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Review Article

Benefit and harm of pregabalin in acute pain treatment: a systematic review with meta-analyses and trial sequential analyses

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Abstract

Pregabalin has demonstrated anti-hyperalgesic properties and was introduced into acute pain treatment in 2001. Our aim was to evaluate the beneficial and harmful effects of pregabalin in postoperative pain management. We included randomized clinical trials investigating perioperative pregabalin treatment in adult surgical patients. The review followed Cochrane methodology, including Grading of Recommendations Assessment, Development, and Evaluation (GRADE), and used trial sequential analyses (TSAs). The primary outcomes were 24 h morphine i.v. consumption and the incidence of serious adverse events (SAEs) defined by International Conference of Harmonisation Good Clinical Practice guidelines. Conclusions were based primarily on trials with low risk of bias. Ninety-seven randomized clinical trials with 7201 patients were included. The 24 h morphine i.v. consumption was reported in 11 trials with overall low risk of bias, finding a reduction of 5.8 mg (3.2, 8.5; TSA adjusted confidence interval: 3.2, 8.5). Incidence of SAEs was reported in 21 trials, with 55 SAEs reported in 12 of these trials, and 22 SAEs reported in 10 trials with overall low risk of bias. In trials with overall low risk of bias, Peto's odds ratio was 2.9 (1.2, 6.8; TSA adjusted confidence interval: 0.1, 97.1). Based on trials with low risk of bias, pregabalin may have a minimal opioid-sparing effect, but the risk of SAEs seems increased. However, the GRADE-rated evaluations showed only moderate to very low quality of evidence. Consequently, a routine use of pregabalin for postoperative pain treatment cannot be recommended.

Key words: analgesics; antipyretics; gamma-aminobutyric acid; Lyrica; pain, postoperative; pregabalin

Pregabalin was synthesized in 1991 and approved for the treatment of neuropathic pain and refractory epilepsy in 2004 and 2005.[1] It is one of two available α_2-δ ligands, pregabalin and gabapentin, known as the gabapentinoids. Pregabalin and gabapentin share a similar mechanism of action, and the use of gabapentinoids in experimental pain models has demonstrated anti-

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Editor's key points

- The authors examined the evidential support for the use of pregabalin in postoperative pain relief.
- They performed a systematic review and meta-analysis, including 97 trials, with >7000 subjects.
- Analysis revealed low-quality evidence overall, and the use of pregabalin in the postoperative period for relief of surgical pain could not be recommended.

hyperalgesic analgesic effects. This effect is mediated through binding to α_2-δ subunits in presynaptic voltage-gated calcium channels, thereby inhibiting calcium influx and the subsequent release of excitatory neurotransmitters.[2] Differences between gabapentin and pregabalin are mainly related to pharmacokinetic and pharmacodynamic characteristics,[3 4] and pregabalin has a faster onset time and a more predictable absorption profile than gabapentin.[5]

Although pregabalin is frequently used for treatment of various chronic pain states, evidence of a beneficial effect is inconclusive, and the incidence of adverse events may be increased.[6 7] The first trial on pregabalin for acute pain treatment was published in 2001, and since then the literature has continued to suggest a beneficial effect of pregabalin in acute postoperative pain management. Furthermore, an increasing number of systematic reviews with meta-analyses have been published suggesting that pregabalin has both opioid-sparing and pain-reducing effects.[8–10] However, the published reviews have only limited focus on the risk of random and systematic errors, and the possible introduction of serious adverse events (SAEs) is sparsely investigated.

The aim of this systematic review, therefore, was to evaluate 24 h opioid consumption, SAEs, pain intensity, and adverse events of perioperative pregabalin compared with placebo or active placebo in adult surgical patients from randomized clinical trials. The results and conclusions were primarily based on meta-analyses of the best evidence defined as trials with overall low risk of bias, and the risk of random error was explored using trial sequential analyses (TSAs) on all outcomes. Finally, the results were evaluated and graded according to their quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[11]

Methods

Search, eligibility criteria, and study selection

This PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)-compliant systematic review followed the methodology recommended by the Cochrane Collaboration. The review protocol was published at the homepage of the International Prospective Register of Systematic Reviews (PROSPERO): https://www.crd.york.ac.uk/PROSPERO/ (accessed August 15, 2017).[12]

Literature search

The search was planned and carried out by a trial search coordinator searching the Cochrane Library's CENTRAL, PubMed, EMBASE, and Science Citation Index Expanded databases for eligible trials using the search terms and MeSH descriptors 'amines', 'gamma-aminobutyric acid', 'pregabalin* or lyrica*' and 'pain'. Published systematic reviews and articles were hand searched for eligible trials. We searched for unpublished trials in: www.clinicaltrials.gov; www.controlled-trials.com; www.centerwatch.com; www.eudraCT.com, and at the homepage of the US Food and Drug Administration (FDA). Non-indexed journals and their published articles were found by searching Google Scholar. The electronic search was last updated on October 28, 2016 (Supplementary Appendix S1).

Inclusion criteria

We included randomized clinical trials evaluating pregabalin for postoperative pain management *vs* a placebo or an active placebo that imitates the sedative effect of pregabalin. Participants were adult (≥18 yr) surgical patients who received pregabalin, regardless of dosage, administration intervals, duration of intervention, and surgical procedure. All trials, irrespective of language, publication status, and year of publication, were included. Non-English trials were translated into English. Exclusion criteria were non-randomized trials, non-surgical patients, experimental pain models, pregabalin treatment for chronic pain conditions, and analgesic co-interventions that were different in the compared groups. Two authors (M.L.F. and C.S.) screened the title and abstracts for eligibility using the predefined inclusion and exclusion criteria.

Data extraction

Two authors assessed full texts independently; M.L.F. (all trials) and one other author (C.S., S.K., A.G., P.J., P.L.P.) extracted data and assessed bias using a data extraction form. The extracted data included the following: participant and trial characteristics, such as publication year, number of participants, surgical procedure, follow-up period, pregabalin dose administration regimen, opioid consumption and consumption of non-opioid analgesics, pain intensity, any adverse event, and SAEs.

If data were missing or bias evaluation was classified as unclear in one or more domains, the corresponding author for the trial was contacted to confirm or obtain data. After a 14 day interval, authors were contacted again if they did not respond to initial contact.

Risk of bias classification

All included trials were evaluated using the Cochrane Handbook risk of bias classification guidelines. Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias, including financial and confirmation bias, were independently evaluated by two authors.[13] Bias domains were classified as high, unclear, or low risk of bias. If one or more domains were classified as high risk of bias, the overall bias classification was high.[14] If one or more bias domains were deemed unclear, the trial was classified as overall unclear risk of bias, and the trial was pooled together with trials with high risk of bias in meta- analyses and subgroup analyses. Conclusions in the review were based on trials with low risk of bias according to protocol.[12]

Any disagreements in screening, study selection, data extraction, or bias assessments were resolved by O.M., J.B.D., or J.W.

Outcomes

The review had two co-primary outcomes: 24 h i.v. opioid consumption and SAE defined according to the International Conference of Harmonization Good Clinical Practice (ICH-GCP) definitions as medical events being life threatening, resulting in

death, disability, or significant loss of function; causing hospital admission or prolonged hospitalization.[15] The secondary outcomes were pain intensity at rest and mobilization 6 and 24 h after surgery, and any adverse events reported.

All opioids were converted to morphine i.v. based upon equivalency (Supplementary Appendix S2). All pain intensity scales reporting pain levels between 0 and 10 were converted to the visual analog scale (VAS) 0–100 mm.

Statistical analyses

We used the Review Manager (RevMan, Version 5.1.6; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for the statistical analyses as predefined in the protocol. The trial sequential analysis (TSA) program version 0.9 beta (www.ctu.dk/tsa) was used for trial sequential analyses on all outcomes.

In trials with more than one treatment arm, we combined means and standard deviations in the intervention groups.[16] Median and range values were converted to mean and standard deviations using the method described by Hozo and colleagues.[17] Interquartile ranges were divided by 1.35 to define the standard deviation.[18] Long ordinal scales were analysed as continuous data. The risk ratio (RR) with a 95% confidence interval (CI) was calculated for dichotomous data.[18]

To assess whether the observed differences in results are compatible with chance alone, we used the χ^2 test to examine the heterogeneity between trials. The heterogeneity was assessed by I^2, which quantifies the observed differences, and D^2 for information size adjustments in the trial sequential analyses.

Whenever I^2 was >0, the results were calculated with both fixed effect model (FEM) and random effect model (REM), and the most conservative estimate was used.[18 19] In the event of rare and few adverse events, Peto's odds ratio (OR) was used to provide the best CI coverage.[16 20 21]

In order to explore heterogeneity, the following preplanned subgroup analyses were used to investigate the risk of bias in low *vs* unclear and high risk of bias: Pain intensity at rest *vs* during mobilization; pain intensity at 6 h postoperative *vs* 24 h postoperative; single dose pregabalin *vs* multiple doses of pregabalin; and add-on treatment (trials investigating pregabalin added to other non-opioid analgesics *vs* trials investigating pregabalin without any other non-opioid analgesics). It was our hypothesis that estimates from subgroups with low risk of bias, pain at rest and late pain, and pregabalin as add-on treatment would be lower than those from the corresponding subgroups.

We used sensitivity analyses to explore whether choice of summary statistics and choices made through the review process, such as selection of event category, were critical for the conclusions of the meta-analyses.

Trial sequential analysis was used to evaluate the risk of type 1 and type 2 errors, with 5 and 90% adjustment of the CIs because of sparse data and repetitive testing in the cumulative meta-analyses.[19 22] If the accrued information size was <5% of the required information size, using the TSA was not possible because of an insufficient amount of data.

Our *a priori* definition of a minimal clinical relevant effect in 24 h opioid consumption was morphine 5 mg i.v. This minimal clinical relevant effect was chosen to detect even a small beneficial effect with regard to previous systematic reviews of pregabalin and a recent review of gabapentin that demonstrated an opioid-sparing effect of <10 mg.[8 12 23] The relative risk reduction was set to 30% for adverse events and 50% for SAEs in the TSA.

Trial size

This *post hoc* analysis explored the effect of small sized trials on primary outcomes. The trials were divided according to the following definition: ≤50 patients in each group, >50–100 patients in each group, and ≥100 patients in each group.

Grading of recommendations assessment, development, and evaluation

Grading of recommendations assessment, development, and evaluation (GRADE) was used to rate the quality of evidence and strength of recommendations for all outcomes in the systematic review. Every outcome was graded as follows: very low, low, moderate, or high quality of evidence using the following prespecified domains: study design, risk of bias, inconsistency (of results across trials), imprecision (sample size, number of events, size of CI), indirectness (generalizability of results), and other considerations. According to our protocol, the conclusions were based on estimates from trials classified as overall low risk of bias. The recommendations are presented in summary of findings tables.[11]

Results

The number of trials screened, assessed for eligibility, and included in the review is presented in the PRISMA flow chart (Fig. 1). One hundred and thirty-four articles were considered for full-text evaluation of the review. We excluded 37 trials because of chronic pain conditions, non-surgical procedures, different analgesic co-interventions, age <18 yr, double publications, intervention initiated >48 h before surgery, observational methodology, study population of healthy adults, abstracts without reply from authors, and a trial that investigated gabapentin.

Trial characteristics

A total of 97 randomized clinical trials with 7201 patients were included in the systematic review.[24–120] Perioperative analgesic treatment with a single dose of pregabalin was investigated in 69 trials, and dosage ranged from 50 to 300 mg.[24–32 34 38–41 45–50 56 57 59–62 64–66 68 69 72 76 78 80–88 91 94 96 99–106 111–117 120] In treatments with more than one dose of pregabalin, accumulated doses ranged from 100 to 600 mg day^{-1} in 28 trials.[33 35–38 42 43 51–53 55 60 63 67 70 71 73–75 79 89 90 92 93 95 97 98 107–110 118 119] Postoperative follow-up time varied from 6 h to 1 yr, with the most common period being 24 h (n=39).[24 25 27–33 39 40 45 47 48 50 51 56 57 59 61 64–66 68 69 72 76 81 83 84 86–88 90 93 94 99–101 103–108 112 119 120]

The number of patients included in each trial ranged from 26 to 228. Various surgical procedures were investigated, with the majority of trials using general anaesthesia for the included patients (n=73; Supplementary Appendix S3).[24–27 29 30 32–36 39 41–43 45–48 50–57 59–66 68–71 73–75 78—85 87 88 92–94 96–98 100 106 108–113 115 116 119 120]

Bias assessment

Twenty trials were classified as having overall low risk of bias.[26 34 35 56 63 69 70 77 83 85–87 89 92 94 98 108 111 117 118] Forty-two trials were classified as overall unclear risk of bias,[24 25 28 30 33 37 39–44 46 48 49 54 57 59 60 67 72 78–81 88 91 93 95 96 99–101 103 104 110 112 115 119 120] and 35 trials were classified as having an overall high risk of bias.[27 29 32 36 38 45 47 50–53 55 61 62 64–66 68 71 73–76 82 84 90 97 102 105–107 109 113 114 116]

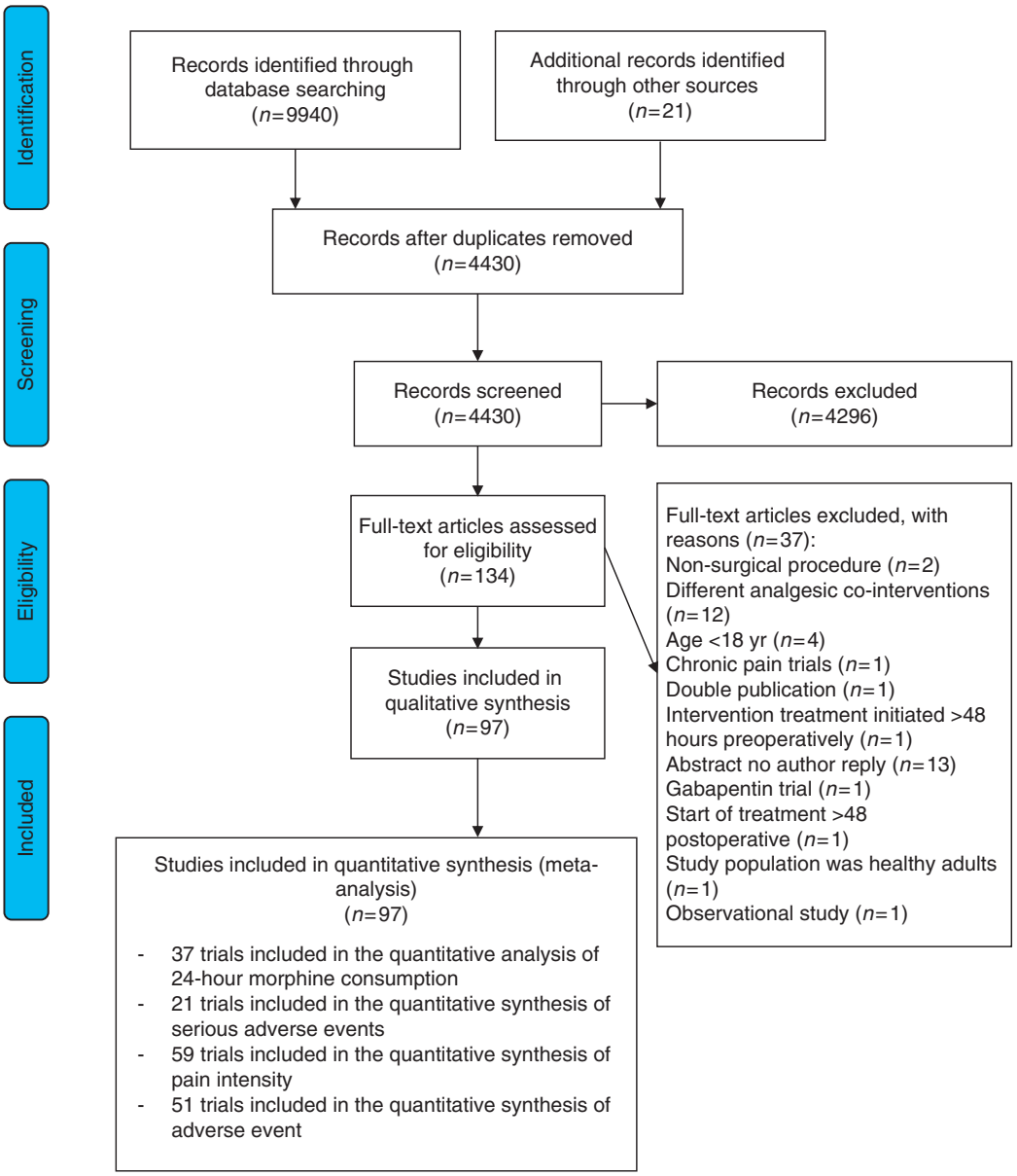

Fig 1 PRISMA flowchart.

Allocation concealment and selective outcome reporting were the most frequent reasons for unclear and high risk of bias assessments (Fig. 2 and Supplementary Appendix S4).

Morphine consumption

The 24 h morphine consumption was reported in 11 trials with overall low risk of bias.[26 70 83 86 87 92 94 98 108 111 118] The reported data found a reduction in 24 h morphine consumption of 5.8 mg [REM 95% CI: 3.2, 8.5; $P<0.0001$; TSA adjusted (adj.) 95% CI: 3.2, 8.5; trials 11; 705 participants; percentage of required information size: 127.5%; GRADE: low]. Results from all trials estimates are presented in Table 1, Figs 3 and 4 and Supplementary Appendix S5.

Add-on effect

In the subgroup analyses of pregabalin as add on to a non-opioid, basic analgesic regimen, the analyses found a mean reduction of 24 h morphine consumption of 3.7 mg (REM 95% CI: 1.5, 6.0; $P=0.0009$; TSA adj. 95% CI: 1.5, 6.0; nine trials; 585 participants; percentage of required information size: 185.7%; GRADE: low; Supplementary Appendix S6).[70 86 87 92 94 98 108 111 118]

No add-on effect

One trial with overall low risk of bias investigating pregabalin without other non-opioid analgesics reported a reduction in 24 h morphine consumption of 13.7 mg (REM 95% CI: 9.6, 17.8;

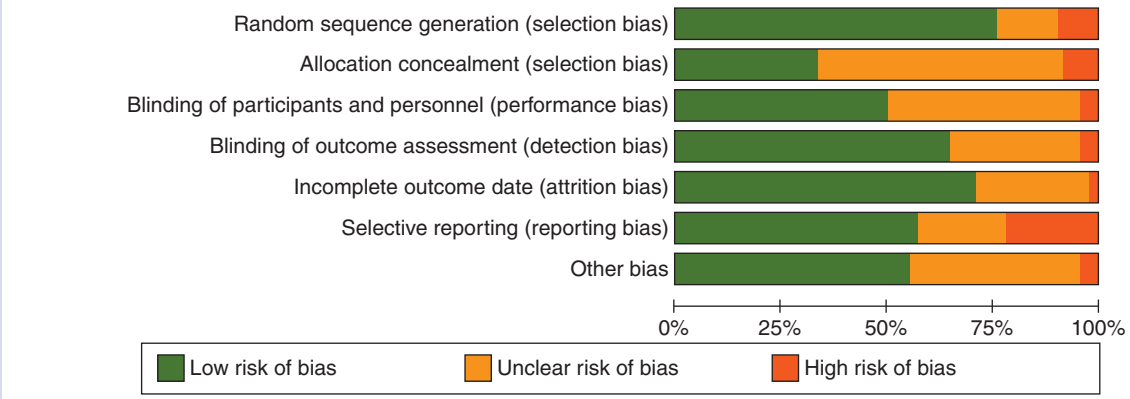

Fig 2 Bias graph of the six bias domains. The 'other bias' domain consists of a financial and confirmatory bias assessment.

$P = <0.00001$; TSA adj. 95% CI: 9.6, 17.8; two trials; 120 participants; percentage of required information size: 54.0%; GRADE: low; Supplementary Appendix S7).[26 83]

Single dose vs multiple dose treatments

In the subgroup analyses exploring the effect of a single dose of pregabalin on 24 h morphine consumption, six trials with overall low risk of bias found a reduction of 10.1 mg (REM 95% CI: 2.4, 18.0; P=0.01; TSA adj. 95% CI: −21.3, 41.5; six trials; 399 participants; accrued percentage of required information size 15.1%; GRADE: low).[26 83 86 87 94 111] Five trials with overall low risk of bias investigating multiple dose administration of pregabalin found a reduction of 2.4 mg (REM 95% CI: 0.5, 4.9; P=0.01; TSA adj. 95% CI: 0.5, 4.9; five trials; 306 participants; percentage of required information size 66.7%; GRADE: low; Supplementary Appendix S8).[70 92 98 108 118]

Serious adverse events

The incidence of SAEs was reported in 21 trials.[34–36 49 52 53 59 77 83 86–88 96 98 106 108–110 114 117 118] A total of 55 SAEs were reported from 13 trials, and 22 of these were reported in 10 trials with low risk of bias.[34 35 77 83 86 87 98 108 117 118] Eight trials reported zero events.[34 49 83 86 96 106 108 114] The reported SAEs were as follows: re-admission to hospital, prolonged hospital stay, postponed operation because of sedation from pregabalin, allergic reaction, stroke, pulmonary embolism, myocardial infarction, acute kidney injury, pneumonia, wound infection, bleeding or haematoma, and death.

In trials with overall low risk of bias, the RR of SAEs was 2.9 (FEM 95% CI: 1.2, 6.8; P=0.02; TSA adj. 95% CI: 0.1, 97.1; 10 trials; 730 participants; percentage of required information size: 8.8%; GRADE: moderate; Table 1 and Fig. 5).[34 35 77 83 86 87 98 108 117 118]

Single dose vs multiple dose treatments

In trials with low risk of bias administrating pregabalin as a single dose, the reported risk of SAE was 1.6 (Peto's OR 95% CI: 0.3, 9.5; P=0.63; TSA adj. 95% CI: –; four trials; 243 participants; percentage of required information size: <5%; GRADE: very low).[34 83 86 87] The RR in trials with multiple administrations of pregabalin was 3.4 (Peto's OR 95% CI: 1.3, 9.2; P=0.01; TSA adj. 95% CI: 0.1, 190.7; six trials; 487 participants; percentage of required information size: 5.8%; GRADE: moderate; Supplementary Appendix S9).[35 77 98 108 117 118]

Pain intensity

Early pain intensity at 6 h after surgery during mobilization and late (24 h) pain intensity at rest or mobilization was not significantly reduced. The meta-analysis of VAS 6 h after surgery at rest found a reduction in pain intensity (Table 1 and Supplementary Appendices S5 and S10–S13).

Adverse events

The risks of nausea, sedation, and headache were not significantly different between groups. Trials reporting on postoperative nausea and vomiting (PONV) indicated a reduction in the pregabalin group compared with the controls, whereas there might be an increase in incidence of vomiting, dizziness, and visual disturbance in the pregabalin groups compared with control groups. (Table 1 and Supplementary Appendices S5 and S14–S20).

Small trial effect

This *post hoc* analysis showed that out of the 97 included trials, 91 were classified as small trials, with ≤50 patients in each group.[24–34 36 38–41 43 45–57 59–76 78–88 90–96 98–108 110–120] Five trials included between 50 and 100 patients in each group,[35 44 89 97 109] and only one trial had >200 patients included.[37]

Of all of the trials reporting 24 h morphine consumption, only one trial had >50 participants in each group.[44] In trials reporting SAEs, one trial had >50 participants in each group.[35]

Discussion

Based on the trials with overall low risk of bias, there may be a beneficial, but small, effect of pregabalin in postoperative pain management. The predefined minimal clinical relevant difference of 5 mg for 24 h morphine consumption was demonstrated as the trial sequential boundary for benefit was crossed. Only few trials reported on SAEs, limiting our ability to draw firm

Table 1 Subgroup analyses on all outcomes from trials with low risk of bias vs all trials.

Outcome	Estimates				Estimates		
Subgroup analyses	Trials with overall low risk of bias				All trials		
	Estimate MD/RR (REM/FEM/RR/Peto's OR) (95% CI; P-value; TSA adj. 95% CI)	I^2 (%)	n Trials/participants/ required information size/accrued information size	Test of interaction P-value	Estimate MD/RR (REM/FEM/RR/Peto's OR) (95% CI; P-value; TSA adj. 95% CI)	I^2 (%)	n Trials/participants/ required information size (n)/ accrued information size (%)
Beneficial outcomes							
24 h morphine consumption	5.8 mg reduction (REM 95% CI: 3.2, 8.5; P<0.0001; TSA adj. CI: 3.2, 8.5)	85	11/705/553/127.5%	P=0.001	10.8 mg reduction (REM 95% CI: 8.5, 13.2; P<0.00001; TSA adj. CI: 8.5, 13.2)	95	37/2423/923/262.5%
24 h morphine consumption: add-on	3.7 mg reduction (REM 95% CI: 1.5, 6.0; P=0.0009; TSA adj. CI: 1.5, 6.0)	76	9/585/318/185.7%	P=0.08	8.5 mg reduction (REM 95% CI: 6.4, 10.5; P<0.00001; TSA adj. CI: 6.4, 10.5)	92	22/1923/923/216.6%
24 h morphine consumption: no add-on	13.7 mg reduction (REM 95% CI: 9.6, 17.8; P<0.00001; TSA adj. CI: 9.6. 17.8)	0	2/120/222/54%	P=0.16	20.4 mg reduction (REM 95% CI: 11.1, 34.0; P=0.0001; TSA adj. CI: −16.6, 56.6)	96	9/560/4928/17.1%
24 h morphine consumption: single administration	10.1 mg (REM 95% CI: 2.4, 17.8; P=0.01; TSA adj. CI: 21.3, 41.5)	92	6/399/2644/15.1%	P=0.93	9.8 mg reduction (REM 95% CI: 6.9, 12.6; P<0.00001; TSA adj. CI 6.9, 12.6)	93	22/1331/1189/111.9%
24 h morphine consumption: multiple administration	2.4 mg (REM 95% CI: 0.6, 4.2; P=0.01; TSA adj. CI: 0.5, 4.9)	41	5/306/459/66.7%	P<0.00001	12.7 mg reduction (REM 95% CI: 8.2, 17.1; P<0.00001; TSA adj. CI: 8.2, 17.1)	97	15/1092/459/237.8%
6 h VAS pain at rest	7.7 mm reduction (REM 95% CI: 2.2, 13.3; P=0.007; TSA adj. CI: −3.6, 19.0)	77	9/588/1996/29.5%	P=0.61	9.3 mm reduction (REM 95% CI: 5.5, 13.1; P<0.00001; TSA adj. CI: 5.5, 13.1)	98	55/3582/1401/255.7%
6 h VAS pain at mobilization	16.3 mm reduction (REM 95% CI: −9.9, 42.6; P=0.22; TSA adj. CI: –)	97	5/323/24 419/<5%	P=0.41	9.8 mm reduction (REM 95% CI: 4.7, 14.9; P=0.0002; TSA adj. CI: 4.7, 14.9)	96%	19/1323/988/133.9%
24 h VAS pain at rest	1.4 mm reduction (REM 95% CI: −2.7, 5.5; P=0.5; TSA adj. CI: −4.6, 7.4)	89	15/1123/2059/54.5%	P=0.10	5.3 mm reduction (REM 95% CI: 1.6, 9.1; P=0.005; TSA adj. CI: 1.6, 9.1)	99	59/4105/1620/253.3%
24 h VAS pain at mobilization	3.7 mm reduction (REM 95% CI: −1.5, 8.9; P=0.16; TSA adj. CI: −6, 13.4)	47	7/502/1469/34.2%	P=0.83	4.2 mm reduction (REM 95% CI: 1.3, 7.0; P=0.004; TSA adj. CI: 1.3, 7.0)	75	23/1629/364/447.5%
Harmful outcomes							
SAEs	RR 2.9 (Peto's OR 95% CI: 1.2, 6.8; P=0.02; TSA adj. CI: 0.1, 97.1)	0	10/730/8312/8.8%	P=0.60	RR 2.4 (Peto's OR 95% CI: 1.4, 4.2 P=0.002; TSA adj. CI: 0.9, 6.33)	0	21/1574/5388/29.2%
SAEs: single administration	RR 1.6 (Peto's OR 95% CI: 0.3, 9.5; P=0.63; TSA adj. 95% CI: –)	0	4/243/7323/<5%	P=0.47	RR 2.8 (Peto's OR 95% CI: 1.1, 6.9; P=0.03; TSA adj. CI: 0.1, 109.5)	0	10/766/6911/11.1%
SAEs: multiple administration	RR 3.4 (Peto's OR 95% CI: 1.3, 9.2; P=0.01; TSA adj. CI: 0.1, 190.7)	0	6/487/8912/5.8%	P=0.20	RR 2.2 (Peto's OR 95% CI: 1.1, 4.4; P=0.03; TSA adj. CI: 0.3, 13.5)	0	11/834/4576/18.2%

Adverse event: nausea	RR 0.8 (REM 95% CI: 0.6, 1.2; P=0.34; TSA adj. CI: 0.4, 1.7)	40	8/631/1895/33.3%	P=0.92	RR 0.8 (REM 95% CI: 0.7, 1.0; P=0.05; TSA adj. CI: 0.7, 1.1)	49	34/2389/2783/85.8%
Adverse event: vomiting	RR 1.3 (REM 95% CI: 0.7, 2.7; P=0.04; TSA adj. CI: 0.1, 15.4)	58	6/461/6325/7.3%	P=0.04	RR 0.7 (REM 95% CI: 0.5, 9.4; P=0.02; TSA adj. CI: 0.5, 1.1)	53	29/2122/3536/61.7%
Adverse event: PONV	RR 0.7 (REM 95% CI: 0.5, 1.0; P=0.04; TSA adj. CI: 0.5,1.2)	25	9/558/1141/55.3%	P=0.66	RR 0.7 (REM 95% CI: 0.6, 0.9; P=0.05; TSA adj. CI: 0.6, 0.8)	40	28/1914/1315/145.6%
Adverse event: sedation	RR 1.1 (REM 95% CI: 0.9, 1.3; P=0.45; TSA adj. CI: –)	83	10/671/–/<5%	P=0.05	RR 1.4 (REM 95% CI: 1.1, 1.7; P=0.009; TSA adj. CI: –)	85	40/2764/–/<5%
Adverse event: dizziness	RR 2.1 (REM 95% CI: 1.1, 3.9; P=0.02; TSA adj. CI: 0.8, 1.0)	49	11/661/5439/12.1%	P=0.22	RR 1.5 (REM 95% CI: 1.2, 1.8; P=0.0007; TSA adj. CI: 1.2, 1.8)	57	51/3461/4665/74.2%
Adverse event: headache	RR 0.7 (REM 95% CI: 0.4, 1.3; P=0.02; TSA adj. CI: 0.02, 8.0)	38	5/285/2263/13.3%	P=0.33	RR 1.0 (REM 95% CI: 0.8, 1.2); P=0.7; TSA adj. CI: 0.7, 1.3)	10	24/1462/2113/69.2%
Adverse event: visual disturbance	RR 3.2 (REM 95% CI: 1.2, 8.3; P=0.02; TSA adj. CI: –)	0	5/299/–/<5%	P=0.55	RR 2.3 (REM 95% CI: 1.3, 4.1); P=0.003; TSA adj. CI: 0.2, 26.5)	12	30/1973/20 555/9.6%

conclusions concerning these results. The estimates indicate an increased incidence of SAEs in the pregabalin group compared with controls, especially in trials with more than one administration of pregabalin. Pain scores and most adverse events did not differ significantly between groups except for early pain intensity at rest, which was significantly reduced, and risk of dizziness, vomiting, and visual disturbance, which was increased; however, the TSAs did not reach firm evidence.

Relationship to other reviews

Other recent systematic reviews with meta-analyses have investigated beneficial and harmful effects of pregabalin on acute pain after surgery.[8 10] Eipe and colleagues[10] included 43 randomized controlled trials in their systematic review and investigated perioperative pregabalin with a special focus on dose–response, and on pro-nociceptive *vs* non-nociceptive pain, thereby making it difficult to compare with the outcomes of the present review. They found a similar small number of studies with low risk of bias as in the present review, although this was not accounted for in their analyses. Mishriky and colleagues[8] conducted a systematic review and found a significant reduction in 24 h morphine consumption (8.27 mg; 95% CI: 6.47, 10.08) based on all trials regardless of bias and similar to the all trials estimates from the present review (10.8 mg; 95% CI: 8.5, 13.2). The results from our subgroup analyses (Table 1) indicated an overestimation of beneficial effects and underestimation of harmful effects in trials with unclear and high risk of bias compared with those with low risk of bias. Mishriky and colleagues[8] did explore the bias effect and found no effect from removal of trials with uncertain risk of bias. However, they explored different outcomes from those in our review, thus making it difficult to draw a direct comparison of primary outcomes and bias effects between reviews.

The present review is, to our knowledge, the first and currently the largest systematic review investigating both benefit and harm of pregabalin for postoperative pain management while assessing and addressing the risk of both random and systematic error (see Table 2 for an overview of recent pregabalin trials and differences in outcome presentations for further details).

Impact of analyses

Our *a priori* definition of a minimal clinical relevant effect in 24 h opioid consumption was 5 mg of morphine i.v. This predefined estimate was chosen based on previous systematic reviews of gabapentin indicating that the opioid-sparing effect of gabapentin was <10 mg.[23 121] Consequently, in order not to ignore any clinical relevant difference in the meta-analyses, the cut-off was set to 5 mg. It may, however, be argued that 5 mg is too small or irrelevant in a clinical setting. None of the CIs reached 10 mg, excluding an effect of >10 mg morphine if this was to be a minimal clinical relevant morphine-sparing effect.

The morphine-sparing effect in trials investigating pregabalin as part of multimodal regimens was slightly less than that of the predefined minimal clinical relevant difference, whereas the treatment with pregabalin without other non-analgesics indicated a morphine-sparing effect >10 mg; however, we found only two trials with low risk of bias in this group. The use of pregabalin in more than one dose treatment compared with a single dose treatment does not seem to increase the opioid-sparing effect of pregabalin. The reduction in 24 h morphine consumption was generally lower in estimates for trials with low risk of

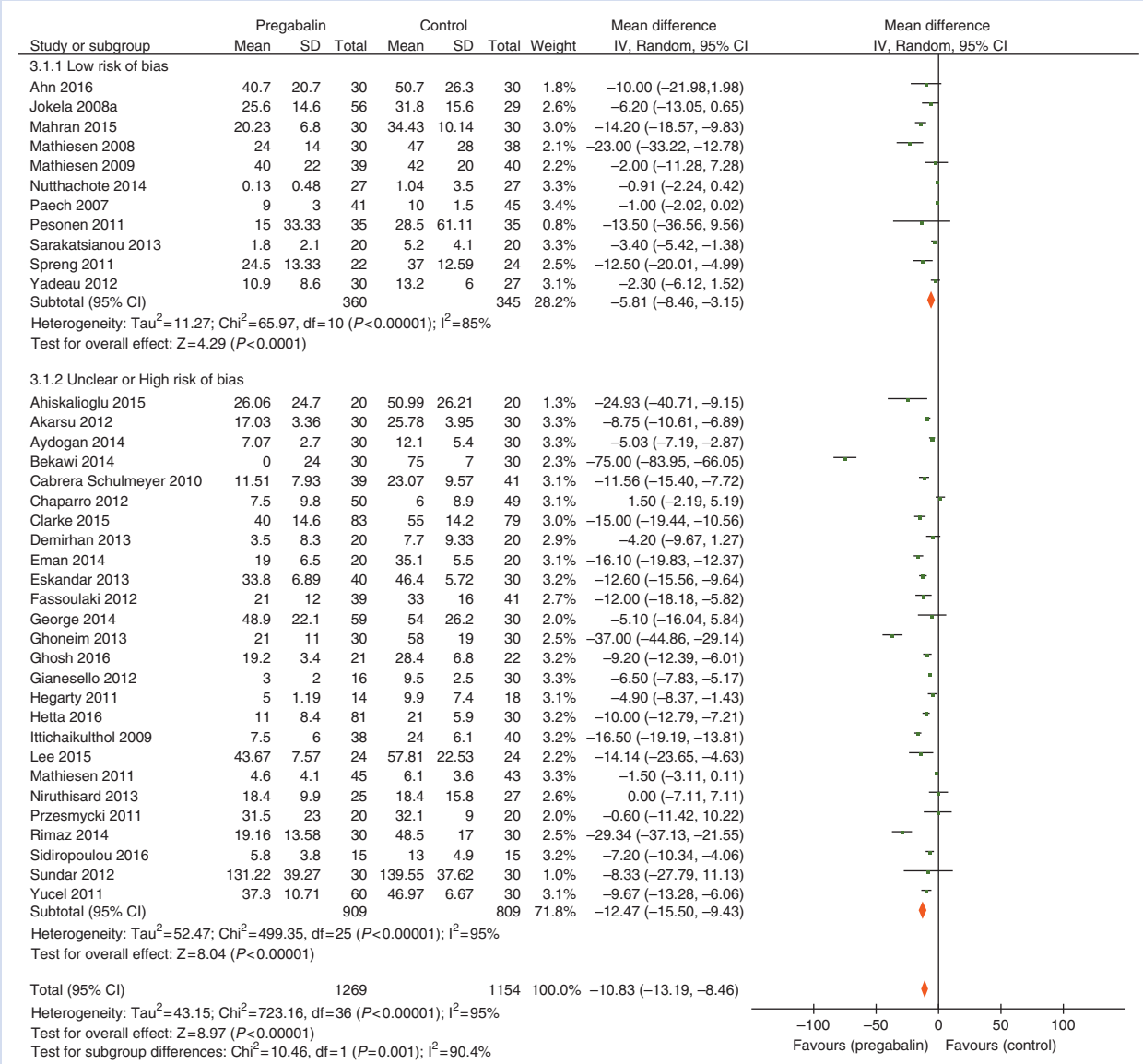

Fig 3 Forest plot of 24 h morphine consumption, including the subgroup analysis of trials with low risk of bias *vs* trials with unclear and high risk of bias.

bias compared with all trials that also included trials with uncertain and high risk of bias, thus confirming that trials with high risk of systematic errors often overestimate beneficial effects.

The incidence of SAEs may be increased in the pregabalin group compared with the controls especially in trials with more than one administration of pregabalin. SAEs were, however, very poorly reported, and only 21 trials reported this outcome. Data did not allow for designation of specific types of patients or surgeries with increased risk. A little more than half of the included trials reported SAEs in the published manuscripts, and the rest found none during their follow-up. The very diverse, incomplete registering, short follow-up and reporting of SAEs limits the reliability of our results. However, it does seem that an increased incidence of SAEs is present in the pregabalin group, and the risk may increase with more than one dose treatment of pregabalin.

For trials investigating the effect of pregabalin on early and late pain intensity at rest and mobilization, we cannot rule out a reduction in pain intensity scores, as the required information size was not reached in any of the TSAs. However, the TSA estimates for pain do not indicate a reduction in beneficial outcomes.

The reporting of adverse events was diverse, with similar limitations to the SAE outcome. This problem of incomplete adverse event reporting has recently been addressed and confirmed in another review.[122] The present analyses indicate that pregabalin treatment was associated with increased levels of

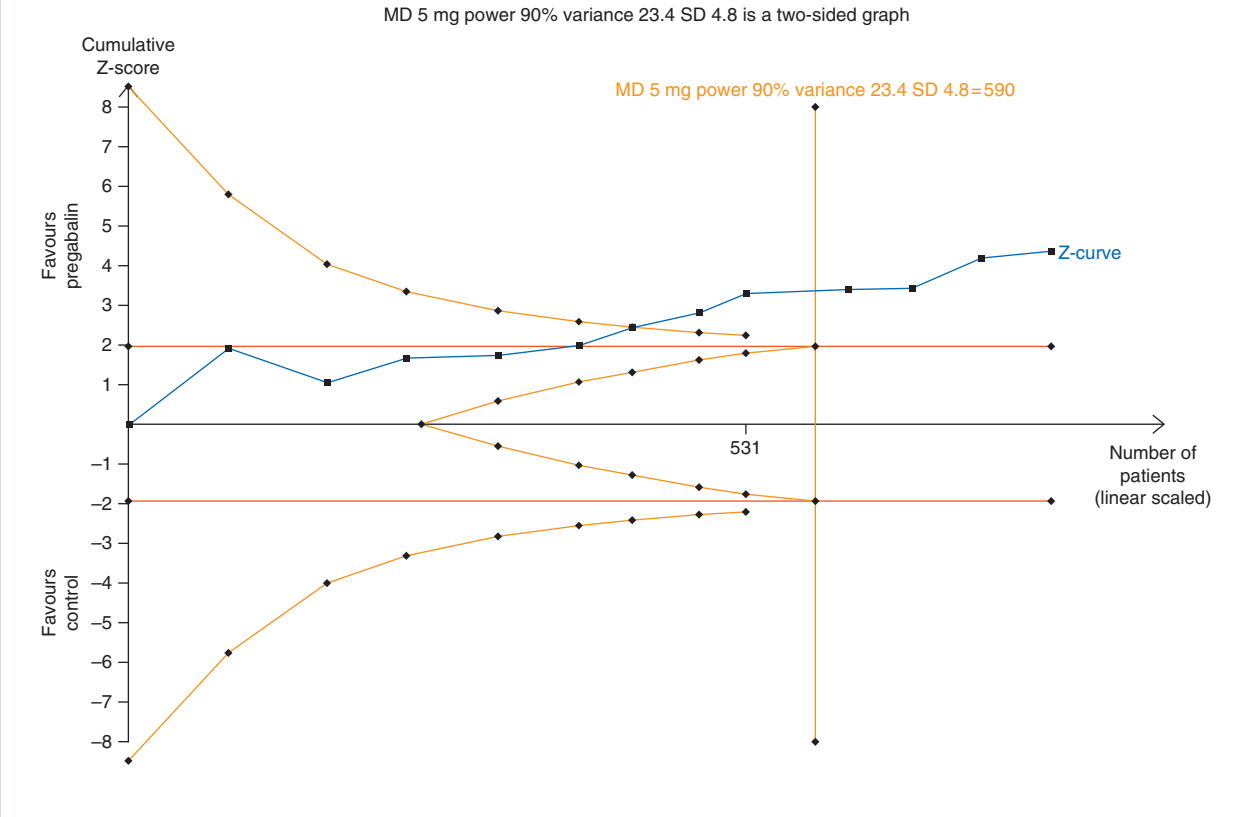

Fig 4 Trial sequential analysis of 24 h morphine consumption from trials with low risk of bias. The minimal clinical difference was 5 mg with an α of 5% and β of 10%. The z-curve crosses the monitoring boundary for benefit after six trials, and the required information size is met. In conclusion, there is firm evidence that pregabalin reduces 24 h morphine consumption; however, we cannot rule out a reduction in 24 h morphine consumption less than the predefined minimal clinical difference of 5 mg, because the trial sequential analysis adjusted confidence interval is 3.2, 8.5 mg.

sedation, dizziness, and visual disturbance and increased risk of vomiting, whereas nausea, PONV, and headaches might be reduced. None of the trials with low risk of bias had enough information to withstand the TSA testing. The all trials estimates do indicate a more homogeneous profile, with possible reductions in incidences of nausea, vomiting, PONV, and headaches, and with an increased risk of sedation, dizziness, and visual disturbances.

Comparative effects of pregabalin and gabapentin in postoperative pain management

A comparable systematic review evaluating gabapentin for postoperative pain management has recently been published.[121] Per-protocol, it was predefined that conclusions from both the review of gabapentin, and the present review of pregabalin, should be based primarily on meta-analyses of the best evidence, defined as trials with overall low risk of bias.[12 123] Comparable data from the two reviews on primary beneficial and harmful outcomes are summarized in Table 3. Furthermore, Table 3 includes available data from meta-analyses of four other frequently used non-opioid analgesics in postoperative pain treatment, namely paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX2) inhibitors, and steroids.

With gabapentin, an overall 24 h morphine-sparing effect of 3.1 mg was demonstrated, which was less than the predefined 5 mg minimal clinical difference. Furthermore, the morphine-sparing effect of gabapentin as monotherapy (8.0 mg) was not statistically significant different from placebo, but this result is based on only two trials with low risk of bias (Table 3).[121]

In contrast, pregabalin reduced overall 24 h morphine consumption by 5.8 mg, thus reaching the predefined 5 mg minimal clinical difference. Furthermore, the reduction in 24 h morphine consumption with pregabalin as add-on to other non-opioid analgesics was 3.7 mg, as opposed to 1.2 mg with gabapentin. Both results with pregabalin reached firm evidence according to TSA. There is, however, still a major probability that a clinically relevant beneficial effect is not present with pregabalin.

The risk of SAEs in trials with low risk of bias was increased in both reviews; however, neither of the reviews has enough data to reach firm evidence.[121] The gabapentin review demonstrated a 1.6 times increased risk of SAEs, whereas the present pregabalin review reports almost twice the odds of SAEs, compared with gabapentin: 2.9. Furthermore, multiple administrations of pregabalin further increased the risk of SAEs to 3.4.

Pain was moderately reduced in trials with low risk of bias in both reviews, but only in the early postoperative period.

The risk of adverse events differs between the two reviews. Although the gabapentin review found no significant differences

Table 2 Overview of recent pregabalin trials and differences in outcome presentations. FEM, fixed effects model; MD, mean difference; OR, odds ratio; REM, random effects model; RR, risk ratio; TSA, trial sequential analysis. *No TSA available †No bias effect found in analyses. ‡Only available in weighted mean difference. ¶Not available; a comparison of regional anaesthesia and general anaesthesia is reported. §Authors state: 'sparse evidence precluded meaningful conclusions'

Pregabalin reviews					
Estimate (MD/RR/OR) (REM/FEM; 95% CI; *P*-value; TSA adj. CI)	**This systematic review**	**Mishriky and colleagues[8]**	**Lam and colleagues[9]**	**Zhang and colleagues[128]**	**Eipe and colleagues[10]**
Low risk of bias					
24 h opioid consumption	5.8 mg reduction (3.2, 8.5; $P<0.0001$; 3.2, 8.5)	Note†	Not available	Not available	Not† available
24 h opioid consumption: plus other non-opioid analgesics	3.7 mg reduction (1.5, 6.0; $P=0.009$; 1.5, 6.0)	Not available	Not available	Not available	Not available
24 h opioid consumption: minus other non-opioid analgesics	13.7 mg reduction (9.6, 17.8; $P<0.00001$; 9.6. 17.8)	Not available	Not available	Not available	Not available
All trials					
24 h opioid consumption	10.8 mg reduction (8.5, 13.2; $P<0.00001$; 8.5, 13.2)	8.27 mg reduction (6.47 to 10.08; $P<0.00001$)*	Not available	Note‡	Not available
24 h opioid consumption: plus other non-opioid analgesics	8.9 mg reduction (6.7, 11.0; $P<0.0001$; 6.7, 11.0)	Note¶	Not available	Not available	Not available
24 h opioid consumption: minus other non-opioid analgesics	20.4 mg (11.1, 34.0; $P=0.0001$; −16.6, 56.6)	Not available	Not available	Not available	Not available
Low risk of bias					
Serious adverse events	2.9 (1.2, 6.8; $P=0.02$; 0.1, 97.1)	Not available	Not available	Not available	Not available
All trials					
Serious adverse events	2.4 (1.4, 4.2 $P=0.002$; 0.9, 6.33)	Not available	Not available	Not available	Note§

between groups for risk of nausea, vomiting, sedation, and dizziness,[121] the risk of vomiting and dizziness seemed increased with pregabalin, compared with controls. However, none of these outcomes reached firm evidence, according to TSA.

It should be noted that no comparable data from meta-analyses of trials with low risk of bias are available in the literature, for four of the most used non-opioid analgesics, namely paracetamol, NSAIDs, COX2 inhibitors, and steroids (Table 3). It must be anticipated, however, that results similar to those presented in our reviews of pregabalin and gabapentin would be found for trials with low risk of bias with other non-opioid analgesics, as indicated in a recent analysis of paracetamol i.v.[126] In this analysis, only very few trials were considered low risk of bias.[126]

Considerations on gabapentinoids as part of enhanced recovery programmes after surgery

Enhanced recovery programmes aim to improve postoperative rehabilitation while reducing the risk of complications in surgical populations. Effective pain relief and opioid sparing, with multimodal regimens that often include two or more non-opioid analgesics, represents a cornerstone in such programmes.

On the basis of the actual reviews, with conclusions based on trials with low risk of bias only, gabapentin cannot be recommended for routine postoperative pain treatment, either as a single analgesic administered together with opioid, or as part of multimodal regimens. Opioid sparing, reduction of opioid-related adverse events, and pain relief are marginal, at best, and the risk of SAEs is imminent.

For pregabalin, a significant but minimal reduction in opioid consumption seems present, but pain reduction is marginal. Although PONV might be reduced, the risk of both dizziness and, especially, visual disturbances is increased. Pregabalin may also display a greater risk of SAEs than gabapentin.

In more general terms, our knowledge of benefit and harm regarding 'multimodal' analgesic regimens is sparse, and we have very limited high-quality information of regimens including more than one non-opioid analgesic.[124 127] Consequently, analgesic regimens using gabapentinoids as part of multimodal analgesic regimens for enhanced recovery programmes should be used only in protocolled situations, with careful considerations of benefit and harm. Based on the two reviews, we find little sound evidence from trials with the best research methodology to support the routine use of gabapentinoids in this context.

Table 3 Comparative data from meta-analyses of pregabalin, gabapentin, paracetamol, NSAIDs, COX2-inhibitors, and steroids in postoperative pain management. COX2, cyclooygenase 2; FEM, fixed effects model; MD, mean difference; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; REM, random effects model; RR, risk ratio; TSA, trial sequential analysis. *See also Mathiesen and colleagues[124] and McDaid and colleagues.[125] †TSA not performed

	Pregabalin	Gabapentin	Paracetamol	NSAIDs	COX2-inhibitors	Steroids
	Estimate MD/RR (REM/Peto's OR) (95% CI; P-value; TSA adj. 95% CI)	Estimate MD/RR (REM/Peto's OR) (95% CI; P-value; TSA adj. 95% CI)	Estimate MD (95% CI; P-value)	Estimate MD (95% CI; P-value)	Estimate MD (95% CI; P-value)	Estimate MD (95% CI; P-value)
Trials with overall low risk of bias						
24 h morphine consumption	5.8 mg reduction (REM 95% CI: 3.2, 8.5; P<0.0001; TSA adj. CI: 3.2, 8.5) (11 trials)	3.1 mg reduction (REM 95% CI: 0.5, 5.6; P=0.02; TSA adj. CI: −0.5, 5.6) (13 trials)	No available data	No available data	No available data	No available data
24 h morphine consumption: add-on	3.7 mg reduction (REM 95% CI: 1.5, 6.0; P=0.0009; TSA adj. CI: 1.5, 6.0) (9 trials)	1.2 mg reduction (REM 95% CI: −0.3, 2.6; P=0.12; TSA adj. CI: −0.3, 2.6) (11 trials)	No available data	No available data	No available data	No available data
24 h morphine consumption: no add-on	13.7 mg reduction (REM 95% CI: 9.6, 17.8; P<0.00001; TSA adj. CI: 9.6. 17.8) (2 trials)	8.0 mg reduction (REM 95% CI: −1.5, 17.4; P=0.10; TSA adj. CI: −15.5, 23.3) (2 trials)	No available data	No available data	No available data	No available data
All trials						
24 h morphine consumption	10.8 mg reduction (REM 95% CI: 8.5, 13.2; P<0.00001; TSA adj. CI: 8.5, 13.2) (37 trials)	7.3 mg reduction (REM 95% CI: 5.9, 8.8; P<0.00001; TSA adj. CI: 5.9, 8.8) (73 trials)	No available data*	No available data*	No available data*	No available data*
24 h morphine consumption: add-on	8.9 mg reduction (REM 95% CI: 6.7, 11.0; P<0.0001; TSA adj. CI: 6.7, 11.0) (21 trials)	4.4 mg reduction (REM 95% CI: 2.4, 6.5; P<0.00001; TSA adj. CI: 2.4, 6.5) (36 trials)	No available data*	No available data*	No available data*	2.33 mg reduction (95% CI: 0.26; 4.39); P=0.03;†[124]
24 h morphine consumption: no add-on	20.4 mg reduction (REM 95% CI: 11.1, 34.0; P=0.0001; TSA adj. CI: −16.6, 56.6) (9 trials)	10.6 mg reduction (REM 95% CI: 8.4, 12.8; P<0.00001; TSA adj. CI: 8.4, 12.8) (37 trials)	6.3 mg reduction (95% CI: 3.7, 9.0); P<0.05;†[125]	10.2 mg reduction (95% CI: 8.7, 11.7); P<0.05;†[125]	10.9 mg reduction (95% CI: 9.1, 12.8); P<0.05;†[125]	No available data*
Trials with overall low risk of bias						
Serious adverse events	OR 2.9 (Peto's OR 95% CI: 1.2, 6.8; P=0.02; TSA adj. CI: 0.1, 97.1) (10 trials)	RR 1.61 (FEM 95% CI: 0.9, 2.9; P=0.10 TSA adj. CI: 0.6, 4.6) (9 trials)	No available data*	No available data*	No available data*	No available data*
All trials						
Serious adverse events	OR 2.4 (Peto's OR 95% CI: 1.4, 4.2 P=0.002; TSA adj. CI: 0.9, 6.33) (21 trials)	RR 1.14 (FEM 95% CI: 0.71, 1.81; P=0.59; TSA adj. CI: 0.6, 2.1) (26 trials)	No available data on RR, but see McDaid and colleagues*[125]	No available data on RR, but see McDaid and colleagues*[125]	No available data on RR, but see McDaid and colleagues*[125]	No available data*

Strengths and limitations of the review

This systematic review has several strengths. The protocol was registered before the study at PROSPERO; it is compliant with the latest Cochrane methodology, and the review is reported according to the PRISMA guidelines. Our search strategies were comprehensive, without language restrictions. Screening of all titles and full texts, data extraction, and bias assessments, were carried out by two independent authors.

We evaluated the risk of random errors using TSA methodology on all outcomes, and the risk of systematic error was assessed using Cochrane bias evaluation tools. All conclusions were based on trials with overall low risk of bias, using GRADE to document the further liability of our results.

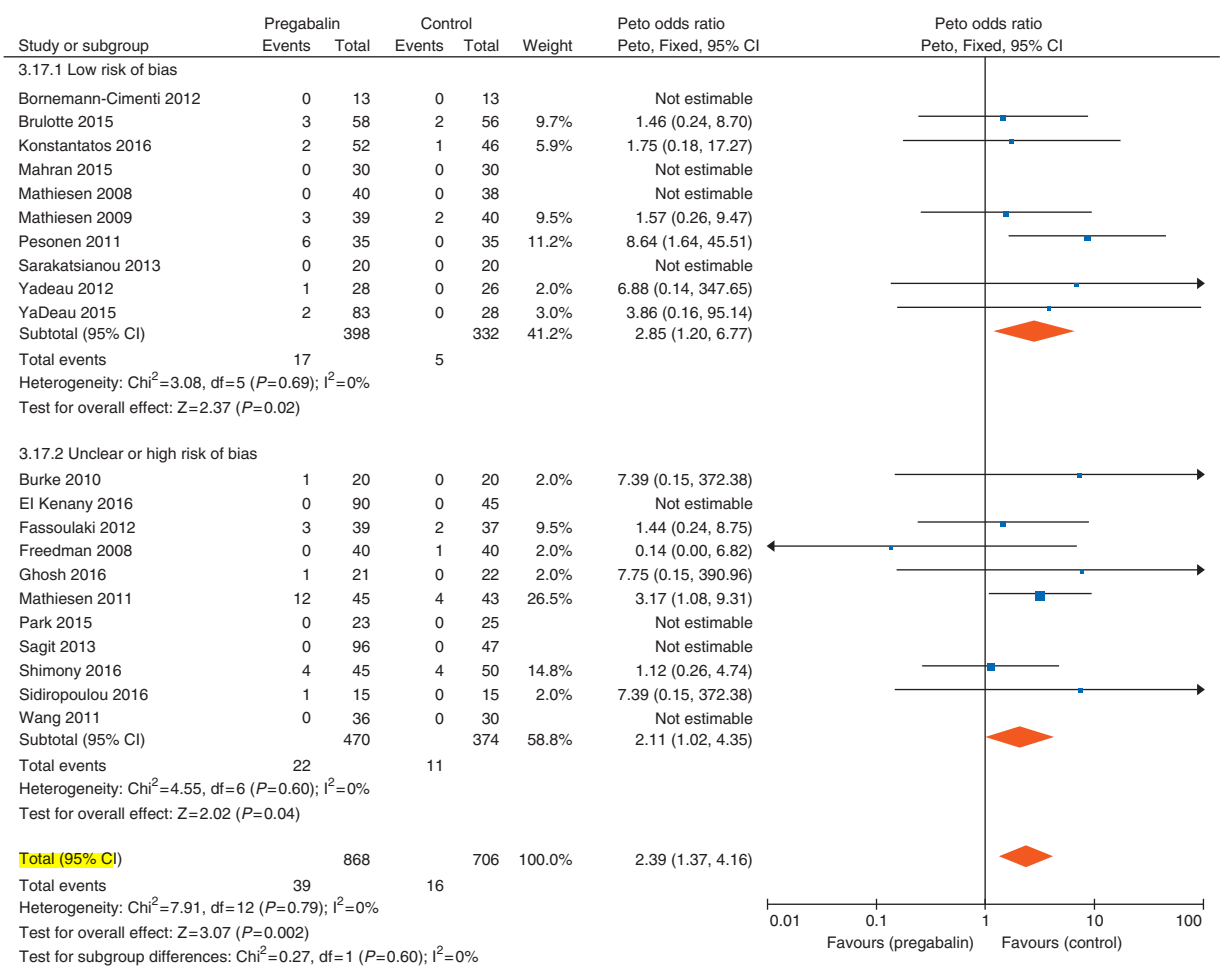

Fig 5 Forest plot of serious adverse events. including the subgroup analysis of trials with low risk of bias *vs* trials with unclear and high risk of bias.

The limitations of the conclusions in this review mirror those of the trials included in the review. The problems identified are that the majority of the included trials are classified as either unclear or high risk of bias, with an inherent risk of systematic error. Very few trials reported on SAEs, and most have a short follow-up period, limiting the ability for firm conclusions and with a huge risk of underestimating incidences of SAEs. Furthermore, a limited number of trials investigated the reduction in opioid consumption beyond 24 h, thus limiting our ability to conclude further than the 24 h investigated in this systematic review.

Major heterogeneity was present, because we included all trials regardless of surgical procedure, dosing regimen, and types of additional analgesics. The conversion of scales for pain intensity scores and calculations of equi-analgesic doses of opioids might introduce heterogeneity and imprecision.

Conclusion

We have found that, based on trials with low risk of bias, pregabalin may have a minimal opioid-sparing effect, but the risk of SAEs seems increased. However, the GRADE-rated evaluations showed only moderate to very low quality of evidence. Consequently, the routine use of pregabalin for postoperative pain treatment cannot be recommended.

Authors' contributions

All authors comply with ICMJE recommendations.
Conception and design: M.L.F., J.B.D., J.W., O.M.
Data acquisition: M.L.F., C.S., S.K., P.L.P., A.G., P.J.
Analysis of data: M.L.F.
Interpretation of data: M.L.F., C.S., S.K., P.L.P., A.G., P.J., J.B.D., J.W., O.M.
Drafting the manuscript: M.L.F.
Revising the manuscript: M.L.F., C.S., S.K., P.L.P., A.G., P.J., J.B.D., J.W., O.M.
Approval of the final version and accountable for all aspects of the work: M.L.F., C.S., S.K., P.L.P., A.G., P.J., J.B.D., J.W., O.M.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

J.W. reports that he is a member of the task force at Copenhagen Trial Unit to develop the software and manual for doing trial sequential analysis (TSA). A.G., P.L.P., C.S., S.K., P.J., J.B.D., O.M., and M.L.F. have no conflicts of interests to declare.

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References

1. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel γ-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007; **29**: 26–48
2. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and $\alpha_2\delta$-1 calcium channel subunit in neuropathic pain. *Pharmacol Res Perspect* 2016; **4**: e00205
3. Calandre EP, Rico-Villademoros F, Slim M. Alpha$_2$delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. *Expert Rev Neurother* 2016; **16**: 1263–77
4. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010; **49**: 661–9
5. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia* 2004; **45(Suppl 6)**: 13–8
6. Mathieson S, Maher CG, McLachlan AJ, *et al*. Trial of pregabalin for acute and chronic sciatica. *N Engl J Med* 2017; **376**: 1111–20
7. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. *Cochrane Database Syst Rev* 2016; **9**: CD011790
8. 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
9. Lam DM, Choi SW, Wong SS, Irwin MG, Cheung CW. Efficacy of pregabalin in acute postoperative pain under different surgical categories: a meta-analysis. *Medicine (Baltimore)* 2015; **94**: e1944
10. Eipe N, Penning J, Yazdi F, *et al*. Perioperative use of pregabalin for acute pain—a systematic review and meta-analysis. *Pain* 2015; **156**: 1284–300
11. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J* 2008; **336**: 924–6
12. Fabritius ML, Strøm C, Koyuncu S, *et al*. Benefits and harms of perioperative pregabalin treatment: a systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. PROSPERO 2015. Available from https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=crd4201025282 (accessed 17 January 2017)
13. Nickerson RS. Confirmation bias: a ubiquitous phenomenon in many guises. *Rev Gen Psych* 1998; **2**: 175–220
14. Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: JPT Higgings, S Green, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Wiley & Sons, 2008. Available from www.cochrane-handbook.org (accessed 21 January 2017)
15. *ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A*. Europe, USA, and Japan: ICH expert working group, 1994; 2–3
16. Higgins JPT, Altman DG, Chapter 16: Special topics in statistics. In: JPT Higgings, S Green, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Wiley & Sons, 2008. Available from www.cochrane-handbook.org (accessed 21 January 2017)
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13
18. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: JPT Higgins, S Green, eds. *Cochrane Handbook for Systematic Reviews of Interventions 2008*. Chichester, UK: John Wiley & Sons, 2008. Available from www.cochrane-handbook.org (accessed 21 January 2017)
19. Thorlund K, Imberger G, Walsh M, *et al*. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis—a simulation study. *PLoS One* 2011; **6**: e25491
20. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007; **26**: 53–77
21. Sweeting MJ, Sutton A, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004; **23**: 1351–75
22. Imberger G, Gluud C, Boylan J, Wetterslev J. Systematic reviews of anesthesiologic interventions reported as statistically significant: problems with power, precision, and type 1 error protection. *Anesth Analg* 2015; **121**: 1611–22
23. Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia* 2015; **70**: 1186–204
24. Abbasabadi FM, Emadi S, Baradari AG, Alipour A, Pashakolai GA, Hashemi SA. Effect of single dose and low dose of pregabalin on postoperative pain of abdominal hysterectomy. *Int J Rev Life Sci* 2015; **5**: 780–4
25. Ahiskalioglu A, İnce İ, Aksoy M, Yalcin E, Ahiskalioglu EO, Kilinc A. Effects of a single-dose of pre-emptive pregabalin on postoperative pain and opioid consumption after double-jaw surgery: a randomized controlled trial. *J Oral Maxillofac Surg* 2016; **74**: 53.e1–7
26. Ahn S, Byun SH, Park K, Ha JL, Kwon B, Kim JC. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: a randomized controlled trial. *Can J Anaesth* 2016; **63**: 283–9
27. Akarsu T, Tür H, Bolat C, ÖZkaynak İ. Comparison of preemptive pregabalin with placebo and diclofenac combination for postoperative analgesia and cognitive functions

after laparoscopic cholecystectomy. *Turkiye Klinikleri J Med Sci* 2012; **32**: 963–70
28. Akhavanakbari G, Entezariasl M, Isazadehfar K, Mirzarahimi T. The effects of oral pregabalin on postoperative pain of lower limb orthopedic surgery: a double-blind, placebo-controlled trial. *Perspect Clin Res* 2013; **4**: 165–8
29. Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. *Anesth Pain Med* 2012; **2**: 72–6
30. Aydogan H, Kucuk A, Yuce HH, *et al*. Adding 75 mg pregabalin to analgesic regimen reduces pain scores and opioid consumption in adults following percutaneous nephrolithotomy. *Rev Bras Anestesiol* 2014; **64**: 335–42
31. Bafna U, Rajarajeshwaran K, Khandelwal M, Verma AP. A comparison of effect of preemptive use of oral gabapentin and pregabalin for acute post-operative pain after surgery under spinal anesthesia. *J Anaesthesiol Clin Pharmacol* 2014; **30**: 373–7
32. Balaban F, Yağar S, Özgok A, Koç M, Güllapoğlu H. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. *J Clin Anesth* 2012; **24**: 175–8
33. Bekawi MS, El Wakeel LM, Al Taher WM, Mageed WM. Clinical study evaluating pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. *Clin J Pain* 2014; **30**: 944–52
34. Bornemann-Cimenti H, Lederer AJ, Wejbora M, *et al*. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. *Br J Anaesth* 2012; **108**: 845–9
35. Brulotte V, Ruel MM, Lafontaine E, Chouinard P, Girard F. Impact of pregabalin on the occurrence of postthoracotomy pain syndrome: a randomized trial. *Reg Anesth Pain Med* 2015; **40**: 262–9
36. Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. *Anesth Analg* 2010; **110**: 1180–5
37. 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
38. 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; **114**: 434–41
39. 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**: 1678–81
40. Cegin MB, Soyoral L, Yuzkat N, Baydi V, Goktas U. Pregabalin administered as an anxiolytic agent in ultrasound-guided infraclavicular block: a controlled, double-blind, dose-ranging trial. *Eur Rev Med Pharmacol Sci* 2016; **20**: 568–74
41. Chang SH, Lee HW, Kim HK, Kim SH, Kim DK. An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. *Anesth Analg* 2009; **109**: 1284–6
42. Chaparro LE, Clarke H, Valdes PA, Mira M, Duque L, Mitsakakis N. Adding pregabalin to a multimodal analgesic regimen does not reduce pain scores following cosmetic surgery: a randomized trial. *J Anesth* 2012; **26**: 829–35
43. Choi YS, Shim JK, Song JW, Kim JC, Yoo YC, Kwak YL. Combination of pregabalin and dexamethasone for postoperative pain and functional outcome in patients undergoing lumbar spinal surgery: a randomized placebo-controlled trial. *Clin J Pain* 2013; **29**: 9–14
44. Clarke H, Page GM, McCartney CJ, *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**: 903–11
45. Laithangbam P, Singh H, Chotton T, Singh N, Singh L. The effect of pregabalin for relief of postoperative pain after abdominal hysterectomy. *J Med Soc* 2014; **28**: 18
46. Clendenen SR, Rajendran S, Kopacz DJ, *et al*. Pregabalin as an adjunct to a multimodal analgesic regimen to achieve opioid sparing in arthroscopic rotator cuff repair. *Rom J Anaesth Intensive Care* 2010; **17**: 5–10
47. Demirhan A, Tekelioglu UY, Akkaya A, *et al*. Effect of pregabalin and dexamethasone addition to multimodal analgesia on postoperative analgesia following rhinoplasty surgery. *Aesthetic Plast Surg* 2013; **37**: 1100–6
48. Demirhan A, Akkaya A, Tekelioglu UY, *et al*. Effect of pregabalin and dexamethasone on postoperative analgesia after septoplasty. *Pain Res Treat* 2014; **2014**: 850794
49. El Kenany S, El Tahan MR. Effect of preoperative pregabalin on post-caesarean delivery analgesia: a dose-response study. *Int J Obstet Anesth* 2016; **26**: 24–31
50. Eman A, Bilir A, Beyaz SG. The effects of preoperative pregabalin on postoperative analgesia and morphine consumption after abdominal hysterectomy. *Acta Med Mediterr* 2014; **30**: 481–5
51. Eskandar AM, Ebeid AM. Effect of pregabalin on postoperative pain after shoulder arthroscopy. *Egypt J Anaesth* 2013; **29**: 363–7
52. Fassoulaki A, Melemeni A, Tsaroucha A, Paraskeva A. Perioperative pregabalin for acute and chronic pain after abdominal hysterectomy or myomectomy: a randomised controlled trial. *Eur J Anaesthesiol* 2012; **29**: 531–6
53. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. *Aesthet Surg J* 2008; **28**: 421–4
54. 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**: 149–53
55. George RB, McKeen DM, Andreou P, Habib AS. A randomized placebo-controlled trial of two doses of pregabalin for postoperative analgesia in patients undergoing abdominal hysterectomy. *Can J Anaesth* 2014; **61**: 551–7
56. Ghai A, Gupta M, Hooda S, Singla D, Wadhera R. A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. *Saudi J Anaesth* 2011; **5**: 252–7
57. Ghai A, Gupta M, Rana N, Wadhera R. The effect of pregabalin and gabapentin on preoperative anxiety and sedation: a double blind study. *Anaesth Pain Intensive Care* 2012; **16**: 257–61
58. Ghoneim A, Hegazy M. The analgesic effect of preoperative pregabalin in radical cystectomy for cancer bladder patients. *Chin Ger J Clin Oncol* 2013; **12**: 113–7
59. Ghosh S, Chattopadhyay S, Sarkar S, Mandal M, Ranjan SB. Addition of dexamethasone injection to pre-emptive oral pregabalin does not improve postoperative analgesia over pregabalin alone for abdominal hysterectomy under general anaesthesia. *J Evolution Med Dent Sci* 2016; **53**: 3544–8

60. Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *J Neurosurg Anesthesiol* 2012; **24**: 121–6
61. 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**: 249–53
62. Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: a comparative evaluation. *Saudi J Anaesth* 2011; **5**: 179–84
63. Gurunathan U, Rapchuk IL, King G, Barnett AG, Fraser JF. The effect of pregabalin and celecoxib on the analgesic requirements after laparoscopic cholecystectomy: a randomized controlled trial. *J Anesth* 2016; **30**: 64–71
64. Hegarty DA, Shorten GD. A randomised, placebo-controlled trial of the effects of preoperative pregabalin on pain intensity and opioid consumption following lumbar discectomy. *Korean J Pain* 2011; **24**: 22–30
65. Hetta DF, Mohamed MA, Mohammad MF. Analgesic efficacy of pregabalin in acute postmastectomy pain: placebo controlled dose ranging study. *J Clin Anesth* 2016; **34**: 303–9
66. 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 salphingo-oopho rectomy: a randomized, double-blind trial. *J Med Assoc Thai* 2009; **92**: 1318–23
67. 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; **46**: 646–52
68. Jadeja HK, Chetna A, Oza V, Parmar V. Comparative study of single dose pre-emptive pregabalin vs. placebo for postoperative pain relief in middle ear surgery. *Int J Biomed Adv Res* 2014; **5**: 170–3
69. 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**: 834–40
70. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. *Pain* 2008; **134**: 106–12
71. Joshi SS, Jagadeesh AM. Efficacy of perioperative pregabalin in acute and chronic post-operative pain after off-pump coronary artery bypass surgery: a randomized, double-blind placebo controlled trial. *Ann Card Anaesth* 2013; **16**: 180–5
72. 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**: 262–7
73. Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. *Spine* 2014; **39**: E363–8
74. Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam KH, Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. *Surg Endosc* 2010; **24**: 2776–81
75. Kim SY, Song JW, Park B, Park S, An YJ, Shim YH. Pregabalin reduces post-operative pain after mastectomy: a double-blind, randomized, placebo-controlled study. *Acta Anaesthesiol Scand* 2011; **55**: 290–6
76. Kohli M, Murali T, Gupta R, Khan P, Bogra J. Optimization of subarachanoid block by oral pregabalin for hysterectomy. *J Anaesthesiol Clin Pharmacol* 2011; **27**: 101–5
77. Konstantatos AH, Howard W, Story D, Mok LY, Boyd D, Chan MT. A randomised controlled trial of peri-operative pregabalin vs. placebo for video-assisted thoracoscopic surgery. *Anaesthesia* 2016; **71**: 192–7
78. Kim JC, Choi YS, Kim KN, Shim JK, Lee JY, Kwak YL. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. *Spine* 2011; **36**: 428–33
79. Kim JH, Seo MY, Hong SD, *et al*. The efficacy of preemptive analgesia with pregabalin in septoplasty. *Clin Exp Otorhinolaryngol* 2014; **7**: 102–5
80. Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blinded, placebo-controlled study. *J Pain Res* 2013; **6**: 471–8
81. Lee C, Lee HW, Kim JN. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparoendoscopic single-site urologic surgery. *Korean J Anesthesiol* 2013; **64**: 19–24
82. 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 Arthroplasty* 2015; **30**: 38–42
83. Mahran E, Hassan ME. Comparison of pregabalin versus ketamine in postoperative pain management in breast cancer surgery. *Saudi J Anaesth* 2015; **9**: 253–7
84. Mansor SH, Choy CY. Effect of preoperative oral pregabalin on postoperative pain after mastectomy. *Middle East J Anaesthesiol* 2015; **23**: 63–8
85. Martinez V, Cymerman A, Ben Ammar S, *et al*. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. *Anaesthesia* 2014; **69**: 46–52
86. 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**: 535–41
87. 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**: 227–35
88. Mathiesen O, Jørgensen DG, Hilsted KL, *et al*. Pregabalin and dexamethasone improves post-operative pain treatment after tonsillectomy. *Acta Anaesthesiol Scand* 2011; **55**: 297–305
89. Meek JM, Rosbolt MB, Taylor KR, Fusco EA, Panday VA, Reilly CD. Pregabalin versus placebo in postoperative pain relief of patients' status post photorefractive keratectomy: a double-masked, randomized, prospective study. *J Ocul Pharmacol Ther* 2014; **30**: 527–32
90. Nimmaanrat S, Tangtrakulwanish B, Klabklay P, Boonriong T. Perioperative administration of pregabalin in patients undergoing arthroscopic anterior cruciate ligament reconstruction: does it help to relieve postoperative pain? *J Med Assoc Thai* 2012; **95**: 1297–301
91. Niruthisard S, Earsakul A, Bunburaphong P, *et al*. Preoperative pregabalin and/or celecoxib for pain management after total knee arthroplasty under intrathecal

morphine: a randomized controlled trial. *Asian Biomed* 2013; **7**: 578–85
92. Nutthachote P, Sirayapiwat P, Wisawasukmongchol W, Charuluxananan S. A randomized, double-blind, placebo-controlled trial of oral pregabalin for relief of shoulder pain after laparoscopic gynecologic surgery. *J Minim Invasive Gynecol* 2014; **21**: 669–73
93. Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y. Perioperative administration of gabapentin 1,200 mg day^{-1} and pregabalin 300 mg day^{-1} for pain following lumbar laminectomy and discectomy: a randomised, double-blinded, placebo-controlled study. *Singapore Med J* 2011; **52**: 883–9
94. 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**: 1449–53; table of contents
95. Pakravan M, Roshani M, Yazdani S, Faramazi A, Yaseri M. Pregabalin and gabapentin for post-photorefractive keratectomy pain: a randomized controlled trial. *Eur J Ophthalmol* 2012; **22(Suppl 7)**: S106–13
96. Park SS, Kim DH, Nam IC, Lee IH, Hwang JW. The effectiveness of pregabalin for post-tonsillectomy pain control: a randomized controlled trial. *PLoS One* 2015; **10**: e0117161
97. Peng PW, Li C, Farcas E, *et al*. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. *Br J Anaesth* 2010; **105**: 155–61
98. Pesonen A, Suojaranta-Ylinen R, Hammarén E, *et al*. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. *Br J Anaesth* 2011; **106**: 873–81
99. Prasad A, Bhattacharyya S, Biswas A, Saha M, Mondal S, Saha D. A comparative study of pre-operative oral clonidine and pregabalin on post-operative analgesia after spinal anesthesia. *Anesth Essays Res* 2014; **8**: 41–7
100. Przesmycki K, Wiater-Kozioł E, Kotarski J, *et al*. Effect of preemptive pregabalin on pain intensity and morphine requirement after hysterectomy. *Anestezjol Intens Ter* 2011; **43**: 14–7
101. Rajappa GC, Vig S, Bevanaguddaiah Y, Anadaswamy TC. Efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. *Anesth Pain Med* 2016; **6**: e34591
102. Rajendran I, Basavareddy A, Meher B, Srinivasan S. Prospective, randomised, double blinded controlled trial of gabapentin and pregabalin as pre emptive analgesia in patients undergoing lower abdominal and limb surgery under spinal anaesthesia. *Indian J Pain* 2014; **28**: 155
103. Ram B, Khanna R, Kumar M, Tiwary PK, Suwalka U. Preemptive gabapentin v/s pregabalin for acute postoperative analgesia following abdominal hysterectomy under spinal anaesthesia: a randomized double blind study. *SEAJCRR* 2015; **4**: 2319–1090
104. Sebastian B, Talikoti 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**: UC01–4
105. Rimaz SAH, Naderi Nabi B, Sedighinejad A, Ashraf A, Emir Alavi C. Pre-emptive gabapentin versus pregabalin for acute postoperative pain after external dacryocystorhinostomy surgery under regional anesthesia: a randomized placebo-controlled trial. *Nautilus* 2014; **128**: 43–51
106. Sagit M, Yalcin S, Polat H, Korkmaz F, Cetinkaya S, Somdas MA. Efficacy of a single preoperative dose of pregabalin for postoperative pain after septoplasty. *J Craniofac Surg* 2013; **24**: 373–5
107. Sahu S, Sachan S, Verma A, Pandey HD, Chitra. Evaluation of pregabalin for attenuation of postoperative pain in below umbilical surgeries under spinal anaesthesia. *J Anaesth Clin Pharmacol* 2010; **26**: 167–71
108. Sarakatsianou C, Theodorou E, Georgopoulou S, Stamatiou G, Tzovaras G. Effect of pre-emptive pregabalin on pain intensity and postoperative morphine consumption after laparoscopic cholecystectomy. *Surg Endosc* 2013; **27**: 2504–11
109. Shimony N, Amit U, Minz B, *et al*. Perioperative pregabalin for reducing pain, analgesic consumption, and anxiety and enhancing sleep quality in elective neurosurgical patients: a prospective, randomized, double-blind, and controlled clinical study. *J Neurosurg* 2016; **125**: 1513–22
110. Sidiropoulou T. Perioperative pregabalin for postoperative pain relief after thoracotomy. *J Anesth Surg* 2016; **3**: 1–6
111. 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**: 571–6
112. Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. *Ann Card Anaesth* 2012; **15**: 18–25
113. Tunc M, Cinar D, Sahin S, Sazak H, Kose SK. The effects of pre-emptive pregabalin on post-thoracotomy pain and epidural analgesia. *Turk J Thorac Cardiovasc Surg* 2014; **22**: 129–37
114. Wang H, Gargano C, Lukac S, *et al*. An enhanced bunionectomy model as a potential tool for early decision-making in the development of new analgesics. *Adv Ther* 2010; **27**: 963–80
115. Wei LA, Davies BW, Hink EM, Durairaj VD. Perioperative pregabalin for attenuation of postoperative pain after eyelid surgery. *Ophthal Plast Reconstr Surg* 2015; **31**: 132–5
116. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. *Anesth Analg* 2009; **108**: 1140–5
117. 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**: 285–93
118. Yadeau JT, Paroli L, 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**: 302–7
119. Yücel A, Özturk E, Aydoğan MS, Durmuş M, Çolak C, Ersoy MÖ. 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**: 173–83
120. Ziyaeifard M, Mehrabanian MJ, Faritus SZ, *et al*. Premedication with oral pregabalin for the prevention of acute postsurgical pain in coronary artery bypass surgery. *Anesth Pain Med* 2015; **5**: e24837
121. Fabritius ML, Geisler A, Petersen PL, *et al*. Gabapentin for post-operative pain management—a systematic review

with meta-analyses and trial sequential analyses. *Acta Anaesthesiol Scand* 2016; **60**: 1188–208
122. Hoffer D, Smith SM, Parlow J, Allard R, Gilron I. Adverse event assessment and reporting in trials of newer treatments for post-operative pain. *Acta Anaesthesiol Scand* 2016; **60**: 842–51
123. Fabritius ML, Geisler A, Hansen MS, *et al*. Benefit and harm of perioperative gabapentin treatment: a systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. PROSPERO 2013. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006538 (accessed 10 March 2017)
124. Mathiesen O, Wetterslev J, Kontinen VK, *et al*. Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anaesthesiol Scand* 2014; **58**: 1182–98
125. McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health Technol Assess* 2010; **14**: 1–153
126. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database Syst Rev* 2016; **5**: CD007126
127. Dahl JB, Nielsen RV, Wetterslev J, *et al*. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anaesthesiol Scand* 2014; **58**: 1165–81
128. Zhang J, Ho K-Y, Wang Y, *et al*. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. *Br J Anaesth* 2011; **106**: 454–62

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