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REVIEW

Dose-related beneficial and harmful effects of gabapentin in postoperative pain management post hoc analyses from a systematic review with meta-analyses and trial sequential analyses

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Background: During the last 15 years, gabapentin has become an established component of postoperative pain treatment. Gabapentin has been employed in a wide range of doses, but little is known about the optimal dose, providing the best balance between benefit and harm. This systematic review with meta-analyses aimed to explore the beneficial and harmful effects of various doses of gabapentin administered to surgical patients.

Materials and methods: Data in this paper were derived from an original review, and the subgroup analyses were predefined in an International Prospective Register of Systematic Reviews published protocol: PROSPERO (ID: CRD42013006538). The methods followed Cochrane guidelines. The Cochrane Library's CENTRAL, PubMed, EMBASE, Science Citation Index Expanded, Google Scholar, and FDA database were searched for relevant trials. Randomized clinical trials comparing gabapentin versus placebo were included. Four different dose intervals were investigated: 0-350, 351-700, 701-1050, and >1050 mg. Primary co-outcomes were 24-hour morphine consumption and serious adverse events (SAEs), with emphasis put on trials with low risk of bias.

Results: One hundred and twenty-two randomized clinical trials, with 8466 patients, were included. Sixteen were overall low risk of bias. No consistent increase in morphine-sparing effect was observed with increasing doses of gabapentin from the trials with low risk of bias. Analyzing all trials, the smallest and the highest dose subgroups demonstrated numerically the most prominent reduction in morphine consumption. Twenty-seven trials reported 72 SAEs, of which 83% were reported in the >1050 mg subgroup. No systematic increase in SAEs was observed with increasing doses of gabapentin.

Conclusion: Data were sparse, and the small number of trials with low risk of bias is a major limitation for firm conclusions. Taking these limitations into account, we were not able to demonstrate a clear relationship between the dosage of gabapentin and opioid-sparing or harmful effects. These subgroup analyses are exploratory and hypothesis-generating for future trialists. Keywords: gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, analgesic, postoperative pain management, dose effect

Introduction

During the last 15 years, gabapentin has become an established component of postoperative analgesia. Gabapentin has been employed in a wide range of doses, but little is known about the optimal dose, providing the best balance between benefit and harm in postoperative pain treatment.

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The number of published, dose-finding gabapentin trials in postoperative pain treatment is limited,^{1–11} and the results are inconsistent. It is well established, however, that oral gabapentin is absorbed in part by diffusion and in part by a carrier-mediated saturable transport mechanism system.¹³ Thus, the bioavailability of oral gabapentin is not linear, but inversely dependent on the dose,¹⁴ ranging from ~60% for a 300 mg dose to ~30% with doses of 1600 mg.^{14–16}

Consequently, the optimal dosing of gabapentin, providing the best balance between benefit and harm, may not be obvious. In this post hoc subgroup analysis, we aimed to explore the relative effects of different doses of gabapentin on 24-hour morphine consumption, pain intensity, risk of serious adverse events (SAEs), and other adverse events.

We hypothesized that increasing doses of gabapentin would lead to increased reduction in 24-hour morphine consumption and/or pain intensity, decreased adverse effects, and probably also increased risk of SAEs and other drug-specific adverse events. We realized, however, that the possible increase in beneficial and harmful effects with increasing doses of gabapentin would probably not be linear due to the nonlinear bioavailability of oral gabapentin.

Materials and methods

This review includes exploratory post hoc analyses from an original systematic review, employing the Cochrane Collaboration methodology. The protocol of the original PRISMA-compliant review is published in the International Prospective Register of Systematic Reviews website (www.crd.york.ac.uk/PROSPERO) with the registration no. CRD42013006538.¹⁷

Literature search

Our comprehensive search strategy was planned by a trial search coordinator and reported in the published systematic review¹⁸ and <u>Supplementary material</u> S1: search strategies.

The Cochrane Library's CENTRAL, PubMed, EMBASE, Science Citation Index Expanded, Google Scholar, and FDA database, and reference lists of trials were searched for relevant trials. Unpublished trials were searched in relevant databases.

Randomized clinical trials comparing gabapentin versus placebo, irrespective of publication type, status, publication year, and language, were included. All non-English articles were translated to English. We updated the search strategy on April 12, 2016.

Data

MLF and one of the independent authors (AG, MSH, PLP, LN) screened the titles and abstracts, evaluated the risk of bias, and extracted data. Extracted data included article publication year, number of participants, surgical procedure, follow-up period and gabapentin dose administered, consumption of morphine (intravenous morphine based on equivalency, <u>Supplementary material</u> S2) and other nonopioid analgesics, pain intensity, and any adverse effects reported, including SAEs.

Pain intensity was reported in different scales in the original trials. All pain intensity scales using intensity scores between 0 and 10 were converted to the visual analog scale (VAS) 0–100 mm.

If data were incomplete or bias assessment was unclear, the corresponding author was contacted. This contact was repeated after 2 weeks in case of no response to initial contact. If the corresponding author did not reply, the involved bias domains were classified as unclear.

Assessment of risk of bias

The risk of bias assessment adhered to the Cochrane Handbook methodology.²⁰ All the included trials were assessed as low, unclear, or high risk of bias using the six bias domains described in the handbook. The "other" bias domain consisted of financial and confirmatory bias evaluations.²¹ Any difference in evaluations between authors on any part of the data extraction and evaluations process was solved by OM, JBD, or JW.

It was protocolled that the review and conclusions would primarily be based on trials with low risk of bias.

Small trial size

This post hoc analysis assessed the number of patients included in each original trial as defined in the original systematic review.¹⁸ Trials with less than 50 participants were defined as small trials, trials with more than 50 participants in each group formed the second group, and the trials with more than 200 participants made up the final group.

Analyses

The dose treatments of gabapentin were divided into four groups: 0–350, 351–700, 701–1050, and more than 1050 mg. The defined groups represent the four most commonly used dose treatments in gabapentin research, which are 300, 600, 900, and 1200 mg.

All doses are considered as 24-hour treatments, regardless of single or multiple administrations, pre- or postoperative treatments, or the duration of the treatment. If an original trial investigated more than one dose, the control group receiving placebo was divided into the corresponding number of intervention groups. The trials in which the divided control groups included less than 20 participants were excluded. The individual dose-finding trials were counted as one trial in all summary statistics. Whenever the trials were included in cumulative analyses, the trials were viewed as separate trials.

Outcomes

Twenty-four-hour morphine consumption represented the beneficial primary outcome, and SAEs represented the harmful primary outcome. SAEs were classified according to the International Conference of Harmonization – Good Clinical Practice definitions: medical events being either life-threatening, resulting in death, disability, or significant loss of function, or causing hospital admission or prolonged hospitalization.¹⁸

The secondary outcomes were divided into beneficial outcomes: reduction in early (6-hour) and late (24-hour) pain postoperatively, both at rest and during mobilization, and harmful outcomes: all other adverse events.

Statistical analysis

Review Manager (RevMan; computer program), Version 5.1.6 was used in the cumulated analyses and subgroup analyses.

The handling of median and range (or interquartile range), longer ordinal scales, and dichotomous data, examination of heterogeneity, employment of fixed- or random-effect models, Peto's odds ratio (OR), and handling of few and rare events were done according to the International Prospective Register of Systematic Reviews published protocol and is described in the published PRISMA-compliant systematic review.^{17,18}

If more than one trial was included in the outcome, the estimates were pooled in meta-analyses and test for subgroup analyses was performed using RevMan in which the method to test for subgroup differences was implemented.

All trials with one intervention group and one control group were included. Handling of trials investigating more than one dose is described above. The mean and standard deviations were divided according to the methodology described in the Cochrane Handbook.^{20,22}

Trial sequential analysis (TSA) was used to adjust for sparse data and repetitive testing in the cumulative analyses.^{23,24} Minimal relevant clinical differences were defined as in the published systematic review.¹⁸ TSA is only reported if the accrued information size was 5% or more of the required information size (RIS), since the TSA program is only able to report trial sequential monitoring boundaries if this is the case.

Results

In the original published systematic review, 19,137 titles were located, and after removal of duplicates, 16,303 titles were screened for inclusion and exclusion criteria. The original systematic review included 135 randomized clinical trials, including 3 observational studies.¹⁸

For the purpose of this review, the 3 observational studies, and 10 dose-finding trials with less than 20 patients in the split control groups, were excluded,^{1-4,6,7,8,10,11,25} leaving 122 trials with 8466 participants for analyses (Supplementary material S3: trial characteristics).^{5,9,19,25-143}

Trial characteristics

In these analyses, 16 trials demonstrated overall low risk of bias, ^{5,9,35,41,55,58,62,76,91,95,107,108,127,128,140} 36 trials showed unclear risk of bias, ^{25,26,30,32,34,36,38,40,42,45,51,52,54,57,59,67,69,70, 73–75,79,84,86,88,99,100,101,103,119,122,124,125,130,139,141,143}, and 70 showed high risk of bias (Figure 1; <u>Supplementary material</u> S4: risk of bias graph). ^{6,8,12,19,27–29,31,33,37,39,43,44,46–50,53,56,60,61,63–66,71,72,77,78, 80–83,85,87,88,90,92–94,97,99,102,105,106,109–118,120,121,123,124,126,129,131,132,134–138,142}

We found that 105 trials were "small trials",^{12,25–27,} ^{29–43,45,47–61,63,65–75,77–84,86–94,96–101,104–106,109–127,131–142} 14 trials included more than 50 participants in each group,^{9,19,28,44,46,62}, ^{76,85,95,107,108,128,130,143} and only 2 trials included more than 200 participants.^{5,102}

 $\label{eq:started} \begin{array}{l} \mbox{Treatment with gabapentin included both single-dose} \\ (84 \ trials)^{9,12,25-29,31-36,40-45,47,49-52,56,58,59,61,63,65-67,69-73,75-78,82-86,} \\ 88,90-94,96,97,99,102-106,109,111-118,120-122,124,125,128-131,133,136,138,139,143 \\ \mbox{and multiple-dose administration (38 \ trials).}^{5,30,37-39,46,48,} \\ 53-55,57,60,62,68,74,79-81,89,95,98,100,101,107,108,110,119,123,126,127,132,134,135,137,140-142 \\ \end{array}$

For further information about the individual trials, see <u>Supplementary material</u> S3: trial characteristics.

Primary outcomes

Total 24-hour morphine consumption

Sixty-five trials with 4851 patients reported 24-hour opioid consumption, and 15 trials (1318 participants) were classified as overall low risk of bias.

Trials with low risk of bias

In the 0–350 mg subgroup, a reduction in 24-hour morphine consumption of 2.2 mg (0.1, 4.4; p=0.04)^{9,140} was reported with gabapentin versus control. The 351–700 mg



Figure I Bias evaluation of the six bias domains.

Note: The "other" bias domain consists of an evaluation of financial and confirmatory bias.

subgroup demonstrated a reduction of 3.4 mg (0.9, 8.5; p=0.12),^{9,91,95,96,107,108,128} the 701–1050 mg subgroup an increase in consumption of 24-hour morphine consumption of 1.1 mg (0.3, 2.0; p=0.01),^{5,41,55,58,62} and the subgroup >1050 mg reported a reduction of 2.9 mg (-1.1, 6.9; p=0.2), as shown in Table 1 and Figure 2.^{5,41,55,62}

The test for subgroup differences was significant for the 701–1050 mg subgroup compared with the other subgroups (p=0.002), but no systematic increase in morphine-sparing effect was observed with increasing doses of gabapentin. With TSA, half the subgroup meta-analyses reached the futility area with the predefined minimal clinical difference and alpha and beta, while the other half did not report firm results (Table 1).

All trials

All subgroups demonstrated a reduction in 24-hour morphine consumption (Table 2 and Figure 3). Differences between the different dose intervals were statistically significant in test for subgroup differences between the 350–700, 701–1050 mg, and >1050 mg subgroups. The 0–350 mg subgroup and the >1050 mg subgroup demonstrated numerically most pronounced reduction in morphine consumption, but no systematic increase in morphine-sparing effect was observed with increasing doses of gabapentin. Only the meta-analysis for the subgroup 701–1050 did not report firm evidence according to TSA (Table 1).

SAE

Twenty-seven trials with 1958 participants reported 72 SAEs, of which 83% were reported in the >1050 mg subgroup. Of the 27 trials, 8 were classified as overall low risk of bias, 59,41,62,76,107,128,140 and these 8 trials reported more than half

the SAEs. The trials with overall low risk of bias reported the following SAEs: death, vein thrombosis, pneumonia, wound infection, admission to intensive care unit, and prolonged hospital stay.

Trials with low risk of bias

In the 0–350 mg subgroup, 9,140 Peto's OR and TSA were not estimable. In the remaining subgroups, the risk of SAEs was: 351–700 mg subgroup: OR 0.9 (0.2, 3.4; p=0.85) 9,76,107,128 ; 700–1050 mg subgroup: OR 0.6 (0.04, 8.6; p=0.70)⁵; and >1050 mg subgroup: OR 2.0 (0.9, 4.5; p=0.1).^{5,41,62} No subgroup differences were demonstrated for this outcome, and no systematic increase in SAEs was observed with increasing doses of gabapentin (Figure 4). It was only possible to conduct TSA on two subgroups (351–700 and >1050 mg), and both subgroups had less than 20% of RIS and none reported firm evidence (Table 1).

All trials

None of the gabapentin subgroups demonstrated statistically significant increases in SAEs compared with controls (Figure 5). No significant differences between the different dose intervals were demonstrated, and no systematic increase in SAEs was observed with increasing doses of gabapentin (Table 2). TSA showed that none of the three subgroups, 351–700, 701–1050, and >1050 mg, reached firm evidence, nor did they reach more than 5% of RIS.

Secondary outcomes Pain intensity

Little data have been reported from trials with low risk of bias, limiting the reliability of the test for subgroup differences. No consistent dose-related trends or subgroup

Surgical procedure	Dose (mg)							
	0–350		351-700		701-1050		>1050	
Outcomes	Reduction (mg) MD or Peto's OR estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mg) MD or Peto's OR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mg) MD or Peto's OR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mg) MD or Peto's OR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference p-value
Beneficial outcomes 24-hour morphine consumption Trials with low risk of bias	2.2 mg (0.1, 4.4; p=0.04; 2 trials; 111 participants; TSA adj. Cl: 0.1, 4.6; 191%)	p=0.69	3.4 mg (0.9, 7.7; p=0.12; 7 trials; 700 participants; TSA adj. CI: −3.3, 11.6; 44%)	p=0.33	-1.1 mg (-0.3, -2.0; p=0.01; 2 trials; 181 participants; TSA adj. C1: 0.3, 2.0; 339%)	p=0.002	2.9 mg (1.1, 6.9; p=0.2; 4 trials; 326 participants; TSA adj. C1: –1.4, 5.6; 89.6%)	p=0.9
24-hour morphine consumption All trials	8.0 mg (6.2, 9.8; <i>p</i> <0.00001; 11 trials; 1070 participants; TSA adj. Cl: 6.2, 9.8; 263.5%)	p=0.25	4.6 mg (3.1 6.1; p<0.0001; 20 trials; 1811 participants; TSA adj. Cl: 3.1, 6.1; 389%)	p=0.004	2.6 mg (-1.4, 6.6; p=0.2; 7 trials; 375 participants; TSA adj. Cl: -2.9, 8.2; 57.5%)	p=0.03	9.0 mg (7.1, 10.9; p⊲0.00001; 27 trials, 1595 participants; TSA adj. Cl: 7.2, 11; 245.6%)	p=0.02
Harmful outcomes Serious adverse events Trials with low risk of bias	, Not estimable (2 trials, 113 participants)		0.9 (0.2, 3.4; p=0.85; 4 trials; 404 participants; TSA adj.	p=0.44	0.6 (0.04, 8.6; <i>p</i> =0.70; 1 trial: 121 patients; TSA	p=0.52	2.0 (0.9, 4.5; p=0.1; 3 trials; 287 participants; TSA adj.	p=0.29
Serious adverse events All trials	Not estimable (3 trials, I 79 participants)		CI: 0.0, ∠20.6; 18.1%) 0.9 (0.2, 3.4; p=0.85; 8 trials; 682 participants; TSA adj. CI: 0.1, 11.7; 22.9%)	p=0.44	acı) 0.6 (0.04, 8.6; <i>p</i> =0.70; 3 trials; 221 participants; TSA adj. CI: <5%)	p=0.52	CI: 0.1, 40.0; 17.6%) 1.3 (0.8, 2.4; p=0.33; 13 trials; 876 participants; TSA adj. CI: 0.6, 3.6; 44.4%)	p=0.29
Abbreviations: MD, mean diff.	erence; OR, odds ratio; TSA, trial	sequential analysis.						

Table I The estimates on primary outcomes from trials with low risk of bias and from all trials despite risk of bias

Beneficial	0–350 mg		351–700 mg		701-1050 mg		>1050 mg	
outcomes	Reduction (mm) MD Estimate (95%	Test for subgroup	Reduction (mm) MD Estimate (95% Cl; p-value;	Test for subgroup	Reduction (mm) MD Estimate (95%	Test for subgroup	Reduction (mm) MD Estimate (95%	Test for subgroup
	Cl; p-value; trials;	difference	trials; participants; TSA	difference	Cl; p-value; trials;	difference	CI; p-value; trials;	difference
	participants; TSA adj.	p-value	adj. CI; accrued percentage	p-value	participants; TSA adj.	p-value	participants; TSA adj.	p-value
	 usi accrued percentage of required information 		or required intormation size)		LI; accrued percentage of required information		 use of the second se second second se	
	size)				size)		size)	
6-hour VAS	6.4 mm	p=0.98	13.2 mm	p=0.23			5.6 mm	p=0.20
at rest	(-1.9, 11.0; <i>p</i> =0.006; 2 trials;		(−1.1, 27.6; <i>p</i> =0.07; 3 trials;				(0.5, 10.7; <i>μ</i> =0.03; 3 trials;	
Low risk of bias	III participants; TSA adj. CI:		289 participants; TSA adj. CI:				206 participants; TSA adj. CI:	
	-5.8, 11.4; 73%)		-28.5, 55.0; 17.8%)				-0.8, 11.9; 141%)	
6-hour VAS	13.7 mm	p=0.53	l5.3 mm	p=0.05	6.0 mm	p=0.006	9.4 mm	p=0.19
at rest	(7.1, 20.0; p<0.0001; 10		(10.7, 20.0; <i>p</i> <0.00001; 18		(2.7, 9.3; p=0.0003; 7 trials;		(5.6, 13.3; <i>p</i> <0.00001; 27	
All trials	trials; 740 participants; TSA		trials; 1275 participants; TSA		294 participants; TSA adj.		trials; 1519 participants; TSA	
	adj. Cl: 7.1, 20.0; 83.7%)		adj. Cl: 10.7, 20.0; 175%)		Cl: 0.9, 11.1; 330%)		adj. Cl: 5.6, 13.3; 241.1%)	
6-hour VAS	ll mm		I2.4 mm	p=0.16			3.8 mm	p=0.19
at mobilization	(5.7, 16.3; p<0.00001; 1 trial;		(8.0, 16.8; p<0.0001; 3 trials;				(-7.9, 15.4; p=0.53; 3 trials;	
Low risk of bias	63 participants; TSA adj.		227 participants; TSA adj. CI:				206 participants; TSA adj. Cl:	
	CI: -)		8.0, 16.1; 258%)				-21.1, 28.6; 26.8%)	
6-hour VAS	II.I mm	<i>þ</i> =0.30	10.2 mm	p=0.24	6.1 mm	p=0.67	6.3 mm	p=0.16
at mobilization	(5.8, 16.4; p<0.0001; 2 trials;		(5.7, 14.7; p<0.0001; 6 trials;		(–3.9, 16.2; <i>p</i> =0.23; 3 trials;		(3.1, 9.6; p=0.0001; 15 trials;	
All trials	95 participants; TSA adj. CI:		438 participants; TSA adj. CI:		121 participants; TSA adj.		898 participants; TSA adj. Cl:	
	-13.1, 19.7; 130.1%)		5.1, 15.3; 176.6%)		Cl: –2.2; 24.4; 36.1%)		3.1, 9.6; 342.7%)	
24-hour VAS	0.6 mm	p=0.02	3.9 mm	p=0.005	1		I.8 mm	p=0.21
at rest	(–3.0, 4.2; <i>p</i> =0.75; 2 trials;		(−0.1, 7.9; p=0.05; 5 trials; 526				(-3.4, 7.0; p=0.51; 4 trials;	
Low risk of bias	107 participants; TSA adj.		participants; TSA adj. Cl: –0.1,				331 participants; TSA adj. CI:	
	CI: -)		7.9; 268%)				-3.7; 7.2%)	
24-hour VAS	7.3 mm	p=0.77	8.9 mm	p=0.19	2.2 mm	p=0.02	6.1 mm	p=0.23
at rest	(1.7, 12.8; p=0.01; 13 trials;		(4.8, 12.9; <i>p</i> <0.0001; 15 trials;		(-1.1, 5.6; <i>p</i> =0.19; 7 trials;		(2.5, 9.7; p=0.0009; 27 trials;	
All trials	806 participants; TSA adj. CI:		1315 participants; TSA adj. CI:		255 participants; TSA adj.		1493 participants; TSA adj.	
	1.7, 12.8; 115.7%)		4.8, 12.7; 224.8%)		CI: –I/, 6.2; 318.8%)		CI: 2.5, 9.7; 280.6%)	
24-hour VAS at	–2.0 mm	ı	5.9 mm	p=0.16	–I.0 mm	ı	0.8 mm	p=0.39
mobilization	(7.2, 11.2; p=0.67; 1 trial, 63		(–0.9, 12.8; <i>p</i> =0.09; 5 trials;		(-3.3, 5.3; <i>p</i> =0.65; l trial;		(–2.9, 4.5; <i>p</i> =0.67; 4 trials;	
Low risk of bias	participants; TSA adj. Cl: -)		526 participants; TSA adj. CI:		121 participants; TSA adj.		326 participants; TSA adj. CI:	
			-2.4, 14.3; 74%)		CI: -)		-2.7, 4.3; 300%)	
24-hour VAS at	– I .0 mm	p=0.27	2.5 mm	p=0.59	5.1 mm	p=0.92	5.9 mm	<i>p</i> =0.52
mobilization	(−7.9, 9.8; <i>p</i> =0.8; 2 trials;		(-6.4, 11.4; p=0.58; 9 trials;		(–5.4, 15.5; <i>p</i> =0.34; 2 trials;		(-1.5, 10.3; <i>p</i> =0.009; 15	
All trials	95 participants; TSA adj. CI:		843 participants; TSA adj. CI:		141 participants; TSA adj.		trials; 922 participants; TSA	
	-I3.I, I5.0; 46.I%)		-I7.4, II.3; I7.4; 45.1%)		Cl: –14.6, 24.8; 33%)		adj. Cl: -3.6, 10.9; 87.0%)	
Abbreviations: Cl,	confidence interval; MD, mean differ	ence; TSA, trial s	equential analysis; VAS, visual analog sca	ale.				

differences were demonstrated in the all trials estimates (Table 2; <u>Supplementary material</u> S5–S12: forest plots of pain intensities).

Adverse events

No consistent dose-related trends or subgroup differences were demonstrated either in data from trials with low risk of bias or in the all trials estimates (Table 3). None of the meta-analyses of trials with low risk of bias reporting risk of AE reached firm evidence according to TSA (Supplementary material S13–S20: forest plot of AE).

Discussion

In this review, we aimed to explore the effect of increasing doses of gabapentin on postoperative morphine consumption, SAEs, pain intensity, and adverse events in four groups of trials that included the most commonly used doses of gabapentin for perioperative pain management: 300, 600, 900, and 1200 mg.

For the primary beneficial outcome, 24-hour morphine consumption, no consistent increase in morphine-sparing effect was observed with increasing doses of gabapentin, either in the analysis of trials with low risk of bias or in the all trials analysis. On the contrary, the smallest (0–350 mg) and the largest (>1050 mg) dose regimens demonstrated comparable and the most pronounced reduction in morphine consumption in the all trials analysis.

Only few SAEs were reported, limiting any reliable conclusion on this outcome. Of 72 stated SAEs, 83% were reported in the >1050 mg subgroup, indicating an increased risk of SAEs with increasing doses. Of the 27 trials reporting SAEs, 10 were classified as overall low risk of bias, and these 10 trials reported more than half the SAEs.

For the secondary outcomes, pain intensity and adverse events, no consistent dose-related trends or subgroup differences were demonstrated, either in data from trials with low risk of bias or in the all trials estimates.

We could not find any clear indication of a dose-related effect of gabapentin. A possible explanation may by the fact that higher doses of gabapentin lead to relatively smaller increases in blood concentrations because of the saturable absorption of gabapentin after oral administration.^{14,15,145} This may potentially provide an upper limit to the effect of beneficial outcomes and adverse events. However, none of our results indicated a clear upper limit or difference between subgroups, confirming this hypothesis. The nonlinear absorption may be the main reason of the less-predictable clinical effect of increased doses, but other explanations also have to be considered.

The analgesic effect of gabapentin is considered to be related to its antihyperalgesic properties, as demonstrated for both single and multiple dosing in human volunteer pain models.^{146,147} In such models, gabapentin did not affect nociceptive pain per se.146-148 Furthermore, gabapentin demonstrated dose-dependent antihyperalgesic effects in rat pain models,149 which, however, has not been investigated in humans. It is, therefore, unknown if increasing doses of gabapentin display increasing antihyperalgesic effects in humans, and if such a dose-response relationship is linear. This may contribute significantly to the shortcoming of detecting a dose-response effect in postoperative pain patients. Furthermore, postoperative pain is related to multiple pain mechanisms, of which hyperalgesia is only one. It is, though, unknown how important the hyperalgesic component is for the total sum of experienced pain. This may, in part, also explain the shortcomings of detecting a dose-response relationship for postoperative gabapentin treatment.

The optimal dose for postoperative pain treatment has been investigated in a few original clinical trials.^{2–11,143} The study by Van Elstraete et al¹⁵⁰ found a relatively high median effective analgesic dose of 21.7 mg/kg gabapentin in spinal fusion surgery. Considering this result, it is possible that the investigated doses, in general, are too low for analgesic efficacy, although higher doses (>1200 mg) most likely will produce profound adverse effects.

Most included trials were small in size, and 86% of the trials included less than 50 participants in each group, which can be a limitation. The large number of small-sized trials leads to repetitive testing in the cumulative meta-analyses, increasing the risk of random error. Accordingly, we applied TSA to compensate for this limitation. The majority of cumulative subgroup analyses of trials with low risk of bias did not reach firm evidence, or the RIS. This limits any firm evidence and conclusions. In addition, the lack of data may cause a type II error.

The strengths of these subgroup analyses are related to the primary systematic review that was carried out using Cochrane methodology and reported according to PRISMA guidelines. All trials were critically assessed using the Cochrane bias evaluation tools, and the risk of random error was assessed using TSA to adjust for sparse data and repetitive testing.

However, there are substantial limitations to our results. The conclusions based on our results are generally weakened

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bits participants: TSA ad, C1:0, 12:33.7% participants: TSA ad, C1:0, 12:33.7% participants: TSA ad, C1:0, 12:33.7% Mutais 0.9 0.8 $p=0.41$ 0.8 $p=0.41$ $p=0.31$	Low risk of			(0.4, 1.6; <i>p</i> =0.54; 3 trials; 218				(0.5, 0.9; p=0.02; 2 trials; 180	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	bias			participants; TSA adj. Cl: 1.9, 15.6; 72.9%)				participants; TSA adj. Cl: 0.1, 1.2; 33.7%)	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Nausea	0.9	p=0.42	0.8	p=0.82	0.8	b=0.9I	0.8	p=0.47
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	All trials	(0.7, 1.1; <i>p</i> =0.16; 9 trials;		(0.6, 1.1; p=0.10; 15 trials;		(0.5, 1.4; <i>p</i> =0.51; 4 trials;		(0.6, 0.9; p=0.003; 21 trials; 1203	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		633 participants; TSA adj.		1019 participants; TSA adj.		271 participants; TSA adj.		participants; TSA adj. Cl: 0.3, 1.8; 50.4%)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Cl: 0.7, 1.1; 70.6%)		Cl: 0.5, 1.3; 40.0%)		CI: 0.1, 7.2; 12.8%)			
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Vomiting			2.0				1.0	p=0.36
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Low risk of			(0.5, 7.3; p=0.3; 1 trial; 46				(0.7, 1.6; p=0.85; 2 trials, 180	
Vomiting 0.8 -0.02 0.7 -0.17 0.7 0.3 -0.035 0.8 0.3 All traits (0.6, 1.2; p-0.6; 9 traits; 1.6) (0.5, 0.9; p-0.007; 14 traits; 0.1, 5.1; 54.8%) (0.1, 37; -0.64; 2 traits; 0.1, 5.1; 71.4%) $p=0.012$ (0.1, 1.7; -0.002; 19 traits; 1188) $p=0.007$ $p=0.007$; 111 participants; TSA adj, C1: 01, 6.1; 71.4%) $p=0.012$ $p=0.11$ $p=0.007$; 111 participants; TSA adj, C1: 01, 6.1; 71.4%) $p=0.012$ $p=0.12$ $p=0.11$ $p=0.05$ $p=0.11$ $p=0.12$ <td>bias</td> <td></td> <td></td> <td>participants; TSA adj. Cl: -)</td> <td></td> <td></td> <td></td> <td>participants; TSA adj. Cl: 0.2, 5.9; 16.5%)</td> <td></td>	bias			participants; TSA adj. Cl: -)				participants; TSA adj. Cl: 0.2, 5.9; 16.5%)	
All traits (0.6, 1.2; $p=0.26; 9 \text{ traits:}$ (0.1, 37; $p=0.64; 2 \text{ traits:}$ (0.1, 37; $p=0.02; 19 \text{ traits:} 1188$ 38 participants: T5A adj. 948 participants: T5A adj. CI: 111 participants: T5A adj. CI: 111 participants: T5A adj. CI: 0.1, 7.2; 12.8%) participants: T5A adj. CI: 0.1, 61; 71, 4%) Sedation 12. 0.41, 1.5; 4.8%) 0.0 1.5; 4.8%) CI: 0.1, 7.2; 12.8%) p=0.10 Low risk of (0.8, 1.6; p=0.4; 2 \text{ traits: 107} p=0.13; p=0.69; 4 \text{ traits: 385} 0.8 1.6; p=0.05; 1 \text{ traits: 180} p=0.10 Low risk of (0.8, 1.6; p=0.4; 2 \text{ traits: 107} p=0.13 (0.4, 1.6; p=0.05; 1 \text{ traits: 180} p=0.10 Sedation 12. p=0.43 traits: 60 (1.6, 1.6, 1; 71.4%) p=0.10 Low risk of (0.8, 1.6; p=0.4; 2 \text{ traits: 305} 0.8 (1.6, 1.6, 1.2, 1.2, 1.8) p=0.10 Sedation 12. p=0.13 (0.4, 1.6; p=0.05; 1 traits: 60 (1.0, 1.5; p=0.05; 2 \text{ traits: 180 All traits (0.9, 71; p=0.08; 8 \text{ traits; 75A adj. CI: 0.4, 2.7 adj. CI: 0.4, 2.7 adj. CI: 0.1, 2.6; 9.05; 1 \text{ traits: 942 p=0.67 1.1 p=0.67 All traits (0.6, 25; p=0.57; 2 \text{ traits; 100	Vomiting	0.8	p=0.82	0.7	p=0.17	0.7	p=0.85	0.8	þ=0.33
Staticipants: TSA adj. 948 participants: TSA adj. Cl: 111 participants: TSA adj. Cl: 0.1, 5.1; 71.4%) C:: 0.4, 1.7; 29.2%) 0.4, 1.1; 54.8%) C:: 0.4, 1.1; 54.8%) 0.4, 1.1; 54.8%) p=0.10 Sectation 1.2 Dewrisk of (0.8, 1.6; p=0.4; 2 trials; 107 0.4, 1.1; 54.8%) C:: 0.4, 1.6; p=0.39; 1 trial; 60 (1.0, 2.5; p=0.05; 2 trials; 180 p=0.10 Low risk of (0.8, 1.5; p=0.4; 2 trials; 107 0.9, 1.1; 54.8%) D=0.04 (1.0, 1.6; p=0.79; 1 trial; 60 (1.0, 2.5; p=0.05; 2 trials; 180 p=0.10 Low risk of 0.8, 7.1; p=0.08; 8 trials; 1.1; 54.8%) p=0.09 1.9 participants; TSA adj. Cl: 0.2, 9.9; 12.4%) p=0.04 All trials (0.9, 7.1; p=0.08; 8 trials; 1.0 0.8, 1.2; p=0.97; 15 trials; 180 p=0.04 1.0 1.0, 1.6; p=0.02; 12.4%) p=0.10 All trials (0.9, 7.1; p=0.06; 8 trials; 305 (0.4, 1.6; p=0.43; 4 trials; 305 (0.4, 1.6; p=0.04; 14; 4.1.7%) p=0.14 All trials (0.9, 7.1; p=0.08; 8 trials; 31 1.0 0.4, 8.7; p=0.43; 4 trials; 305 p=0.14 1.0 1.0, 1.6, 1; 71.4%) p=0.04 C::	All trials	(0.6, 1.2; <i>p</i> =0.26; 9 trials;		(0.5, 0.9; <i>p</i> =0.007; 14 trials;		(0.1, 3.7; <i>p</i> =0.64; 2 trials;		(0.7, 1.1; p=0.002; 19 trials; 1188	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		538 participants; TSA adj.		948 participants; TSA adj. CI:		III participants; TSA adj.		participants; TSA adj. Cl: 0.1, 6.1; 71.4%)	
Sedation 1.2 $p_{0.7}$ $p_{0.7}$ $p_{0.1}$ $p_{-0.16}$ 1.6 1.6 $p_{-0.16}$		Cl: 04, 1.7; 29.2%)		0.4, 1.1; 54.8%)		CI: 0.1. 7.2; 12.8%)			
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Sedation	1.2	p=0.79	0.1	p=0.35	0.8	ı	1.6	p=0.10
bias participants; TSA adj. CI: 0.3, participants; TSA adj. CI: 0.4, participants; TSA adj. CI: 0.2, 9.9; 12.4%) 4.2; 15.2%) 1.1; 54.8%) $-1.1; 54.8\%$ p=0.13 1.0 $-1.1; 54.8\%$ p=0.03 1.9 participants; TSA adj. CI: 0.2, 9.9; 12.4%) Sedation 2.5 $p=0.13$ 1.0 $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.1; 54.8\%$ $-1.2; 9-0.07$ 1.3 -1.0 $-1.2; 9-0.07$ 1.3 -1.0 $-1.3; p=0.94$ $-1.1; 2.9$ -1.057 1.3 -1.067 1.3 -1.009 1.9 -1.057 1.3 -1.067 1.3 -1.01 -1.01 -1.01 -1.05 -1.055 $-1.057; 2 trials; 942$ -1.0000 $-1.2; -5.5\%$ -1.0000 $-1.2; -5.5, -0.57; 2 trials; 941 -1.0 -1.03 -1.03 -1.04 1.0 -1.2; -9.04; 1 trial; -1.0000 -1.2; -5.5, -0.57; 2 trials; 741 -1.00 -1.03; -1.2; -0.04; 1 trial; -1.0000 -1.2; -5.5, -0.57; 2 trials; 741 - 1.0000 -1.1; -0.04; 1 trial; -1.0000 -1.2; -5.5, -0.57; 2 trials; 741 - 1.0000 -1.2; -5.5, -0.057; 2 trials; 741 - 1.0000 -1.1; -1.0000 -1.1; -1.00000 -1.0; -1.$	Low risk of	(0.8, 1.6; <i>p</i> =0.4; 2 trials; 107		(0.9, 1.3; $p=0.69$; 4 trials; 385		(0.4, 1.6; <i>p</i> =0.59; 1 trial; 60		(1.0, 2.5; p=0.05; 2 trials; 180	
4.2: 15.2%) 1.1: 54.8%) $4.2: 15.2\%$ $1.1: 54.8\%$ $p=0.67$ 1.3 $p=0.67$ 1.3 $p=0.94$ All trials $(0.9, 7.1; p=0.08; 8 \text{ trials}; 942$ $(0.4, 8.7; p=0.43; 4 \text{ trials}; 942$ $p=0.67$ 1.3 $p=0.67$ 1.3 $p=0.94$ All trials $(0.9, 7.1; p=0.08; 8 \text{ trials}; 942$ $(0.8, 1.2; p=0.97; 15 \text{ trials}; 912$ $(0.4, 8.7; p=0.43; 4 \text{ trials}; 912$ $(1.0, 1.6; p=0.02; 15 \text{ trials}; 942$ All trials $(0.9, 7.1; p=0.08; 8 \text{ trials}; 912$ $(0.8, 1.2; p=0.97; 3 \text{ trials}; 75A adj. (1.6, 1.6; p=0.02; 15 \text{ trials}; 942 p=0.95 Dizziness 1.2 p=0.64 1.0 p=0.37 8.0 -1.0 p=0.95 Dizziness 1.2 p=0.57; 2 \text{ trials}; 941 (1.1, 6.0.1; p=0.04; 1 \text{ trial}; 940; 1.0; 0.7, 1.7; 21.9%) p=0.95 Uov risk of (0.6, 2.5; p=0.57; 2 \text{ trials}; 75A adj. (1.1, 6.0.1; p=0.04; 1 \text{ trial}; 940; 1.0; 0.7, 1.7; 21.9%) p=0.95 Low risk of (0.6, 1.3; p=0.45; 1.2 \text{ trials}; 12 \text{ trials}; 100 p=0.11 1.2 p=0.20, 1.2; 0.7, 1.2; 21.9\% Dizziness 0.5, 1.3; p=0.45; 1.2 \text{ trials}; 100 p=0.30; 1.12; p$	bias	participants; TSA adj. Cl: 0.3,		participants; TSA adj. Cl: 0.4,		participants; TSA adj. Cl: -)		participants; TSA adj. Cl: 0.2, 9.9; 12.4%)	
Sedation2.5 $p=0.13$ 1.0 $p=0.07$; 1.5 trials; $p=0.000$ 1.9 $p=0.67$ 1.3 $p=0.97$; 1.5 trials; $p=0.97$; 1.0; 1.1; 2.1 SM $p=0.95$; 1.1; 2.1 SM $p=0.95$; 2.40 participants; TSA adj. Cl: 0.7, 1.7; 2.1 SM $p=0.95$; 1.2 trials; $p=0.95$; 1.2 trials; $p=0.94$; 1.1 trial; $p=0.64$; 1.0; 0.7, 1.7; 2.1 SM $p=0.20$ Low risk of(0.6, 2.5; p=0.57; 2 trials;0.03, 1.3; p=0.77; 3 trials; 3.41(1.1, 60.1; p=0.04; 1 trial;(0.9, 1.3; p=0.68; 3 trials; 2.39) $p=0.95$; 1.1; 2.1 SMLow risk of(0.6, 2.5; p=0.57; 2 trials;1.3; 2.89%;2.0; 0.7; 1.7; 21.9%;0.0; 1.1; p=0.68; 3 trials; 2.39; $p=0.20$ Dizziness0.8p=0.341.0p=0.341.00.9, 1.1; p=0.45;1.0; 0.1; 1.7; 21.9%;All trials(0.5, 1.3; p=0.45; 1.2 trials;1.0; 0.1; 1.2; 5.9-0.10; 6 trials;0.0, 1.1; 2.9-0.89; 1.2; 87.2%;Low risk of(0.5, 1.3; p=0.45; 1.2 trials;1.0; 0.7; 1.3; 6.4.8%;2.0; 0.7, 1.3; 6.4.8%;2.0; 0.1; 2.5, 2.8%;All trials(0.2, 4.4; 1.4.6%;1.0; 0.7, 1.3; 6.4.8%;2.1; 0.		4.2; 15.2%)		I.I; 54.8%)					
All trials $(0, 7, 1; p=0.08; 8 \text{ trials};$ $(0.8, 1.2; p=0.97; 15 \text{ trials}; 15 \text{ trials}; 942$ 734 participants; TSA adj. 1317 participants; TSA adj. 240 participants; TSA adj. 21.65% Ci: <5%)	Sedation	2.5	p=0.13	0.1	<i>b</i> =0.009	6.1	p=0.67	1.3	p=0.94
734 participants; TSA adj. 1317 participants; TSA adj. 240 participants; TSA adj. participants; TSA adj. <td>All trials</td> <td>(0.9, 7.1; <i>p</i>=0.08; 8 trials;</td> <td></td> <td>(0.8, 1.2; $p=0.97$; 15 trials;</td> <td></td> <td>(0.4, 8.7; <i>p</i>=0.43; 4 trials;</td> <td></td> <td>(1.0, 1.6; p=0.02; 15 trials; 942</td> <td></td>	All trials	(0.9, 7.1; <i>p</i> =0.08; 8 trials;		(0.8, 1.2; $p=0.97$; 15 trials;		(0.4, 8.7; <i>p</i> =0.43; 4 trials;		(1.0, 1.6; p=0.02; 15 trials; 942	
CI: <5%) CI: <5%) CI: <5%) CI: <5%) Dizziness 1.2 $p=0.64$ 1.0 $p=0.37$ 8.0 - 1.0 $p=0.95$ Low risk of (0.6, 2.5; $p=0.57$; 2 trials; (0.7, 1.3; $p=0.77$; 3 trials; 341 (1.1, 60.1; $p=0.04$; 1 trial; (0.9, 1.3; $p=0.68$; 3 trials; 239 $p=0.75$; 5.8%) $p=0.11$ (0.9, 1.3; $p=0.68$; 3 trials; 239 bias 107 participants; TSA adj. (1.1, 60.1; $p=0.04$; 1 trial; (0.9, 1.3; $p=0.68$; 3 trials; 239 $p=0.75$; 5.8%) $p=0.34$ (1.1, 60.1; $p=0.04$; 1 trial; $p=0.77$; 21.9%) Dizziness 0.8 (1.2, 2.5; 5.8%) 1.8; 28.9%) $C: -1$ $(1.1, 60.1; p=0.04; 1 trial; p=0.77; 1.7; 21.9%) All trials (0.5, 1.3; p=0.45; 12 trials; 1.0 p=0.34 1.0 p=0.36 p=0.36 p=0.20 All trials (0.5, 1.3; p=0.45; 12 trials; 1.0 p=0.16 1.2 p=0.38 p=0.16; 6 trials; 1.0^{-1} 1.7; 21.9%) All trials (0.5, 1.3; p=0.45; 12 trials; 1.0 p=0.36 p=0.11 1.2 1.2 p=0.34 p=0.11 1.2 p=0.20 p=0.20 p=0.11 $		734 participants; TSA adj.		1317 participants; TSA adj.		240 participants; TSA adj.		participants; TSA adj. Cl: 0.9, 1.9; 41.7%)	
Dizziness 1.2 $p=0.64$ 1.0 $p=0.37$ 8.0 - 1.0 $p=0.95$ Low risk of (0.6, 2.5; $p=0.57$; 2 trials; (0.7, 1.3; $p=0.77$; 3 trials; 341 (1.1, 60.1; $p=0.04$; 1 trial; (0.9, 1.3; $p=0.68$; 3 trials; 239 $p=0.75$; $p=0.77$; 3 trials; 341 (1.1, 60.1; $p=0.04$; 1 trial; (0.9, 1.3; $p=0.68$; 3 trials; 239 $p=0.75$; $p=0.28$; $p=0.17$; $p=0.28$; $p=0.17$; $p=0.28$; $p=0.20$; $p=0.20$; $p=0.11$; $p=0.20$;		CI: <5%)		Cl: 0.8, 1.2; 98.7%)		CI: <5%)			
Low risk of (0.6, 2.5; $p=0.57$; 2 trials; (0.7, 1.3; $p=0.77$; 3 trials; 341 (1.1, 60.1; $p=0.04$; 1 trial; (0.9, 1.3; $p=0.68$; 3 trials; 239 bias 107 participants; TSA adj. participants; TSA adj. 0.9, 1.3; $p=0.68$; 3 trials; 239 CI: 0.1, 26.5; 5.8%) 1.8; 28.9%) 60 participants; TSA adj. 0.1.7; 21.9%) Dizziness 0.8 1.2, $p=0.34$ 1.0 $p=0.36$ 3.0 All trials (0.5, 1.3; $p=0.45;$ 12 trials; (0.8, 1.2; $p=0.89;$ 13 trials; (0.8, 11.2; $p=0.10;$ 6 trials; (1.0, 1.5; $p=0.11;$ 21 trials; 1400 All trials (0.5, 1.3; $p=0.45;$ 12 trials; (0.8, 1.2; $p=0.016;$ 6 trials; (1.0, 1.5; $p=0.11;$ 21 trials; 1400 CI: 0.2, 4.4; 14.6%) CI: 0.7, 1.3; 64.8%) CI: <5%)	Dizziness	1.2	p=0.64	0.1	p=0.37	8.0	ı	1.0	p=0.95
bias 107 participants; TSA adj. participants; TSA adj. Cl: 0.5, 60 participants; TSA adj. participants; TSA adj. Cl: 0.7, 1.7; 21.9%) Cl: 0.1, 26.5; 5.8%) 1.8; 28.9%) Cl: 0.1, 26.5; 5.8%) $= 0.34$ 1.0 $= 0.36$ 3.0 $= 0.11$ 1.2 $= 0.34$ 1.0 $= 0.36$ 3.0 $= 0.11$ 1.2 $= 0.11$ 1.2 $= 0.20$ All trials (0.5, 1.3; $p=0.45$; 12 trials; 140 (0.8, 1.2; $p=0.88$; 13 trials; (0.8, 11.2; $p=0.10$; 6 trials; (1.0, 1.5; $p=0.11$; 21 trials; 1400 1209 participants; TSA adj. Cl: 0.7, 1.3; 64.8%) Cl: 0.2, 4.4; 14.6%) Cl: 0.7, 1.3; 64.8%) Cl: <5%)	Low risk of	(0.6, 2.5; <i>p</i> =0.57; 2 trials;		(0.7, 1.3; p=0.77; 3 trials; 341		(1.1, 60.1; p=0.04; 1 trial;		(0.9, 1.3; p=0.68; 3 trials; 239	
CI: 0.1, 26.5; 5.8%) I.8; 28.9%) CI: -) CI: -) Dizziness 0.8 $p=0.34$ 1.0 $p=0.36$ 3.0 $p=0.11$ 1.2 $p=0.20$ All trials (0.5, 1.3; $p=0.45$; 12 trials; (0.8, 1.2; $p=0.89$; 13 trials; (0.8, 11.2; $p=0.10$; 6 trials; (1.0, 1.5; $p=0.11$; 21 trials; 1400 1209 participants; TSA adj. 1101 participants; TSA adj. 312 participants; TSA adj. (1.0, 1.5; $p=0.11$; 21 trials; 1400 CI: 0.2, 4.4; 14.6%) CI: 0.7, 1.3; 64.8%) CI: <5%)	bias	107 participants; TSA adj.		participants; TSA adj. Cl: 0.5,		60 participants; TSA adj.		participants; TSA adj. Cl: 0.7, 1.7; 21.9%)	
Dizziness 0.8 $p=0.34$ 1.0 $p=0.36$ 3.0 $p=0.11$ 1.2 $p=0.20$ All trials (0.5, 1.3; $p=0.45$; 12 trials; (0.8, 1.2; $p=0.00$; 6 trials; (1.0, 1.5; $p=0.11$; 21 trials; 1400 $p=0.20$ All trials (0.5, 4.4; 14.6%) C1: 0.7, 1.3; 64.8%) C1: <5%)		Cl: 0.1, 26.5; 5.8%)		I.8; 28.9%)		CI: -)			
All trials (0.5, 1.3; <i>p</i> =0.45; 12 trials; (0.8, 1.2; <i>p</i> =0.89; 13 trials; (0.8, 11.2; <i>p</i> =0.10; 6 trials; (1.0, 1.5; <i>p</i> =0.11; 21 trials; 1400 1209 participants; TSA adj. 1101 participants; TSA adj. 312 participants; TSA adj. participants; TSA adj. CI: 0.9, 1.2; 87.2%) CI: 0.2, 4.4; 14.6%) C2: 0.7, 1.3; 64.8%) C1: <5%)	Dizziness	0.8	p=0.34	0.1	p=0.36	3.0	p=0.11	1.2	þ=0.20
1209 participants; TSA adj. 101 participants; TSA adj. 312 participants; TSA adj. participants; TSA adj. C1: 0.9, 1.2; 87.2%) C1: 0.2, 4.4; 14.6%) C1: 0.1, 1.3; 64.8%) C1: <5%)	All trials	(0.5, 1.3; <i>p</i> =0.45; 12 trials;		(0.8, 1.2; p=0.89; 13 trials;		(0.8, 11.2; p=0.10; 6 trials;		(1.0, 1.5; p=0.11; 21 trials; 1400	
CI: 0.2, 4.4; 14.6%) CI: 0.7, 1.3; 64.8%) CI: <5%)		I 209 participants; TSA adj.		1101 participants; TSA adj.		312 participants; TSA adj.		participants; TSA adj. Cl: 0.9, 1.2; 87.2%)	
		Cl: 0.2, 4.4; 14.6%)		Cl: 0.7, 1.3; 64.8%)		Cl: <5%)			

	Expe	rimental		C	ontrol			Mean difference	Mean difference
Study or subgroup	Mean (mg)	SD (mg)	Total	Mean (mg)	SD (mg)	Total	Weight	IV, Random, 95% CI (mg)	IV, Random, 95% CI (mg)
3.1.1 0–350 mg									
Short et al ⁹	5.7	5.3	42	7.9	3.8	21	9.3%	- 2.20 (-4.48, 0.08)	-
Waikakul et al140	15.5	9.25	24	18	15.5	24	5.2%	- 2.50 (-9.72, 4.72)	-+
Subtotal (95% CI)			66			45	14.6%	- 2.23 (-4.40, -0.05)	•
Heterogeneity: Tau ² =	0.00; Chi ² =0.	01, df=1 (j	o=0.94); /²=0%					
lest for overall effect	: Z=2.01 (p=0	.04)							
3.1.3 351–700 mg									
Misra et al ⁹¹	24.6	19.6	37	29.15	25.2	36	3.5%	- 4.55 (-14.93, 5.83)	
Monks et al ⁹⁵	10	11.9	100	10	7.4	97	9.0%	0.00 (-2.76, 2.76)	+
Moore et al ⁹⁶	3	3	21	4	5	23	9.2%	-1.00 (-3.41, 1.41)	+
Paul et al ¹⁰⁷	27.94	22.99	52	26.77	18.96	49	4.6%	1.17 (-7.03, 9.37)	+-
Paul et al ¹⁰⁸	19.7	16.39	48	25.1	14.5	54	6.1%	-5.40 (-11.44, 0.64)	
Short et al ^{9a}	6.7	3.6	42	7.9	3.8	21	9.5%	-1.20 (-3.16, 0.76)	+
Srivastava et al ¹²⁸	25.39	4.48	60	37.58	8.35	60	9.2%	-12.19 (-14.59, -9.79)	-
Subtotal (95% CI)			360			340	51.2%	-3.41 (-7.67, 0.86)	◆
Heterogeneity: Tau ² =	26.58; Chi ² =6	67.74, df=6	6 (p<0.	00001); /2=9	1%				
Test for overall effect	: Z=1.57 (p=0	.12)							
3 1 5 701 1050 mg									
Ghai at al ⁵⁸	5 44	4 50	00	4.00	4.07	20	40.40/	4.40 (0.00, 0.00)	
l unn et al ⁵	5.44	1.50	30	4.28	1.87	30	10.1%	1.16 (0.29, 2.03)	
Subtotal (95% CI)	45.4	35.7	122	50.2	41.4	29	1.7%	-4.80 (21.54, 11.94)	
Hotorogonoity: Tou ² =	0.00. Chi2-0	10 df=1 (122 n=0.40	12-09/		55	11.7 /0	1.14 (0.27, 2.01)	
Test for overall effect	· 7=2 58 (n=0	49, 01=1 (J 010)	0=0.49); /-=0%					
	. z-z.50 (p-0	.010)							
3.1.6 >1050 mg									
Brogly et al ⁴¹	0	1.48	22	0	4.4	21	9.5%	0.00 (-1.98, 1.98)	+
Fassoulaki et al55	20.3	7.9	29	25.7	11.2	30	7.1%	-5.40 (-10.33, -0.47)	
Grosen et al62	11.2	21.62	52	17.92	23.55	52	4.3%	-6.72 (-15.41, 1.97)	
Lunn et al ^{5a}	46.2	41.1	91	50.5	41.4	29	1.6%	-4.30 (-21.57, 12.97)	
Subtotal (95% CI)			194			132	22.5%	-2.89 (-6.90, 1.12)	
Heterogeneity: Tau ² =	7.48; Chi ² =5.	84, df=3 (j	o=0.12); <i>I</i> ²=49%					
lest for overall effect	: Z=1.41 (p=0	.16)							
Total (95% CI)			742			576	100.0%	-2.81 (-5.18, -0.44)	•
Heterogeneity: Tau ² =	14.31; Chi ² =1	17.37, df=	=14 (p<	:0.00001): / ² =	-88%				
Test for overall effect	Z=2.32 (p=0	.02)	v.	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					-50 -25 0 25 50
Test for subgroup diff	erences: Chi ²	=14.05 dt	f=3 (n=	0 003) 12=78	8.6%				Gabapentin Control

Figure 2 Forest plot of 24-hour morphine consumption from trials with overall low risk of bias.

Abbreviations: df, degrees of freedom; CI, confidence interval; SD, standard deviation; IV, inverse variance.

by the low number of trials classified as overall low risk of bias, which limits the test for subgroup differences, and pooled estimates in meta-analyses. The few number of trials with low risk of bias means that all trials estimates must be factored into the evaluation and interpretation of these subgroup analyses. It is well described that estimates from trials with unclear and high risk of bias have an inherent risk of overestimating beneficial outcomes and underestimating harmful events, which must be taken into account upon conclusions and further use in future hypothesis based on these analyses.¹⁴⁴

Few of the included trials reported SAEs, and most of the trials exhibited a short follow-up period, further limiting the analyses exploring the risks of gabapentin treatment.¹⁸

Further, this review consists of post hoc analyses, which limit the reliability of the results. The subgroups of our analyses must be interpreted as observational studies, with the inherent limitations of such studies: Confounding by other study characteristics may bias the analyses. Some of these study characteristics, such as gabapentin with other nonopioid analgesics, have been explored in the original work,¹⁸ while the effect of gabapentin in six different procedures was explored in a separate published article finding no difference between surgical procedures on beneficial and harmful outcomes from trials with overall low risk of bias.¹⁵¹

Our post hoc analysis was meant to explore the dose effect of gabapentin in published randomized clinical trials, since there is no previously published systematic on the topic. Based on the combined analyses, we cannot recommend a specific dose or regimen, if any, for perioperative gabapentin treatment. We hope that our analyses may inspire the hypotheses of future trials.

Conclusion

Data were sparse in all subgroups, and the small number of trials with low risk of bias is a major limitation for firm conclusions. Taking these limitations into account, we were not able to demonstrate a clear relationship between the dosage of gabapentin and opioid-sparing or harmful effects. Numerically, most SAEs were reported in the higher dosing groups, and trials with low risk of bias reported the most SAEs. These subgroup analyses are exploratory and hypothesis-generating for future trialists.

	Experi	mental		Cor	itrol			Mean difference	Mean difference
Study or subgroup	Mean (mg) S	SD (mg)	Total	Mean (mg)	SD (mg)	Total	Weight	IV, Random, 95% CI (mg)	IV, Random, 95% Cl (mg)
3.3.1 0–350 mg	10 5	0.5	50	22	0.4	50	0.40/	0.50 (0.40 7.00)	
Amr et al ³⁰ Bang et al ³⁴	13.5	20.07	50 23	22	2.1	50	2.1%	-8.50 (-9.10, -7.90)	_
Clarke et al ⁴⁶	37	1.5	95	48	1.33	84	2.1%	-11.00 (-11.41, -10.59)	•
Ghafari et al57	15.78	1.15	33	26.94	2.28	33	2.1%	-11.16 (-12.03, -10.29)	•
Panday et al ¹⁰²	40.42	31.26	153	53.03	27.48	153	1.4%	–12.61 (–19.21, –6.01)	
Panday et al ¹⁰³	90.85	34.1	28	92.49	41.77	28	0.4%	-1.64 (-21.61, 18.33)	
Seknavel et al	40.1	14.5	49 42	52.7	21.1	49	1.4%	-12.60(-19.77, -5.43) -2.20(-4.48, 0.08)	-
Vahedi et al ¹³⁶	18.61	9.03	36	21.53	11.3	40	1.7%	-2.92 (-7.50, 1.66)	-+
Waikakul et al140	15.5	9.25	24	18	15.5	24	1.4%	-2.50 (-9.72, 4.72)	
Yoon et al ¹⁴¹	24.1	9.9	16	32.7	14.6	16	1.2%	-8.60 (-17.24, 0.04)	•
Subtotal (95% CI)			549			521	16.4%	-8.02 (-9.84, -6.19)	•
Heterogeneity: lau ² =4	54; Chi²=114. Z=8.61 (n<0.0)	81, <i>dt</i> =10 001)) (p<0.0	00001); / ² =919	%				
	2 0.01 (p 0.0								
3.3.2 351-700 mg Bharti et al ⁴⁰	0.4	2.2	20	10	2.4	20	0.40/	2 90 (4 57 1 02)	-
Clarke et al ⁴⁵	2.1	2.2	76	4.5	- 3.4 - 4	39	2.1%	-1.90(-3.44 - 0.36)	-
Khademi et al71	2.83	1.29	44	3.51	1.51	43	2.1%	-0.68 (-1.27, -0.09)	1
Maleh et al ⁸³	2.5	2.6	40	2.7	2.7	40	2.1%	-0.20 (-1.36, 0.96)	1
Mardani-Kivi et al ⁸⁵	2.5	2.3	55	3.7	2.5	53	2.1%	-1.20 (-2.11, -0.29)]
Menda et al ⁶⁶	6	8.5	30	15.1	20	30	1.3%	-9.10 (-16.88, -1.32)	-
Misra et al ⁹¹	24.6	19.6	67	29.2	9.6	36	1.9%	-13.10 (-10.62, -9.36) -4.55 (-14.93, 5.83)	-+
Monks et al ⁹⁵	10	11.9	100	10	7.4	97	2.0%	0.00 (-2.76, 2.76)	t
Moore et al ⁹⁶	3	3	21	4	5	23	2.0%	-1.00 (-3.41, 1.41)	1
Panday et al ¹⁰⁴	59.37	23.17	40	92.47	41.75	20	0.4%	-33.10 (-52.76, -13.44)	
Panday et al ^o	39.19	26.31	125	67.66	25.27	125	1.5%	-28.47 (-34-87, -22.07)	+
Paul et al ¹⁰⁷	31.7	20.3	30	31.9	19.84	30 40	1.0%	-0.20 (-10.36, 9.96) 1 17 (-7 03 9 37)	+
Paul et al ¹⁰⁸	27.94	16.39	48	20.77	14.5	49 54	1.5%	-5.40 (11.44, 0.64)	-
Sava et al ¹¹⁸	35.6	14.14	25	54.7	13.02	25	1.3%	–19.10 (–26.63, –11.57)	
Short et al ^{9a}	6.7	3.6	42	7.9	3.8	21	2.0%	-1.20 (-3.16, 0.76)	1
Soltanzadeh et al ¹²⁶	2.5	0.9	30	4	1.5	30	2.1%	-1.50 (-2.13, 0.87)	-]
Srivastava et al	25.39	4.48	60	37.58	8.35	60	2.0%	-12.19 (-14.59, -9.79)	-
Subtotal (95% CI)	15.5	5	962	19	4.2	849	33.7%	-4.56 (-6.08, -3.03)	•
Test for overall effect:	Z=5.87 (p<0.00	0001)							
3.3.3 701–1050 mg									
Badawy et al ³²	11.5	2.3	19	13	2.9	19	2.1%	-1.50 (-3.16, 0.16)	1
Deniz et al ⁴⁷	22.2	11.9	25	25.6	10.5	26	1.5%	-3.40 (-9.57, 2.77)	T
Ghai et al ³⁰ Kim et al ⁷⁵	5.44	1.56	30	4.28	1.87	30	2.1%	-1.16 (0.29, 2.03)	<u> </u>
Lunn et al ⁵	35.0 45.4	20.0	92	33.5 50.2	20.1 41.4	20	0.6%	2.30 (-12.19, 10.79) -4.80 (-21.54, 11.94)	-+-
Marashi et al ⁸⁴	18.3	15.6	22	65.7	31	22	0.6%	-47.40 (-61.90, -32.90)	<u> </u>
Prabhakar et al ¹⁰⁹	23.8	5	10	20.04	2.09	10	1.9%	3.76 (0.40, 7.12)	A
Subtotal (95% CI)	C 00. Chi2-EE	04 46-0	219	0001) 12-000/		156	9.4%	-2.61 (-6.58, 1.35)	1
Test for overall effect:	Z=1.29 (p=0.20	24, <i>ui</i> -0))	(p<0.0i	5001), 7 -69%)				
3 3 4 >1050 mg									
Abdelmageed et al ²⁶	6.6	13	30	12.2	11	30	2 1%	-5 60 (-6 21 -4 99)	
Al-Mujadi et al ²⁹	15.2	7.6	35	29.5	9	37	1.8%	-14.30 (-18.14, -10.46)	-
Bekawi et al ³⁸	0	2.2	30	7.5	0.7	32	2.1%	-7.50 (-8.32, -6.68)	•
Brogly et al ⁴¹	0	1.48	22	0	4.4	21	2.0%	0.00 (-1.98, 1.98)	I
Dierking et al**	43	23.7	40	63	25.9	40	0.9%	-20.00 (-30.88, -9.12)	
Durmus et al ⁵¹	39.9	33 10	30	42.7	36.1	29	0.5%	-2.00 (-20.47, 14.07)	-
Fassoulaki et al53	23.8	5	25	23.2	5.8	25	1.9%	0.60 (-2.40, 3.60)	t
Fassoulaki et al54	20.3	7.9	29	25.7	11.2	30	1.7%	-5.40 (-10.33, -0.47)	
Fassoulaki et al ⁵⁵	22	2.9	30	35	4.8	30	2.0%	–13.00 (–15.01, –10.99)	· .
Gilron et al ⁶⁰	1.2	0.29	25	5.2	2.8	25	2.1%	-4.00 (-5.10, -2.90)	
Grosen et al ⁶²	56.78	32.41	23	82.11 17.92	40.Z	24 52	0.3%	-25.33 (-48.72, -1.94) -6.72 (-15.41 1.97)	
Hout et al ⁶⁶	2.36	21.02	23	2.65	23.55	28	2.1%	-0.29 (-1.85, 1.27)	t
Joseph et al68	38.65	18.04	25	44.29	16.02	25	1.1%	-5.64 (-15.10, 3.82)	
Khan et al ⁷²	13.21	4.71	34	24.31	9.28	35	1.9%	-11.10 (-14.56, -7.64)	
Lunn et al ⁵ a	25.9	8.3	29	44	11	31	1.7%	-18.10 (-23.01, -13.19)	
Ménigaux et al ⁸⁷	46.2	41.1	91 20	5U.5 20	41.4 10	29	1.0%	-4.30 (-21.57, 12.97) 1 00 (-8.85, 10.85)	+
Omran et al98	∠ı 23.9	26	20	20 31.5	278	20	2.1%	-7.60 (-9.096.11)	•
Sen et al ¹²¹	31	12	20	48	17	20	1.1%	-17.00 (-26.12, -7.88)	
Sen et al ¹²²	20	11.5	30	28	11.5	29	1.6%	-8.00 (-13.87, -2.13)	
oyai ei al™ Turan et al ¹²	40.2	35.2	30	46.7	35.8	30	0.5%	-6.50 (-24.47, 11.47)	
Turan et al ¹³¹	27.04	14.44 8 0	25	41.96	8.36 10.0	25	1.5%	-14.92 (-21.46, -8.38) -26 50 (-32 02 -20 08)	-
Ucak et al ¹³⁵	10.3	5.38	20 20	42.8 14 94	7.25	25 20	1.8%	-5.04 (-9.00 -1.08)	-1
Ozgencil et al ¹⁰⁰	29.47	9.64	30	37.33	9.5	30	1.7%	-7.86 (-12.70, -3.02)	T
Subtotal (95% Cl)	E 0E, 0H ² 000		823	000041 12 -	20/	772	40.5 %	-8.98 (-10.85, -7.10)	'
Heterogeneity: Tau ² =1 Test for overall effect:	ວ.95; Chi²=36(Z=9.38 (ກ<0 ∩).74, df=2 2001)	α (p<0	1.00001); / ² =9:	5%				
	2.20 (2.00)	,							
Iotal (95% Cl) Heterogeneity: Tau ² -2	3 83. Chi2=24)8 40 <i>AF</i> -	2553 64 (n-	0 000011. 12-0	97%	2298	100.0%	-7.06 (-8.46, -5.66)	
Test for overall effect:	Z=9.90 (p<0.00	2001)	24 (p<	5.55550 r J, r =					-50 -25 0 25 50
Test for subgroup diffe	rences: Chi2=1	9.30 df=3	3 (<i>p</i> =0.	002), / ² =84.5	%				Gabapentin Control

Figure 3 Forest plot of 24-hour morphine consumption from all trials estimates regardless of bias evaluation. **Abbreviations:** *df*, degrees of freedom; CI, confidence interval; SD, standard deviation; IV, inverse variance.

	Gabape	entin	Contr	rol		Peto's odds ratio		Peto's odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, fixed, 95% C		Peto, fixed, 95% Cl
3.4.1 0–350 mg Short et al ⁹	0	42	0	21		Not estimable		
Waikakul et al ¹⁴⁰	Ő	26	0	24		Not estimable		
Subtotal (95% CI)		68		45		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not applie	cable						
3.4.2 351–700 mg								
Kinney et al ⁷⁶	4	57	5	63	25.0%	0.88 (0.23, 3.40)		
Paul et al ¹⁰⁷	0	52	0	49		Not estimable		
Short et al ^{9a}	0	42	0	21		Not estimable		
Srivastava et al ¹²⁸	0	60	0	60	05.00/	Not estimable		
Subtotal (95% CI)		211		193	25.0%	0.88 (0.23, 3.40)		
Total events	4		5					
Heterogeneity: not ap	plicable							
Test for overall effect:	Z=0.19 (µ)= 0.85)						
3.4.4 701–1050 mg								
Lunn et al ⁵	2	92	1	29	6.4%	0.59 (0.04, 8.59)		
Subtotal (95% CI)		92		29	6.4%	0.59 (0.04, 8.59)		
Total events	. 2		1					
Heterogeneity: not ap	plicable							
lest for overall effect:	Z=0.38 (p	p=0.70)						
3.4.5 >1050 mg								
Brogly et al ⁴¹	0	22	0	21		Not estimable		_
Grosen et al ⁵²	13	52	8	52	50.5%	1.81 (0.70, 4.68)		
Lunn et al ^{3a}	6	91 165	1	49	18.2%	2.59 (0.53, 12.67)		
Subtotal (95% CI)	10	105	0	122	00.0%	1.99 (0.66, 4.50)		
	19	(9	,				
Test for overall effect:	Z=1.65 (p	(<i>p</i> =0.7) (p=0.10)	0); 12=0%	0				
Total (95% CI)		536		389	100.0%	1.50 (0.76, 2.95)		•
Total events	25		15					-
Heterogeneity: Chi ² =1	.67, df=3	(p=0.6	64); /2=0%	6			H	· · · · · · · · · · · · · · · · · · ·
	7=1 17 (r	= 0.24					0.01 0.	1 1 10 100

Figure 4 Forest plot of the odds of serious adverse events from trials with overall low risk of bias. **Abbreviations:** *df*, degrees of freedom; Cl, confidence interval.

Acknowledgments

These are post hoc subgroup analyses from a systematic review with meta-analyses and trial sequential analyses: Fabritius ML, Geisler A, Hansen MS, Nikolajsen L, Hamunen K, Kontinen V, Wetterslev J, Dahl JB, Mathiesen O. Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiol Scand*. 2016;60:1188–1208.

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interpretation of data, have revised the article critically for important intellectual content, and have given their final approval of the version to be published. All authors have agreed to be accountable for all aspects of the work.

Figure 5 Forest plot of the odds of serious adverse events from all trials estimates, regardless of bias evaluation. **Abbreviation:** *df*, degrees of freedom.

Author contributions

All authors meet the criteria, ICMJE recommendations for authorship and have made substantial contributions to conception and design, acquisition of data, or analysis and

	Gabapen	tin	Contro	ol		Peto's odds ratio	Peto's odds ratio
Study or subgroup	Events -	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
3 6 1 0–350 mg							
Lichtinger et al ⁸¹	0	20	0	20		Not estimable	
Short of al9	0	12	0	21		Not estimable	
	0	26	0	40		Not estimable	
	0	08	0	40 81		Not estimable	
Subtotal (95% CI)	0	50	0	01		Not Cotimabic	
Iotal events	0		0				
Heterogeneity: Not appli	icable						
Test for overall effect: No	ot applicabl	le					
0.0.0.051.700							
3.6.2 351–700 mg							
Ajori et al ²⁷	0	69	0	69		Not estimable	
Kavitha et al ⁶⁹	0	28	0	28		Not estimable	
Kinney et al ⁷⁶	4	57	5	63	15.2%	0.88 (0.23, 3.40)	
Paul et al ¹⁰⁷	0	52	0	49		Not estimable	
Short et al ^{9a}	0	42	0	21		Not estimable	
Srivastava et al ¹²⁸	0	60	0	60		Not estimable	
Waikakul et al ¹⁴⁰	0	26	Ō	24		Not estimable	
Zaldivar Ramirez et al ¹⁴	2 0	18	Õ	16		Not estimable	
Subtotal (95% CI)	-	352	-	330	15.2%	0.88 (0.23, 3.40)	
Total events	4		5				
Heterogeneity: Not appli	icable		U				
Test for overall effect: 7-	-0.10(n-0)	85)					
Test for overall effect. 2-	-0.19 (p=0.	.05)					
3 6 3 701_1050 mg							
Lupp of al5	2	റാ	1	20	2 00/		
	2	92	1	29	3.9%	0.59 (0.04, 8.59)	-
Prabnakar et al ¹⁰⁹	0	20	0	20		Not estimable	
Rajendran et al ¹¹²	0	142	0	30	3 0%		
Subtotal (95% CI)	•	142		19	3.9%	0.59 (0.04, 6.59)	
Total events	2		1				
Heterogeneity: Not appli	icable						
Test for overall effect: Z=	=0.38 (<i>p</i> =0.	.70)					
2.0.4 > 1050 mm							
3.6.4 >1050 mg							
Bartholdy et al ³⁵	7	38	3	38	16.0%	2.48 (0.66, 9.30)	
Brogly et al41	0	22	0	21		Not estimable	
Dierking et al ⁴⁸	0	39	0	32		Not estimable	
Dirks et al ⁴⁹	0	31	0	34		Not estimable	
Fassoulaki et al ⁵³	0	25	0	25		Not estimable	
Fassoulaki et al ⁵⁴	0	30	0	30		Not estimable	
Gilron et al ⁶⁰	1	20	2	22	5.2%	0.55 (0.05, 5.59)	
Grosen et al ⁶²	13	52	8	52	30.7%	1.81 (0.70, 4.68)	+
Hout et al ⁶⁶	1	28	0	28	1.8%	7.39 (0.15, 372.38)	
Khan et al ⁷²	0	34	Õ	35		Not estimable	
Lunn et al ^{5a}	6	91	1	29	8.8%	1.76 (0.30, 10.42)	
Pathak et al ¹⁰⁶	0 0	40	0	40	5.070	Not estimable	
Ucak et al ¹³⁵	7	20	11	20	18 4%	0.45 (0.13, 1.56)	_ _
Subtotal (95% CI)	1	470		406	80.9%	1 34 (0 75 2 41)	-
Total events	35		25		00.070	1.01 (0.10, 2.41)	
Hotorogonoity: Chi?-E E	30 7 df-5/r-	-0 25	2J				
Test for overall officet: 7-	-0 08 (n-0	-0.30) 331	1. 14-10%				
rest for overall effect: Z=	-0.90 (p=0.	.33)					
Total (95% CI)	4	1062		896	100.0%	1 22 (0 72 2 06)	
Total events	11	1002	21	000	100.070		
Hotorogonoity: Chi2-6 4	41 7 df-7 /r-	0 5 2	ن ان /۱۵–۱۷				
Toot for overall offects 7	-0 72 (n=0	-0.3Z) 471	1.10%				0.01 0.1 1 10 100
Test for overall effect: Z=	-0.13 (p=0.	.47)		0.74	12 001		
lest for subgroup differe	ences: Chi ²	=6.17	', dt=2 (p=	=0.74)	: /2=0%		Favors gabapentin Favors control

Disclosure

The authors report no conflicts of interest in this work.

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