REVIEW ARTICLE

Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses

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Conflict of interest
All authors have completed the ICMJE disclosure form available upon request from corresponding author. VK reports personal fees from Grünenthal, Janssen-Cilag, MSD, Mundipharma, Orion, Pfizer and Steripolar outside of the submitted work. JW 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). AG, PLP, MSH, LN, KH, JBD, OM, and MLF have no conflicts of interests to declare.

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Background: Perioperative pain treatment often consist of combinations of non-opioid and opioid analgesics, 'multimodal analgesia', in which gabapentin is currently used. The aim was to document beneficial and harmful effects of perioperative gabapentin treatment.
Methods: Randomized clinical trials comparing gabapentin vs. placebo or active placebo in adult surgical patients receiving gabapentin perioperatively were included. This review was conducted using Cochrane standards, trial sequential analysis (TSA), and Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The primary outcomes were 24-h opioid consumption and incidence of serious adverse events (SAE).
Results: One hundred and thirty-two trials with 9498 patients were included. Thirteen trials with low risk of bias reported a reduction in 24-h opioid consumption of 3.1 mg [0.5, 5.6; TSA-adjusted CI: −0.2, 6.3]. In the analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen, a mean reduction in 24-h morphine consumption of 1.2 mg [−0.3, 2.6; TSA-adjusted CI: −0.4, 2.8] in trials with low risk of bias was found. Nine trials with low risk of bias reported a risk ratio of SAEs of 1.61 [0.91; 2.86; TSA-adjusted CI: 0.57, 4.57].
Conclusion: Based on GRADE assessment of the primary outcomes in trials with low risk of bias, the results are low or very low quality of evidence due to imprecision, inconsistency, and in some outcomes indirectness. Firm evidence for use of gabapentin is lacking as clinically relevant beneficial effect of gabapentin may be absent and harm is imminent, especially when added to multimodal analgesia.

Editorial Comment
In this trustworthy systematic review, use of gabapentin for post-operative pain management was scrutinized. In summary, the quality of evidence for a clinically relevant benefit of gabapentin is low, and, importantly, harm may be present.

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The World Health Organization (WHO) estimated that 321.5 million surgical procedures were needed in 2010 to meet the burden of diseases in the global population.[1] Optimal management of post-operative pain is a critical component in care of the surgical patient and is often performed by combinations of non-opioid and opioid analgesics, referred to as 'multimodal analgesia'.[2–4] At present, a diversity of combinations of analgesics is used in clinical practice.

Gabapentin was introduced as an anti-epileptic and has been recommended for treatment of chronic neuropathic pain conditions.[5] It is presumed that gabapentin exhibits its effects through α2δ-subunits of voltage-gated calcium channels causing a decrease in excitatory neurotransmitters, e.g., glutamate, substance P, and calcitonin gene-related peptide (CGRP).[6–8] The anti-hyperalgesic effect of gabapentin has been demonstrated in several experimental and clinical trials.[9–12] The potential post-operative analgesic effects have been investigated in a growing number of randomized clinical trials (RCTs). Gabapentin is becoming an established component in multimodal post-operative analgesia.[13] Therefore, an updated systematic documentation of benefit and harm of perioperative gabapentin treatment is needed. It was our hypothesis that gabapentin would reduce 24-h opioid consumption and that adverse events would not be of a severity which will prevent treatment with gabapentin.

This systematic review aim to evaluate the effects of perioperative gabapentin on post-operative opioid consumption, pain intensity, and adverse and serious adverse effects in surgical patients receiving gabapentin for post-operative pain management with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology for rating quality of evidence.[14]

Methods

This systematic review followed the methodology recommended by the Cochrane Collaboration and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15,16] The protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO) registration no. CRD42013006538.

Search strategy and selection criteria

We searched 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', 'gaba* or neurontin* or neurotonin* or horizant*', and 'pain'. Language was not a restriction. Relevant publications were also identified from reference lists of previous reviews and Google Scholar. Unpublished trials were identified through the following trial registries: 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). The electronic search was last updated 12 April 2016 (Supplemental digital content 1: search strategies).

Randomized clinical trials investigating perioperative gabapentin intervention vs. placebo or an active placebo group mimicking the sedative effect of gabapentin were considered

eligible. Prospective observational and quasi-randomized trials were included for evaluation of harm and detection of rare serious adverse events but not for benefit. The prospective observational and quasi-randomized trials are not included in any of the meta-analyses of outcomes.

The study population included surgical patients of 18 years or above who received gabapentin for post-operative pain. Trials were included regardless of dosage, administration intervals, duration of treatment, or type of surgery.

Exclusion criteria were trials of non-surgical pain conditions, experimental pain models, chronic pain conditions, or different analgesic co-interventions in compared groups.

Study selection

Two authors (MLF, AG) independently screened titles and abstracts for inclusion after removal of duplicates. MLF and one other independent author (AG, MSH, PLP, LN) assessed full texts. Non-English articles were translated to English.

Data extraction

Two authors [MLF (all trials), AG, PLP, MSH, and LN] independently extracted data and assessed bias of the included trials using a data extraction form. The extracted data included participant and trial characteristics: Year of publication, number of participants, type of surgery, follow-up period and dose regimen, consumption of opioid and non-opioid escape medication, pain intensity, any adverse effects described in the trials, including serious adverse events (SAEs) defined according to the International Conference of Harmonization – Good Clinical Practice (ICH-GCP) definitions as medical events being either life-threatening, resulting in death, disability or significant loss of function, and causing hospital admission or prolonged hospitalization.[17]

The corresponding author was contacted whenever data were insufficiently reported and contact was repeated after 14 days. In case of no response, the involved bias domains were classified as unclear.

Risk of bias assessment

The included trials were assessed for risk of bias according to the Cochrane Handbook and we decided a priori to report and conclude based on primarily results from trials classified as low risk of bias.[18,19] The following domains were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias, including funding and confirmation bias.[20] Each domain was categorized as low, unclear, or high risk of bias. If one or more domains were categorized as high risk of bias, the trial was classified as overall high risk of bias. When one or more domains were categorized as unclear, trials were added to high risk of bias trials in the meta-analyses and subgroup analyses as we aimed for estimates based on the trials with reliable low risk of bias.

Any discrepancies in study selection, data extraction, or bias assessment were resolved by OM, JBD, or JW.

Outcomes

The co-primary outcomes were 24-h post-operative opioid consumption and incidence of serious adverse events (SAE).

Secondary outcomes were pain at rest and during mobilization at 6 and 24 h after surgery, opioid-related adverse effects, and all other adverse events.

All opioids were converted to intravenous morphine based upon equivalency (Supplemental digital content 2: Opioid conversion). Various scales were used to report pain intensity in the trials. All pain intensity scales reporting pain levels between 0 and 10 were converted to the Visual Analog Scale (VAS) 0 to 100 mm.

Statistical analysis

Review Manager (RevMan) [Computer program], Version 5.1.6, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used for statistical analyses as predefined in the protocol.

In trials with more than one active treatment arm, including trials testing doses delivered pre- and immediate post-operatively, means and

standard deviations were combined for the intervention groups.[21]

Mean and standard deviations were estimated from median and range values according to the method described by Hozo et al.[22] Standard deviations were calculated by dividing the difference in interquartile ranges with 1.35.[23]

Longer ordinal scales were analyzed as continuous data. For dichotomous data, RR with a 95% confidence interval was calculated.

We examined the heterogeneity between trials using chi-squared test. The heterogeneity was measured by I^2, which quantifies inconsistencies and D^2 for information size adjustments. If the I^2 was greater than zero, the results were calculated using both a fixed effect model (FEM) and random effect model (REM) and the most conservative estimation was presented.[24,25] Whenever FEM resulted in a significant result with an estimate lower than REM, this was reported.

Predefined subgroup analyses were calculated investigating the risk of bias in low vs. unclear and high risk of bias; pain intensity at rest vs. during mobilization; pain intensity at different time points (early pain vs. late pain); add-on treatment (trials investigating gabapentin as add-on to other analgesic regimens vs. trials investigating gabapentin as single analgesic). We hypothesized that the estimates of effect would be lower in subgroups of trials with low risk of bias, late pain and pain at rest, and gabapentin as add-on treatment compared with the corresponding subgroups.

Sensitivity analyses were undertaken to explore whether choice of summary statistic and selection of the event category was critical for the conclusions of the meta-analysis.

To adjust the confidence intervals due to sparse data and repeated testing in cumulative meta-analyses, trial sequential analysis (TSA) program version 0.9 beta (www.ctu.dk/tsa) was used.[26,27] We performed the TSA analyses to preserve the risk of type-1 and two errors within 5% and 90%, respectively considering sparse data and sequential testing in a cumulative meta-analysis with repeated testing after each new trial is added.[28] We used a priori definition for opioid sparing effect of 5 mg of morphine equivalent as the minimally clinical relevant effect, the pooled standard deviation, and the diversity calculated from the actual meta-analyses, for estimating the required information size and the TSA-adjusted CI on all outcomes.

Minimal relevant difference was defined as 5 mg reduction in 24-h intravenous morphine consumption. This cut-off was used to detect even a small beneficial effect in light of previous reviews of other non-opioid analgesics demonstrating less than 10 mg reduction in 24-h opioid consumption.[3] The relative risk reduction (RRR) used for categorical outcomes in the TSA was 30% for adverse events and for SAE 50%.

Grading of recommendations assessment, development, and evaluation (GRADE)

We used GRADE to rate the quality of evidence and strength of recommendations for individual outcomes of the review, based on estimates from trials with 'low risk of bias'.[29] The recommendations are presented in a summary of findings table (SoF).

Results

The search result is summarized in the PRISMA flowchart (Fig. 1: PRISMA flowchart). One hundred and forty-seven articles were included for full-text evaluation. Forty-eight full-text articles were excluded based on the following: Not retrievable, non-surgical procedure, inadequately described analgesic regimen, patient age < 18 years, chronic pain trials, no placebo or only active comparator, review article, and double publication.

Trial characteristics

A total of 135 studies were included.[30–164] One hundred and thirty-two trials with 9498 patients were included for the evaluation of benefit and furthermore, three non-randomized studies[154–156] were included for the evaluation of harm.

Gabapentin treatment ranged from 100 to 1200 mg in trials with single-dose therapy (n = 96), and from 900 to 2400 mg/day in trials with multiple doses (n = 36). Initiation of gabapentin treatment varied from 30 min to 48 h pre-operatively.

Included trials investigated gabapentin intervention in a range of surgical procedures

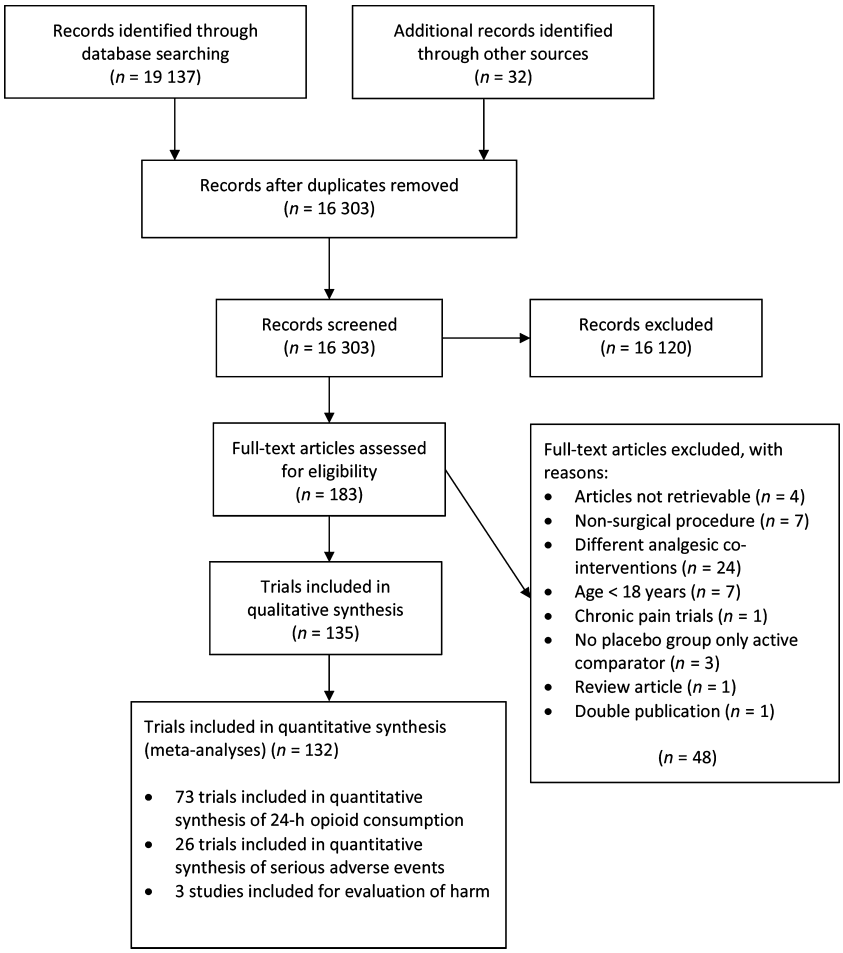

Fig. 1. PRISMA flowchart.

(Supplemental digital content 3: Characteristics of included trials). Number of included patients in the trials ranged from 20 to 306.

The follow-up period for acute pain of the trials varied from 2 h to 6 weeks, with 24 h as the most frequent assessment period (58 trials).

Bias risk assessment

Sixteen trials had overall low risk of bias.[30,45,61,65,68,82,89,98,102,103,116,117,133,136,137,151] Seventy-seven trials had high[32–34,36,39,41,43,47–49,51,53–56,59,62,63,67,69–71,73,76,78,83,84,86–88,90,93,95,96,99–101,104,106,109,112–115,118–127,129,130,135,138,139,142–149,153,157–164] and 39 trials unclear risk of bias.[31,35,37,38,40,42,44,46,50,52,57,58,60,64,66,72,74,75,77,79–81,85,92,94,97,105,107,108,110,111,128,131,134,140,141,150,152]

Reasons for unclear and high risk of bias were mainly 'selective outcome reporting' or 'other bias' (Fig. 2: Bias graph and Supplemental digital content 4: Bias assessment).

Opioid consumption

Trials with low risk of bias (for all trials reporting the outcome, please see Table 1)

Thirteen trials with low risk of bias reported on opioid consumption,[45,61,65,68,89,98,102,103,116,117,133,137,151] which indicates a reduction in 24-h post-operative morphine consumption of 3.1 mg (REM: 95% CI 0.5, 5.6; $P < 0.02$; $I^2 = 90\%$; 13 trials; 1362 patients; TSA-adjusted CI: −0.2, 6.3; Required information size: 1919 patients; Accrued percentage of required information size: 71%; FEM: Reduction 0.8 mg [−0.2, 1.4, $P = 0.01$]; GRADE = very low) (Table 1: Subgroup

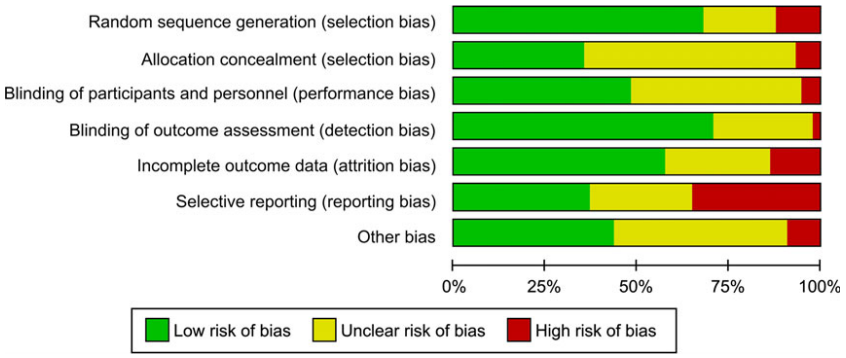

Fig. 2. Bias graph: The 'Other' bias domain consists of an evaluation of risk of financial bias and confirmatory bias.

analyses and all trial analyses, Fig. 3: Forest plot of 24-h morphine consumption, Fig. 4: Trial sequential analysis of trials with low risk of bias on 24-h opioid consumption and Supplemental digital content 5: SoF and GRADE of trials with low risk of bias, Supplemental digital content 6: Trial Sequential Analysis of all trials on 24-h morphine consumption, Supplemental digital content 7: SoF of all trials).

Add-on effect (for all trials reporting the outcome, please see Table 1)

For trials with low risk of bias, the predefined subgroup analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen indicated a mean reduction in 24-h morphine consumption of 1.2 mg (REM: 95% CI −0.3, 2.6; $P < 0.12$; $I^2 = 61\%$; 11 trials; 1194 patients, TSA-adjusted CI −0.4, 2.8; Required information size: 562 patients; Accrued percentage of required information size: 47%) (Table 1: Subgroup analyses and all trial analyses, Supplemental digital content 8: Forest plot of add-on effect).[45,61,65,68,89,98,102,103,116,117,133]

Trials with no non-opioid basic analgesic treatment did not indicate a statistically significant reduction in the 24-h morphine consumption in trials with low risk of bias [8.0 mg (REM: 95% CI −1.5, 17.4; $P = 0.10$; $I^2 = 84\%$; 2 trials; 168 patients, TSA-adjusted CI −30.5, 46.3; Required information size: 3271 patients; Accrued percentage of required information size: 5%)].[137,151] (Table 1: Subgroup analyses and all trial analyses, Supplemental digital content 9: Forest plot of no-add-on treatment).

Bias effect

For trials with low risk of bias in the domain 'other risk of bias' (confirmatory and funding bias), a mean reduction of 3.8 mg (REM: 95% CI 2.1, 5.5; $P < 0.0001$; $I^2 = 92\%$; 30 trials; 2285 patients; TSA-adjusted CI 2.1, 5.5; Required information size 1968 patients; Accrued percentage of required information size: 116%)[42,44,45,53,54,56,60,61,65,68,73,78,81,84,89,95,98,102,103,114,116–118,120,133,137,139,148,151,160] as compared to a mean reduction in trials with unclear or high risk of bias of 9.9 mg (REM: 95% CI 8.1, 11.7; $P < 0.00001$; $I^2 = 99\%$; 43 trials; 3345 patients; TSA-adjusted CI: 8.1, 11.7; Required information size: 2522 patients; Accrued percentage of required information size: 132%; FEM: Reduction 5.2 mg [5.1, 5.4]) was found on 24-h morphine consumption (Supplemental digital content 10: Forest plot of bias effect in the 'other' bias domain).[31,34,35,37,38,49,50,52,57,59,62–64,67,71,76,78,91–94,96,105–107,109–113,126–128,130,131,135,138,142,143,147,152,159,164]

Serious adverse events

Twenty-six trials reported on incidences of SAEs.[30,33,45,54,55,60,62,67,68,71,74,78,82,88,89,115,116,118,120,121,133,137,147,148,151,153] Seven trials found a total of 69 SAEs,[30,67,68,71,82,89,147] whereas 19 RCTs reported no SAEs during the trial period.[33,45,54,55,60,62,74,78,88,115,116,118,120,121,133,137,148,151,153] The reported SAEs were: death, pneumonia, readmission or prolonged admission to hospital, admission to intensive care unit, respiratory arrest, atrial fibrillation, vein thrombosis, major

Table 1 Analyses of subgroup and all trial analyses.

	Subgroup: Trials with overall Low Risk of Bias					All Trials reporting the outcome			
Outcome Subgroup analysis	Estimate MD/RR (REM) (95% CI; TSA-adjusted 95% CI)	*P*-value	I^2	N Trials/ Participants/ Required information size	*P*-value for test of interaction between trials with low vs. high or unclear risk of bias*	Estimate MD/RR (REM) (95% CI; TSA-adjusted 95% CI)	*P*-value	I^2	N Trials/ Participants/ Required information size
Subgroup analyses of beneficial outcomes									
24-h opioid consumption	3.1 mg (0.5 to 5.6; −0.2 to 6.3)	0.02	90%	13/1362/1919	0.0005	7.3 mg (5.9 to 8.8; 5.9 to 8.8)	< 0.00001	98%	73/5630/2194
24-h opioid consumption + add-on regimen	1.2 mg (−0.3 to 2.6; −0.4 to 2.8)	0.12	61%	11/1194/562	0.002	4.4 mg (2.4 to 6.5; 2.4 to 6.5)	< 0.00001	98%	36/2727/2131
24-h opioid consumption − add-on regimen	8.0 mg (−1.5 to 17.4; −30.5 to 46.3)	0.10	84%	2/168/3271	0.57	10.6 mg (8.4 to 12.8; 8.4 to 12.8)	< 0.00001	97%	37/2903/2591
24-h opioid consumption − Other bias domain	3.8 mg (2.1 to 5.5; 2.1 to 5.5)	< 0.0001	92%	30/2285/1918	< 0.00001	9.9 mg (8.1 to 11.7; 8.1 to 11.7)	< 0.00001	99%	43/3345/2522
VAS 6 h at rest	9 mm (−1 to 19; −13 to 30)	0.07	87%	9/745/4114	0.47	12 mm (9 to 13; 9 to 13)	< 0.00001	96%	71/4556/1907
VAS 6 h at mobilization	9 mm (4 to 13; 4 to 18)	< 0.0002	82%	7/572/636	0.63	8 mm (5 to 11; 5 to 11)	< 0.0001	59%	25/1552/599
VAS 24 h at rest	3 mm (−0 to 6; −1 to 6)	0.07	87%	11/1027/554	0.006	8 mm (5 to 10; 5 to 10)	< 0.0001	93%	68/4319/922
VAS 24 h at mobilization	5 mm (−2 to 11; −5 to 14)	0.15	94%	8/795/1629	0.71	5 mm (−0 to 11; −0 to 11)	0.05	97%	25/1760/582
Subgroup analyses of harmful outcomes									
Serious adverse events	RR 1.61 (0.9 to 2.9; 0.6 to 4.6)	0.10	0%	9/1014/3139	0.05	RR 1.14 (0.71 to 1.81; 0.6 to 2.1)	0.59	7%	26/2051/3973
Nausea	RR 0.83 (0.6 to 1.1; 0.6 to 1.1)	0.21	53%	6/524/3075	0.93	RR 0.82 (0.7 to 0.9; 0.7 to 0.9)	0.0003	9%	56/3756/1004
Vomiting	RR 1.04 (0.7 to 1.5; 0.5 to 2.2)	0.85	0%	4/352/1299	0.11	RR 0.80 (0.7 to 0.9; 0.7 to 0.9)	0.002	0%	51/3446/1648
Sedation	RR 1.08 (0.9 to 1.2; 0.9 to 1.2)	0.29	0%	10/858/1931	0.03	RR 1.33 (1.0 to 1.3; 1.0 to 1.3)	0.005	60%	51/4003/3751
Dizziness	RR 1.04 (0.8 to 1.2; 0.8 to 1.3)	0.64	0%	9/747/2422	0.71	RR 1.02 (0.9 to 1.1; 0.9 to 1.1)	0.77	0%	58/4510/2401

MD: mean difference; RR: relative risk; REM: random effects model; TSA: trial sequential analysis; RIS; required information size; *Test for subgroup differences.

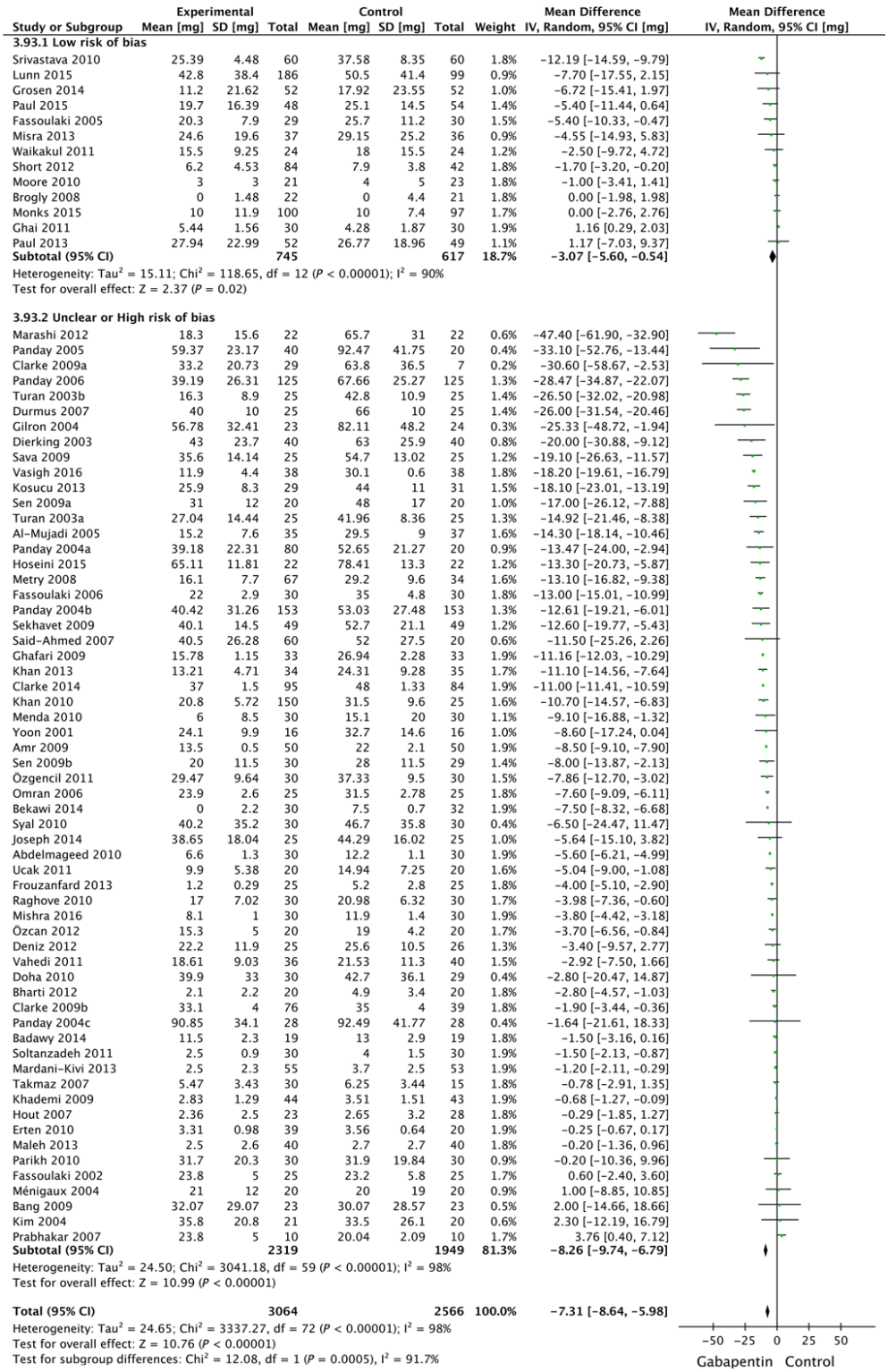

Fig. 3. Forest plot of mean difference in 24-h morphine consumption.

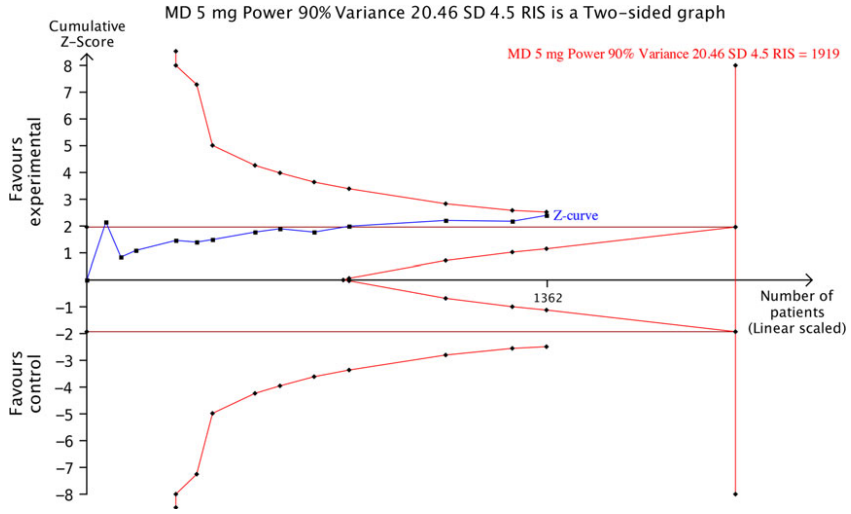

Fig. 4. Trial sequential analysis of trials with low risk of bias on 24-h morphine consumption: TSA of the effect of gabapentin on morphine consumption using the pooled SD of 4.5 mg. An estimated required information size (RIS) of 1919 patients to detect or discard a sparing effect of 5 mg morphine was calculated using the actual diversity between trials of 90%, a random-effects meta-analysis, an α of 0.05, and a β of 0.10. After 13 trials, the cumulative *z*-curve does cross the traditional boundary for benefit ($z = 1.96$ or $P = 0.05$) 95% CI 0.5 to 5.6), but not the trial sequential boundary for benefit (TSA-adjusted CI −0.2 to 6.3). In conclusion, the *z*-curve does not surpass the boundary for benefit and a firm conclusion cannot be made, however an effect beyond 6.3 mg is unlikely.

bleeding, urticarial rash, pleura effusion, and atelectasis.

Trials with low risk of bias reporting SAE (for all trials reporting the outcome, please see Table 1)
The RR of SAE of patients treated with gabapentin vs. placebo was 1.61 (REM: 95% CI 0.91, 2.86; $P < 0.10$; $I^2 = 0\%$; nine trials, 1014 patients; TSA-adjusted CI 0.57, 4.57; Required information size: 2408 patients; Accrued percentage of required information size: 42%; GRADE = low)[30,45,68,82,89,116,133,137,151] (Table 1: Subgroup analyses and all trial analyses, Fig. 5: Forest plot of serious adverse events, Fig. 6: Trial Sequential Analysis of trials with low risk of bias on serious adverse events, Supplemental digital content 11: Trial sequential analysis of all trials reporting serious adverse events).

Pain

Trials with low risk of bias (for all trials reporting the outcome, please see Table 1)
At 6-h post-operatively, pain at rest was not significantly reduced,[30,45,61,68,82,103,133,137,151] whereas pain during mobilization was reduced.[30,45,61,68,103,133,137]

At 24-h post-operatively, neither pain at rest[45,61,68,82,102,103,117,133,136,137,151] nor pain during mobilization were significantly reduced (Table 1: Subgroup analyses and all trial analyses and Supplemental digital content 12–15: Forest plot of pain intensity 6 and 24 h at rest and mobilization).[45,61,68,102,103,117,133,137]

Adverse effects

Trials with low risk of bias (for all trials reporting the outcome, please see Table 1)
Risk of nausea, vomiting, sedation, and risk of dizziness were not significantly different between groups (Table 1: Subgroup analyses and all trial analyses and Supplemental digital content 16–19: Forest plot adverse events: nausea, vomiting, sedation, and dizziness).

Other studies
Three non-randomized clinical studies[154–156] were included for the evaluation of harm and reported one patient with delirium and three with urinary retention in the control groups. In the gabapentin groups, the following adverse effects were reported: One patient with numbness of fingers, tongue, and mouth, three

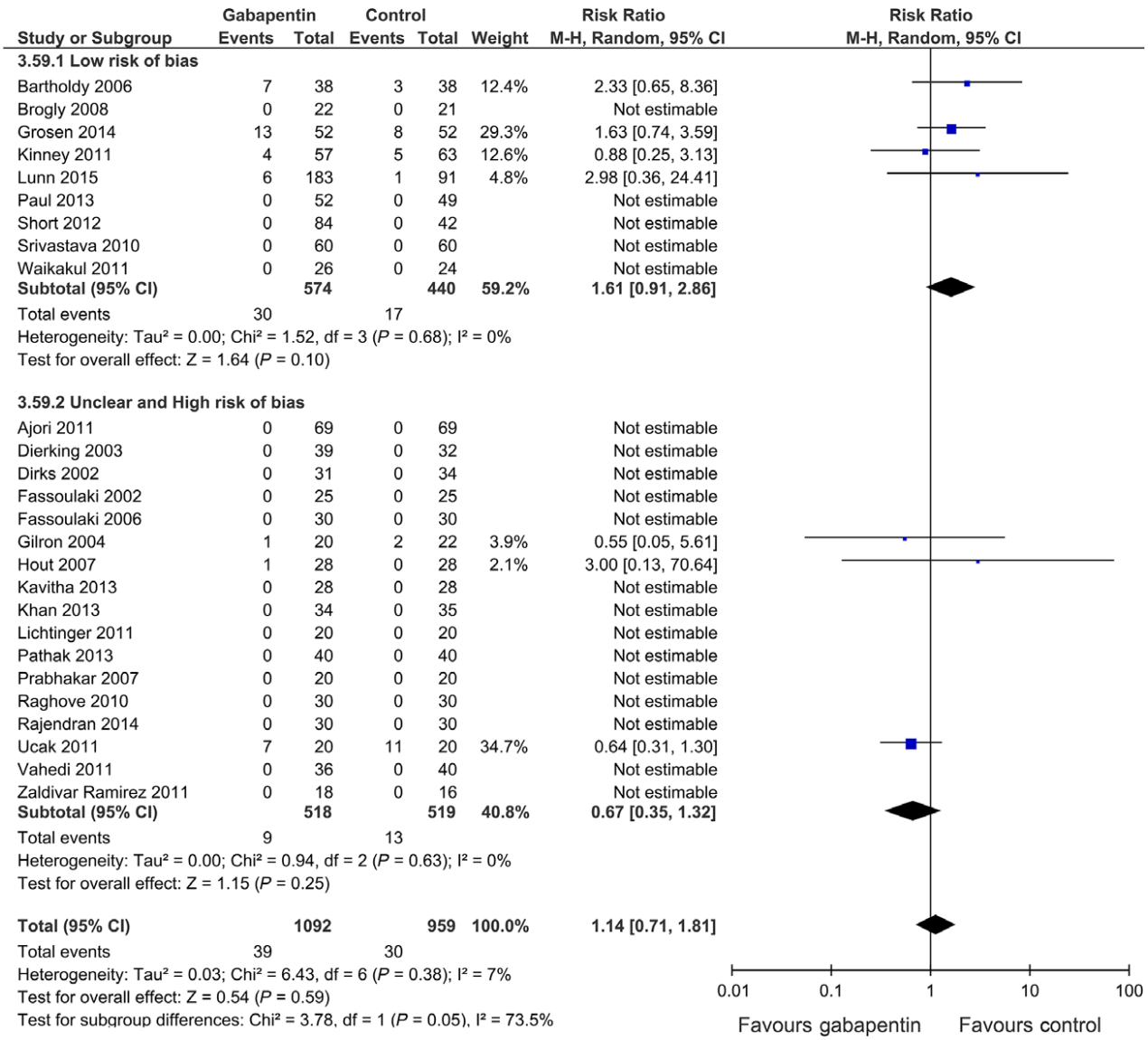

Fig. 5. Forest plot of serious adverse events.

patients with urinary retention, and one patient feeling jittery.

The small trial size effect on primary outcomes

One hundred and nineteen trials had less than 50 patients in each group and were defined as small trials.[30–32,34–47,49,50,52–67,70–81,83–88,90–92,94–101,103–109,111,112,114–120,122–136,138,139,141–153,158–163]

Thirteen trials had more than 50 patients included in each group.[33,48,51,68,82,89,93,102,110,113,137,140,157] Only four trials included more than 200 patients in their trial.[89,110,113,140]

In a post hoc sensitivity analysis, the effect of small trial size on 24-h morphine consumption showed a reduction of 1.1 mg (REM: −0.5, 2.6; $P = 0.18$; $I^2 = 62\%$; 9 trials; 656 patients) in trials with low risk of bias (Supplemental digital content 20: post hoc analysis of small trial size effect on 24-h morphine consumption in trials with low risk of bias).[45,61,65,98,103,116,117,133,151]

In trials with low risk of bias, the post hoc sensitivity analysis of small size trial effect on SAE demonstrated a risk ratio of 2.33 (REM:

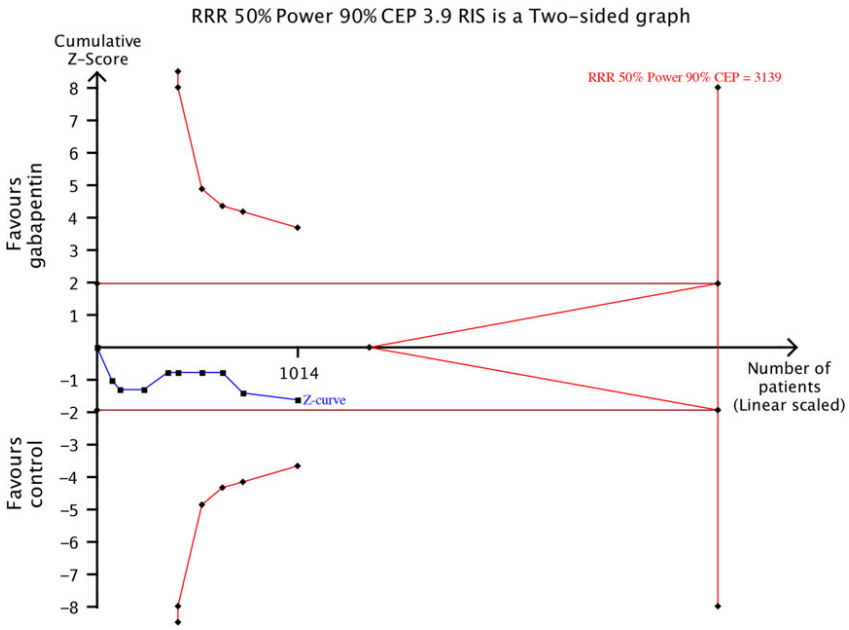

Fig. 6. Trial sequential analysis of trials with low risk of bias on serious adverse events: Trial sequential analysis (TSA) of gabapentin vs. controls in nine trials with low risk of bias reporting serious adverse events, including zero-events trials with a required information size (RIS) of 3139 patients to detect or discard a RRR of 50% and a diversity of 0%. $\alpha = 0.05$ and $\beta = 0.10$ (power 0.90). The number of accrued patients is 1014 and the TSA-adjusted confidence interval for the RR of patients with one or more SAE is 1.61 [0.57 to 4.57]. In conclusion, the *z*-curve does not cross the boundary for harm or reach futility area and a firm conclusion cannot be made.

0.65, 8.36; $P = 0.19$; 5 trials; 396 patients) (Supplemental digital content 21: post hoc analysis of small size trial effect on SAE in trials with low risk of bias).[30,45,116,133,151]

Numbers needed to treat and no more than mild pain

Data from all trials on numbers needed to treat and no more than mild pain calculations were extracted post hoc. None of the included randomized controlled trials planned to analyze or reported number needed to treat. Only one trial reported data on no more than mild pain defined as NRS ≤ 3.[101]

Discussion

Based on trials with overall low risk of bias, the benefits of perioperative gabapentin seems almost absent. The TSA of opioid requirements demonstrate that the accrued information size is only about two-thirds of that required for firm evidence, and the trial sequential boundary for benefit is not crossed. The GRADE-rated quality of evidence is low. Serious adverse events are poorly reported, and the incidence may increase with use of gabapentin.

Strength and limitations of the study

Our systematic review has several strengths. It was based on a PROSPERO pre-study registered protocol and is compliant with the Cochrane methodology and reported according to PRISMA. We applied a comprehensive literature search with no language restrictions, independent screening of all titles, and data extraction and bias assessment by two authors. The risk of random errors was evaluated using TSA on all outcomes. Bias evaluation assessed risk of systematic error, and conclusions were presented using GRADE to document the liability of our findings.

The limitations of our review mirror the limitations of the included trials. The vast majority of trials were classified as unclear or high risk of bias, and trial size was small leading to high risk of imprecision. A minority of the included trials reported on SAE, thus limiting reliable conclusions. Heterogeneity of reporting was present. Trials were included regardless of dose or

duration, type of surgery, and type of additional analgesics. Furthermore, different opioid analgesics were converted to their morphine-equivalent dose, which may have introduced heterogeneity and imprecision of the results.

The different pain intensity scores were all converted to VAS range of 0 to 100 mm, implying some imprecision of the outcomes. However, the sensitivity analyses did not indicate differences between trials where pain scores were converted to VAS, and trials where VAS was reported.

The limitations in choosing 24-h opioid consumption as an outcome are the use of mean, standard deviation, or standard error, despite the non-Gaussian distribution and the use of parametric statistics.[165] The outcome is classified as indirect according to GRADE recommendations and the results on 24-h opioid consumption have been downgraded accordingly.

Strength and weakness in relation to other reviews

A number of systematic reviews with meta-analyses on gabapentin for post-operative pain treatment have previously been published.[166–170] Most reported a more favorable outcome for gabapentin treatment, including reduced opioid consumption, pain levels, and opioid-related adverse effects, than the present review. Doleman et al. found in a recently published review, an opioid-reducing effect of gabapentin similar to the all trials estimate from the present review, but the authors did not focus on best evidence defined as trials with low risk of bias and did not address harmful effects of gabapentin.[171] The authors hypothesized that their results may be due to a small trial size effect. Post hoc analyses on the small trial size effect in meta-analysis of trials included in the present review could not confirm this hypothesis. We did, however, find a bias effect in 24-h opioid consumption, which is greatest in the 'other' bias domain. This indicates that conclusions based on all trials, including trials with unclear or high risk of bias, may lead to an overestimation of benefits and underestimation of adverse effects from intervention with gabapentin perhaps due to outcome reporting bias and other bias, e.g. financial or confirmatory bias[21]. The present review uses a systematic review methodology including GRADE-rated recommendations based on high-quality trials.

Impact of the study

The bias effect on the primary outcome of 24-h morphine consumption was explored on each of the seven bias domains and in the funnel plot. Analyses of trials with low risk of bias demonstrate a clear bias impact on this outcome primarily based on risk of 'other bias', as this bias domain showed a relatively large difference in morphine consumption between the trials with 'low risk of bias 'and the trials with 'unclear or high' risk of bias. The 'other' bias domain includes confirmatory bias and funding bias, and especially lack of information regarding funding is an issue in a large number of the included trials. This bias effect was not demonstrated for any other domains.

TSA on trials with low risk of bias demonstrated that neither boundaries for benefit or futility were crossed for detecting a predefined clinically relevant reduction of morphine consumption of 5 mg. The TSA of 24-h morphine consumption for all trials, including trials with high and unclear risk of bias, showed a statistically significant reduction, which may be a result of bias. Consequently, there is not enough information in the trials with low risk of bias to establish firm evidence for either the presence or absence of a clinically relevant morphine sparing effect with gabapentin.

The morphine sparing effect of combining gabapentin with other analgesics appears even less. It is close to absent in the trials with low risk of bias with less effect than 5 mg and a TSA-adjusted CI (−0.4 to 2.8 mg), which is hardly clinically relevant.

Trials with low risk of bias found a reduction in pain intensity at mobilization 6-h post-operatively. Gabapentin reduced pain levels both 6 and 24 h after surgery in all trials.

Trials with low risk of bias indicated excess of SAEs in the gabapentin group and report twice as many SAEs compared to trials with unclear and high risk of bias. The pooled analysis of all trials reporting SAEs was inconclusive. However, the analysis was influenced by trials of poor quality with high risk of systematic error. TSA widened the confidence intervals of

the conventional meta-analysis and the cumulated *z*-curve reached the futility area. The follow-up period in the majority of trials was short, typically 24 h, which may increase the risk of underestimating incidences of SAEs. The included non-randomized studies did not report previously undescribed SAEs.

The adverse effects nausea and vomiting were not reduced with gabapentin in trials with low risk of bias, but reduced in all trials. Risk of sedation and dizziness were not increased in the trials with low risk of bias. In all trials, the risk of sedation was increased in the gabapentin group. However, reporting of adverse events in the trials with high or unclear risk of bias was only one half of that reported in trials with low risk of bias, and a high percentage of the trials achieved a high risk of 'reporting bias' because of incomplete reporting of the adverse effects although intentionally declared in their method section. Furthermore, most trials only reported on adverse effects for a short period post-operatively, which may be insufficient for a full evaluation. The inconsequent and diverse reporting of adverse events complicates a reliable evaluation.

Conclusion

GRADE assessment of the primary outcome from trials with low risk of bias show that the evidence for perioperative gabapentin treatment is of low or very low quality due to imprecision and inconsistency and for some outcomes indirectness. The SAEs were poorly reported limiting our ability to conclude. The reduction in 24-h morphine consumption is apparently less than the predefined minimal clinical effect of 5 mg, and as add-on therapy, the beneficial effect seems non-existent. Firm evidence for the use of gabapentin in post-operative pain management is lacking. Thus, clinically relevant beneficial effect of gabapentin seems absent and harm is pending. Future trialists must ensure that their trials can be classified as low risk of bias, have sufficient power to detect relevant beneficial effects, and explore the risks of harmful effects.

Systematic review registration

PROSPERO registration number: CRD420 13006538.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1. Supplemental Digital Content 1–21.