin played an important role in reducing postoperative pain after laparoscopic hysterectomy; however, another recent study questioned its efficacy and reported that it had limited ability to reduce pain intensity in hysterectomy patients.¹⁴

The current meta-analysis aimed to determine if pregabalin was an effective treatment for managing acute postoperative pain following hysterectomy and to determine the risk of drug-related adverse effects.

Materials and methods

This meta-analysis was based on previously published studies and did not require ethical approval or patient consent. This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Item for Systematic

Review and Meta-analysis (PRISMA) guidelines.^{15,16}

Search strategy

Two trained researchers (Jie Ni and Juan Jiang) independently searched the PubMed, Cochrane Library, and Web of Science databases, without restrictions on publication date, to identify relevant trials. We used a hierarchical approach based on titles, abstracts, and full texts to assess the relevance of the trials. The following search terms and their synonyms were used: "Trachelectomy (All Fields)," "Hysterectomy, Vaginal (All Fields)," "Hysterectomy" "pregabalin (All Fields)," "gamma-Aminobutyric Acid (All Fields)," and "3-(aminomethyl)-5-methylhexanoic acid (All Fields)." The researchers used the Boolean operators "and" or "or" to combine search terms. To ensure the comprehensiveness of the study, we also manually searched the reference lists of relevant articles to identify other trials.

Inclusion criteria and study selection

Trials were included if they met the following criteria: 1) patients underwent hysterectomy under general anesthesia or spinal anesthesia; 2) intervention group received pregabalin; 3) control group received placebo; 4) data available for at least one of the following outcomes: postoperative morphine consumption, pain intensity at rest or mobilization at 2, 6, 24, 48, and 72 hours following hysterectomy, and side effects (occurrence of nausea, vomiting, sedation and visual disturbances); and 5) comparative study. The reliability of the study selection was determined by Cohen's kappa test with an acceptable threshold value of 0.61.^{17,18}

Studies were excluded if they met the following criteria: 1) pregabalin compared with gabapentin without a control group;

2) design of the experiment not reasonable; 3) duplicate reports, systematic reviews and meta-analyses; and 4) animal experiments.

Data extraction

All potentially relevant studies retrieved from the literature search were imported into Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA), and duplicate studies were excluded by the software. The two above researchers read the titles and abstracts of each article to rule out those that did not meet the requirements. The same researchers then read the full texts of the remaining articles to further exclude trials that did not meet the selection criteria. Any disagreements were resolved by discussion with a third researcher (Rui-fang Sun).

Quality assessment

We assessed the quality of each included trial according to the Cochrane risk of bias tool for randomized trials.¹⁹ We assessed the following items: generation of random sequence, concealment of allocation sequence, blinding of participants, incomplete outcome data, selective outcome reporting, and other sources of bias. For each included study, each type of bias was rated as high, low, or unclear and entered into the risk of bias table. The risk of bias was examined by two reviewers concurrently, and discrepancies were resolved by consensus.

Outcome measures and statistical analysis

The efficacy and safety of pregabalin compared with placebo for treating postoperative pain after hysterectomy were assessed using categorical and continuous data, and relative risks (RRs) and standard mean differences (SMDs) with 95% confidence intervals (CIs), respectively, were calculated before data pooling. Pain scores were

measured by visual analogue scale, with 100 mm for the most severe pain and 0 mm for no pain at all. Pooled analyses for all outcomes were carried out using the random effects model considering the underlying variables across the included trials. Heterogeneity among the included trials was assessed using the I^2 and Q statistics with $I^2 > 50\%$ or $P < 0.10$ indicating significant heterogeneity.²⁰ The robustness of the pooled results was assessed using sensitivity analysis. Moreover, subgroup analysis for the efficacy of outcomes was conducted based on pregabalin dose, risk of bias, and hysterectomy category between subgroups evaluated using the interaction P -value, which assumed that the data in each subgroup were normally distributed.²¹ The quality of the evidence was assessed according to each outcome using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method, which grades the evidence as high, moderate, low, or very low quality. Sensitivity analysis was carried out by removing one study at a time (leave-one-out) to identify sources of heterogeneity. Publication bias was assessed using funnel plots and Egger's and Begg's test results.²² The inspection level for pooled results was two-sided, and $P < 0.05$ was considered statistically significant. STATA software (Version 12.0; StataCorp, TX, USA) was used to conduct all analyses in this study.

Results

Search results

The flowchart of the study search and selection process is shown in Figure 1. A total of 628 articles (database = 625, other sources = 3) were identified through the literature search and manual searching. The titles and abstracts of 453 articles were reviewed after duplicates were removed.

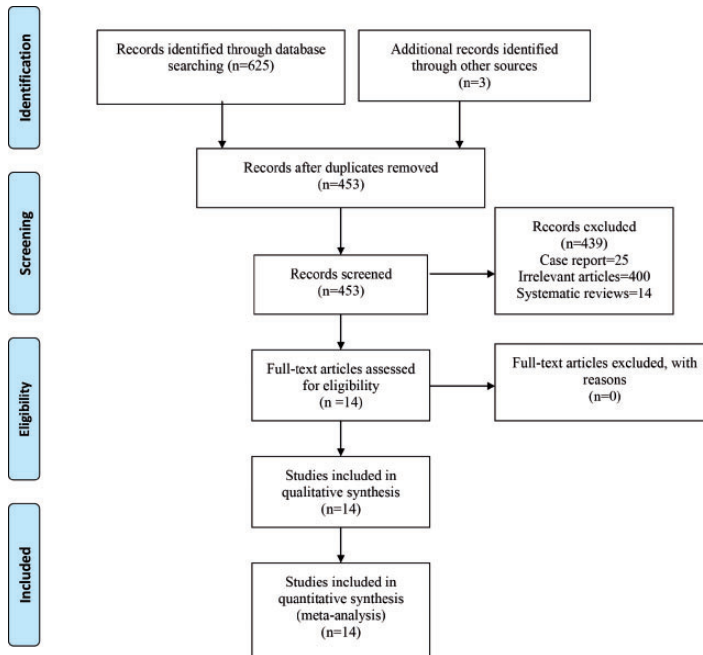


Figure 1. Flow diagram of study selection.

A total of 439 studies were excluded after reviewing the titles and abstracts and the full texts of the remaining 14 studies were reviewed. Fourteen studies^{13,14,19,23–33} were finally included in the current meta-analysis. The general characteristics of the included studies are shown in Table 1.

Quality assessment

All studies had a low risk of bias regarding the blinding of outcome assessment, incomplete outcome data, and selective reporting. Nine studies had a low risk of bias regarding the blinding of participants and personnel. One study²¹ did not mention allocation concealment and blinding of participants and personnel. Five studies^{3,19,20,23,26} had an unclear risk of other bias, and one study²⁰ had a high risk of other bias. The quality assessment for each study and the results of the included studies are shown in Figure 2.

Results of meta-analysis

Postoperative morphine consumption. Trials involving 118 patients reported postoperative morphine consumption as an outcome (Table 2). Compared with the control group, the pregabalin group had a significantly lower postoperative morphine consumption ($P < 0.001$).

Pain intensity with rest following hysterectomy. Compared with the control group, the administration of pregabalin was associated with a significant reduction in pain intensity with rest at 2 hours ($P = 0.002$; Table 2). The pain intensity with rest at 6 hours is shown in Table 2. Pooled analysis showed that pregabalin also relieved pain intensity with rest at 6 hours ($P < 0.001$; Table 2), 24 hours ($P < 0.001$; Table 2), 48 hours ($P = 0.001$; Table 2), and 72 hours ($P = 0.104$; Table 2) after hysterectomy.

Table 1. General characteristics of the included studies.

Study	Country	Control group	Surgery	Intervention group			Outcomes ^a	Follow-up	Total dose (mg/day)
				No of patients	Preoperative	Postoperative			
George et al. ²⁴	Canada	Placebo (n=30)	Abdominal hysterectomy	Arm 1: 31	Pregabalin 75 mg 2 hours before surgery	12 hours after initial dose	1,2,3,4,5,7,8,9,10,11	6 months	150
				Arm 2: 28	Pregabalin 150 mg 2 hours before surgery	12 hours after initial dose			
Mathiesen et al. ²⁶	Denmark	Placebo (n=40)	Abdominal hysterectomy	39	Pregabalin 300 mg/day 1 hour before anesthesia	No	1,2,3,4,5,7,8,9,10,11,12,13	48 h	300
Fassoulaki et al. ²³	Greece	Placebo (n=40)	Abdominal hysterectomy	37	Pregabalin 150 mg 8 hours before surgery	No	2,3,4,5,6,7,8,9	3 months	150
Singla et al. ²⁹	USA	Placebo (n=167)	Hysterectomy	Arm 1: 161	Pregabalin 150 mg 12 hours and 2 hours before surgery	No	1,10,11,12,13	1 year	150
				Arm 2: 166	Pregabalin 300 mg 12 hours and 2 hours before surgery	No			
Yucel et al. ³⁰	Turkey	Placebo (n=30)	Abdominal hysterectomy	Arm 1: 30	Pregabalin 150 mg 4 hours before anesthesia induction	Pregabalin 150 mg 12 hours after operation	2,4,5,6,7,8,9,10,11	48 h	300
				Arm 2: 30	Pregabalin 300 mg 4 hours before anesthesia induction	Pregabalin 300 mg 12 hours after operation			
Rajappa et al. ²⁸	India	Placebo (n=30)	Vaginal hysterectomy	Arm 1: 45	Pregabalin 75 mg 1 hour before patient moved to operating theatre	No	2,3,4,5,8,9,10,11	48 h	75
				Arm 2: 45	Pregabalin 150 mg 1 hour before patient moved to operating theatre	No			
Ittichaikulthol et al. ¹⁹	Thailand	Placebo (n=40)	Abdominal hysterectomy	38	Pregabalin 300 mg 1 hour before surgery	No	1,4,5,7,10,11,12,13	300	
Ghai et al. ²⁵	India	Placebo (n=30)	Abdominal hysterectomy	30	Pregabalin 300 mg 1-2 hours before surgery	No	2,4,5,8,9,10	300	

(continued)

Table 1. Continued.

Study	Country	Control group	Surgery	Intervention group			Outcomes ^a	Follow-up	Total dose (mg/day)
				No of patients	Preoperative	Postoperative			
Eman et al. ³¹	Turkey	Placebo (n=20)	Abdominal hysterectomy	20	Pregabalin 150 mg 1 hour before surgery	No	1,7,10	150	
Przesmycki et al. ²⁷	Polish	Placebo (n=20)	Abdominal hysterectomy	Arm 1: 20 Arm 2: 20	Pregabalin 75 mg 1 hour before surgery Pregabalin 150 mg 1 hour before surgery	No No	12,13	75 150	
Jokela et al. ¹⁴	Finland	Placebo (n=29)	Laparoscopic hysterectomy	Arm 1: 27 Arm 2: 29	Pregabalin 300 mg 1 hour before surgery Pregabalin 600 mg 1 hour before surgery	12 hours after premedication 12 hours after premedication	1,2,4,5,6,7,8,9 10,11,12,13	300 600	
Asgari et al. ¹³	Iran	Placebo (n=24)	Laparoscopic hysterectomy	Arm 1: 24 Arm 2: 24	Pregabalin 75 mg 1 hour before surgery Pregabalin 150 mg 1 hour before surgery	No No	1,2,3,4,5,8,9 10,11,12,13	75 150	
El-Refai et al. ³²	Egypt	Placebo (n=25)	Abdominal hysterectomy	Arm 3: 24	Pregabalin 300 mg 1 hour before surgery	No	3,4,6,9,10, 11,12,13	300 150	
Kiatchai et al. ³³	Thailand	Placebo (n=58)	Abdominal hysterectomy	61	Pregabalin 150 mg 1 hour before surgery	No	1,2,3,4,5,6,8, 9,10,11,12,13	150	

^a1, postoperative morphine consumption; 2, pain intensity with rest at 2 hours; 3, pain intensity with rest at 6 hours; 4, pain intensity with rest at 24 hours; 5, pain intensity with rest at 48 hours; 6, pain intensity with rest at 72 hours; 7, pain intensity with mobilization at 2 hours; 8, pain intensity with mobilization at 6 hours; 9, pain intensity with mobilization at 24 hours; 10, nausea; 11, vomiting; 12, sedation; 13, visual disturbances.

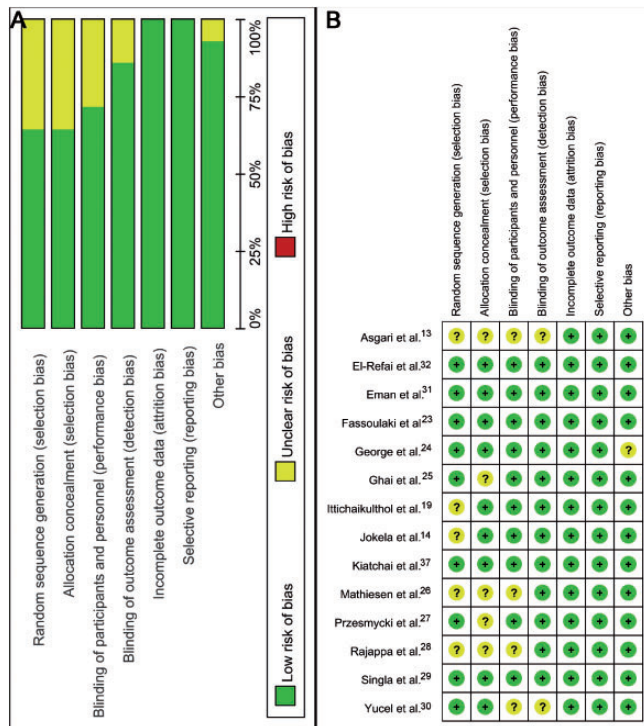


Figure 2. Risk of bias summary for the included studies.

Table 2. Summary of meta-analysis results.

Outcome	Effect size (95% CI)	P-value	I ² (%)	P for heterogeneity
Postoperative morphine consumption	-1.09 (-1.73, -0.45)	<0.001	96.2	<0.001
Pain intensity with rest at 2 hours	-1.07 (-1.52, -0.62)	0.002	90.9	<0.001
Pain intensity with rest at 6 hours	-1.06 (-1.53, -0.60)	<0.001	91.8	<0.001
Pain intensity with rest at 24 hours	-0.23 (-0.35, -0.11)	<0.001	34.2	0.947
Pain intensity with rest at 48 hours	-0.44 (-0.60, -0.27)	0.001	45.2	0.026
Pain intensity with rest at 72 hours	-0.69 (-0.97, -0.41)	0.001	46.2	0.084
Pain intensity with rest at 2 hours	-0.27 (-0.73, 0.20)	0.003	88.6	<0.001
Pain intensity with rest at 6 hours	-0.34 (-0.56, -0.12)	<0.001	66.9	<0.001
Pain intensity with mobilization at 24 hours	-0.76 (-1.13, -0.39)	<0.001	88.0	<0.001
Nausea	0.80 (1.00, 1.20)	<0.001	70.7	<0.001
Vomiting	0.72 (0.59, 0.87)	<0.001	4.4	0.403
Sedation	0.86 (0.74, 1.00)	0.129	0.0	0.944
Visual disturbances	1.64 (0.95, 2.82)	0.349	0.0	0.529

CI, confidence interval.

Pain intensity with mobilization following hysterectomy. Compared with the control group, the administration of pregabalin was associated with a reduction in pain intensity during mobilization at 2 hours ($P=0.003$; Table 2), 6 hours ($P<0.001$; Table 2), and 24 hours ($P<0.001$; Table 2) after hysterectomy.

Side effects

Pooling data showed that pregabalin significantly decreased the occurrence of nausea ($P<0.001$; Table 2) and vomiting ($P<0.001$; Table 2), as shown by forest plots. However, there was no significant difference between the pregabalin and control groups in terms of the occurrence of sedation ($P=0.129$; Table 2) and visual disturbances ($P=0.349$; Table 2).

Subgroup analysis, sensitivity analysis, and publication bias

The results of subgroup analyses are shown in Table 3. In terms of the primary outcome of postoperative morphine consumption, there was a significant difference between patients treated with laparoscopic

hysterectomy and abdominal hysterectomy ($P=0.002$). There was no significant difference between studies with a low risk of bias and those with an unclear/high risk of bias or between studies with different doses of pregabalin (75 mg, $P<0.001$; 150 mg, $P=0.005$; 300 mg, $P=0.036$; 600 mg, $P=0.001$).

The results of sensitivity analysis for postoperative morphine consumption are shown in Table 3. None of the included studies was identified as a source of heterogeneity.

The assessment of publication bias using Egger's and Begg's tests showed no potential publication bias among the included trials.

GRADE assessment

The GRADE framework revealed low qualities of evidence for postoperative morphine consumption and pain intensity with rest at 2, 24, 48, and 72 hours, and moderate quality of evidence for pain intensity with rest at 6 hours following hysterectomy (Supplementary material S1).

Discussion

The current meta-analysis demonstrated that pregabalin reduced pain scores with

Table 3. Subgroup analysis in terms of morphine consumption.

Variable	Studies (n)	Patients (n)	P-value	Incidence			Subgroup difference
				Weighted mean difference (95% CI)	Heterogeneity P-value (I^2)	Model	
Daily dose of pregabalin							
75 mg	1	326	<0.001	0.14 (-0.43, 0.70)	-	Random	0.016
150 mg	6	160	0.005	-0.91 (-1.54, -0.27)	<0.001 (92.0)	Random	
300 mg	6	264	0.036	-1.48 (-2.87, -0.09)	<0.001 (97.8)	Random	
600 mg	1	625	0.001	-0.91 (-1.45, -0.37)	-	Random	
Risk of bias							
Low	8	852	0.028	-1.12 (-2.21, -0.12)	<0.001 (97.6)	Random	0.175
Unclear/high	6	523	<0.001	-1.00 (-1.56, -0.45)	<0.001 (83.7)	Random	
Hysterectomy category							
Laparoscopic	4	370	0.109	-0.52 (-1.16, 0.12)	<0.001 (96.8)	Random	0.002
Abdominal	10	1005	0.002	-1.13 (-2.21, -0.50)	0.001 (83.0)	Random	

CI, confidence interval.

rest following hysterectomy by 1.06 points at 2 hours, 0.23 at 6 hours, 0.44 at 24 hours, and 0.69 points at 48 hours, based on a 110-point visual analog scale. However, these reductions were not clinically significant. Pregabalin use also reduced morphine consumption, but this was also not clinically important, especially at doses <150 mg. The quality of evidence for these effects was low or moderate.

The results of this study contradicted previous meta-analyses assessing the use of pregabalin for the management of acute pain in hysterectomy patients.⁶ Notably, previous meta-analyses included trials that applied abdominal hysterectomy, and two trials with large samples were missed. In comparison, the present meta-analysis included patients who received either abdominal or laparoscopic hysterectomy. Moreover, we also used the GRADE framework to assess the quality of evidence in relation to the final outcomes to provide guidance for policy makers.

Hamilton et al.³⁴ conducted a meta-analysis and found no evidence to support the routine use of gabapentinoids for the management of acute pain following total knee arthroplasty. The current meta-analysis found little pain reduction in the pregabalin group, and limited opioid-sparing effects compared with the control group ($P < 0.001$). Subgroup analysis showed that pregabalin 75 mg had no significant effect on pain intensity from 2 to 72 hours after hysterectomy.

This study had some potential limitations. First, the test power was limited by the sample size. Only 14 studies were included in this meta-analysis, all of which had relatively small sample sizes ($n < 100$). However, they were all randomized controlled trials, which are considered highly reliable, and all had evidence-based study designs. The GRADE framework therefore indicated that the evidence was of moderate quality, and the main reason for the lower

grade was the small sample sizes. Second, the included studies were performed in different patient groups, using different pregabalin doses and different follow-ups, and in various clinical settings, thus increasing the risk of heterogeneity. Finally, the number of included trials was too small (< 10 for most outcomes) to conduct an additional analysis of publication bias. However, the systematic review and meta-analysis was carried out in strict adherence to the PRISMA guidelines, to improve the quality of the study.

Conclusion

Pregabalin appeared to be more effective than placebo in reducing pain and morphine consumption in patients undergoing hysterectomy. However, the results were not clinically significant due to the limitations of this meta-analysis, and further high-quality randomized controlled trials are necessary to verify our pooled results.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Lirk P, Thiry J, Bonnet MP, et al. Pain management after laparoscopic hysterectomy: systematic review of literature and PROSPECT recommendations. *Reg Anesth Pain Med* 2019; 44: 425–436. DOI: 10.1136/rapm-2018-100024.

2. Steinberg AC, Schimpf MO, White AB, et al. Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. *Am J Obstet Gynecol* 2017; 217: 303–313.e6. DOI: 10.1016/j.ajog.2017.03.013.
3. Kim NS, Lee JS, Park SY, et al. Oxycodone versus fentanyl for intravenous patient-controlled analgesia after laparoscopic supracervical hysterectomy: A prospective, randomized, double-blind study. *Medicine (Baltimore)* 2017; 96: e6286. DOI: 10.1097/md.0000000000006286.
4. Jarahzadeh MH, Harati ST, Babaeizadeh H, et al. The effect of intravenous magnesium sulfate infusion on reduction of pain after abdominal hysterectomy under general anesthesia: a double-blind, randomized clinical trial. *Electron Physician* 2016; 8: 2602–2606. DOI: 10.19082/2602.
5. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia* 2004; 45: 13–18. DOI: 10.1111/j.0013-9580.2004.455003.x.
6. Wang YM, Xia M, Shan N, et al. Pregabalin can decrease acute pain and postoperative nausea and vomiting in hysterectomy: A meta-analysis. *Medicine (Baltimore)* 2017; 96: e7714. DOI: 10.1097/md.00000000000007714.
7. Jiang Y, Li J, Lin H, et al. The efficacy of gabapentin in reducing pain intensity and morphine consumption after breast cancer surgery: A meta-analysis. *Medicine (Baltimore)* 2018; 97: e11581. DOI: 10.1097/md.00000000000011581.
8. Federico CA, Mogil JS, Ramsay T, et al. A systematic review and meta-analysis of pregabalin preclinical studies. *Pain* 2020; 161: 684–693. DOI: 10.1097/j.pain.0000000000001749.
9. Wang X, Narayan SW, Penm J, et al. Efficacy and safety of tapentadol immediate release for acute pain: a systematic review and meta-analysis. *Clin J Pain* 2020; 36: 399–409. DOI: 10.1097/ajp.0000000000000809.
10. Onakpoya IJ and Thomas ET. Benefits and harms of pregabalin in the management of neuropathic pain: A rapid review and meta-analysis of randomised clinical trials. *BMJ Open* 2019; 9: e023600. DOI: 10.1136/bmjopen-2018-023600.
11. Davari M and Amani B. Pregabalin and gabapentin in neuropathic pain management after spinal cord injury: a systematic review and meta-analysis. *Korean J Pain* 2020; 33: 3–12. DOI: 10.3344/kjp.2020.33.1.3.
12. Derry S, Bell RF, Straube S, et al. Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev* 2019; 1: Cd007076. DOI: 10.1002/14651858.CD007076.pub3.
13. Asgari Z, Rouholamin S, Nataj M, et al. Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: A randomized, double blinded, placebo controlled, clinical trial. *J Clin Anesth* 2017; 38: 13–17. DOI: 10.1016/j.jclinane.2017.01.015.
14. Jokela R, Ahonen J, Tallgren M, et al. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. *Pain* 2008; 134: 106–112. DOI: 10.1016/j.pain.2007.04.002.
15. Higgins JPT and Green S. *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0, [http://www.cochrane-handbook.org]. (2011).
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700. DOI: 10.1136/bmj.b2700.
17. Landis JR and Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics* 1977; 33: 363–374.
18. Landis JR and Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159–174.
19. Ittichaikulthol W, Virankabutra T, Kunopart M, et al. 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.
20. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses.

- BMJ* 2003; 327: 557–560. DOI: 10.1136/bmj.327.7414.557.
21. Song F and Gilbody S. Bias in meta-analysis detected by a simple, graphical test. Increase in studies of publication bias coincided with increasing use of meta-analysis. *BMJ* 1998; 316: 471.
 22. Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
 23. Fassoulaki A, Melemini A, Tsaroucha A, et al. Perioperative pregabalin for acute and chronic pain after abdominal hysterectomy or myomectomy: a randomised controlled trial. *Eur J Anaesthesiol* 2012; 29: 531–536. DOI: 10.1097/EJA.0b013e32835800e0.
 24. George RB, McKeen DM, Andreou P, et al. A randomized placebo-controlled trial of two doses of pregabalin for postoperative analgesia in patients undergoing abdominal hysterectomy. *Can J Anaesth* 2014; 61: 551–557. DOI: 10.1007/s12630-014-0147-4.
 25. Ghai A, Gupta M, Hooda S, et al. A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. *Saudi J Anaesth* 2011; 5: 252–257. DOI: 10.4103/1658-354x.84097.
 26. Mathiesen O, Rasmussen ML, Dierking G, et al. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. *Acta Anaesthesiol Scand* 2009; 53: 227–235. DOI: 10.1111/j.1399-6576.2008.01821.x.
 27. Przesmycki K, Wiater-Kozioł E, Kotarski J, et al. [Effect of pre-emptive pregabalin on pain intensity and morphine requirement after hysterectomy]. *Anestezjol Intens Ter* 2011; 43: 14–17.
 28. Rajappa GC, Vig S, Bevanaguddaiah Y, et al. Efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. *Anesth Pain Med* 2016; 6: e34591. DOI: 10.5812/aapm.34591.
 29. 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. DOI: 10.2147/jpr.s67841.
 30. Yucel A, Ozturk E, Aydogan MS, et al. Effects of 2 different doses of pregabalin on morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind clinical trial. *Curr Ther Res Clin Exp* 2011; 72: 173–183. DOI: 10.1016/j.curtheres.2011.06.004.
 31. Eman A, Bilir A and Beyaz SG. The effects of preoperative pregabalin on postoperative analgesia and morphine consumption after abdominal hysterectomy. *Acta Med Mediterr* 2014; 2014: 481.
 32. El-Refai NA, Shehata JH, Lotfy A, et al. Role of preoperative pregabalin in reducing inhalational anaesthetic requirements in abdominal hysterectomy: randomized controlled trial. *Minerva Anesthesiol* 2019. DOI: 10.23736/s0375-9393.19.13734-0.
 33. Kiatchai T, Sanansilp V, Triyasunant N, et al. Effects of pregabalin on postoperative pain after hysterectomy under spinal anesthesia with intrathecal morphine: a randomized controlled trial. *J Anesth* 2017; 31: 861–868. DOI: 10.1007/s00540-017-2406-3.
 34. Hamilton TW, Strickland LH and Pandit HG. A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. *J Bone Joint Surg Am* 2016; 98: 1340–1350. DOI: 10.2106/jbjs.15.01202.