ANESTHESIOLOGY

Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain

A Systematic Review and Meta-analysis

Michael Verret, M.D., M.Sc., François Lauzier, M.D., M.Sc., Ryan Zarychanski, M.D., M.Sc., Caroline Perron, M.Sc., Xavier Savard, M.D. candidate, Anne-Marie Pinard, M.D., M.Sc., Guillaume Leblanc, M.D., M.Sc., Marie-Joëlle Cossi, Ph.D., Xavier Neveu, M.Sc., Alexis F. Turgeon, M.D., M.Sc., and the Canadian Perioperative Anesthesia Clinical Trials (PACT) Group*

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Gabapentinoids such as gabapentin and pregabalin are often included in perioperative multimodal analgesia regimens in an attempt to reduce acute, subacute, and chronic pain after surgery
- Current American Pain Society and European Society of Regional Anaesthesia and Pain Therapy guidelines offer conflicting recommendations for the use of gabapentinoids in the perioperative period

What This Article Tells Us That Is New

- In a meta-analysis of 281 randomized controlled trials comparing gabapentinoids with controls, no clinically meaningful difference in acute, subacute, or chronic pain was observed
- Although the risk of postoperative nausea and vomiting was slightly lower, adverse events of dizziness and visual disturbance were greater with gabapentinoids use

ABSTRACT

Background: Widely used for acute pain management, the clinical benefit from perioperative use of gabapentinoids is uncertain. The aim of this systematic review was to assess the analgesic effect and adverse events with the perioperative use of gabapentinoids in adult patients.

Methods: Randomized controlled trials studying the use of gabapentinoids in adult patients undergoing surgery were included. The primary outcome was the intensity of postoperative acute pain. Secondary outcomes included the intensity of postoperative subacute pain, incidence of postoperative chronic pain, cumulative opioid use, persistent opioid use, lengths of stay, and adverse events. The clinical significance of the summary estimates was assessed based on established thresholds for minimally important differences.

Results: In total, 281 trials (N = 24,682 participants) were included in this meta-analysis. Compared with controls, gabapentinoids were associated with a lower postoperative pain intensity (100-point scale) at 6 h (mean difference, −10; 95% CI, −12 to −9), 12 h (mean difference, −9; 95% CI, −10 to −7), 24 h (mean difference, −7; 95% CI, −8 to −6), and 48 h (mean difference, −3; 95% CI, −5 to −1). This effect was not clinically significant ranging below the minimally important difference (10 points out of 100) for each time point. These results were consistent regardless of the type of drug (gabapentin or pregabalin). No effect was observed on pain intensity at 72 h, subacute and chronic pain. The use of gabapentinoids was associated with a lower risk of postoperative nausea and vomiting but with more dizziness and visual disturbance.

Conclusions: No clinically significant analgesic effect for the perioperative use of gabapentinoids was observed. There was also no effect on the prevention of postoperative chronic pain and a greater risk of adverse events. These results do not support the routine use of pregabalin or gabapentin for the management of postoperative pain in adult patients.

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Gabapentinoids, a class of drugs including gabapentin and pregabalin, were originally marketed in the 1990s for use as anticonvulsants and subsequently approved to treat specific chronic neuropathic pain conditions.[1–5] Over the last decade, the off-label use of gabapentinoids for the control of acute nociceptive or neuropathic pain has drastically increased in several countries,[6–8] and they are now routinely used for the management of postoperative analgesia to decrease pain and opioid use.[9–14] However, scientific data supporting the increased use are divergent, which may reflect clinical agnosticism rather than new evidence of clinical effectiveness.[15–21]

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 251. This article has a related Infographic on p. 17A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version.

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*Members of the Canadian Perioperative Anesthesia Clinical Trials (PACT) Group are listed in the appendix.

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Recommendations concerning the use of gabapentinoids for the management of postoperative pain are inconsistent. The American Pain Society (Glenview, Illinois) supports the perioperative use of gabapentinoids, while the European Society of Regional Anaesthesia and Pain Therapy (Geneva, Switzerland) does not.[22,23] Previous systematic reviews have weaknesses. First, most were designed to look at specific surgical populations[24–33] with often a limited sampling frame or a specific type of drugs[34–40] when pregabalin and gabapentin share the same mechanism of action and comparable pharmacologic properties.[41,42] Second, the concept of minimally important difference[43] for pain intensity was never considered in previous work, neither was the statistical reliability of the findings quantified.[44] Third, search strategies were not always exhaustive, and additional trials have been conducted since the publication of the more recent systematic reviews.[35–37] These methodologic limitations led to conflicting results, as well as suboptimal conclusions and strength of the evidence. Recently, health authorities have raised serious concerns about potential adverse events (risk of abuse and respiratory depression) and net clinical benefit of gabapentinoids.[16,45–52] Despite all this, the off-label use of gabapentinoids is still increasing worldwide.[6–8,15,16,45–53] This systematic review with meta-analysis of randomized controlled trials was performed to evaluate the analgesic effect and adverse events of perioperative use of gabapentinoids in adult surgical patients.

Materials and Methods

Study Design

This systematic review and meta-analysis was conducted following the recommendations of the Cochrane Handbook for Systematic Reviews and Meta Analyses, and our results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[54] The protocol was registered in PROSPERO-CRD42017067029 (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017067029) and previously published.[55]

Search Strategy

The search strategy was developed using the Medline (Ovid), EMBASE (Embase), Cochrane Central Register of Controlled Trials, and Web of Science databases (from their inception to January 2018). Clinical Trials.gov database was also searched. The search strategy was developed with an information specialist and validated according to the Peer Review of Electronic Search Strategies (PRESS) 2015 guidelines.[56] The Medline search strategy is presented in online supplements (Supplemental Digital Content 1, efig. 1, http://links.lww.com/ALN/C409). Data from unpublished clinical trial reports that were released to the public after litigation in the United States and bibliographies of included trials were also reviewed to retrieve pertinent publications.[57]

Eligibility Criteria

Randomized controlled trials comparing gabapentinoids to placebo, any other analgesic regimen, or usual care were included. Trials performed in adults (defined as 18 yr of age and older for at least 80% of the study population) undergoing elective or emergent surgery under any type of anesthesia were considered. Included trials had to evaluate gabapentinoids (pregabalin or gabapentin) initiated between 1 week before and 12 h after surgery. At least one outcome measure had to be assessed to be considered for inclusion. No restriction was used for language or type of publication. Trials were excluded when the comparator was regional analgesia (neuraxial or peripheral) and when participants were already taking gabapentinoids for another condition.

Outcome Measures

The coprimary outcomes were postoperative acute pain at 6, 12, 24, 48, and 72 h after surgery measured by any quantitative pain scale.[58] Secondary outcomes were postoperative subacute pain (defined as pain intensity during postoperative weeks 4 to 12); incidence of postoperative chronic pain (defined as pain lasting for 3 months or more); cumulative dose of opioids administered within 24, 48, and 72 h after surgery; persistent opioid use (defined as more than 60 days of opioid utilization during postoperative days 90 to 365); lengths of stay (postanesthesia care unit, day care unit, intensive care unit, and hospital); and incidence of adverse events such as dizziness, fall or ataxia, delirium, drug addiction or abuse, visual disturbance, respiratory failure, opioid-related adverse events (Opioid-Related Symptom Distress Scale), and postoperative nausea or vomiting.[59,60]

Study Selection and Data Extraction

Three reviewers (M.V., X.S., and F.C.) independently assessed trials (screened titles, abstracts, and full publications) for eligibility and extracted data using a standardized and piloted data extraction form. Disagreements were resolved by a fourth reviewer (A.F.T.). The authors were contacted when information to be extracted was missing. Duplicate citations were removed.

For each trial, data extraction included study characteristics (year, country, sample size, duration of study, sources and types of funding, and conflict of interest), participant demographic and surgical procedure information (age, sex, prior chronic use of opioids and dependence, preoperative pain, type of surgery and anesthesia [local/sedation *vs.* regional *vs.* general anesthesia], and surgery setting [ambulatory *vs.* in-hospital]), intervention and comparator details (drug names, timing of the first dose, and dosage regimen), coanalgesia characteristics (type and regimen), and duration of the follow-up. Information about trial methodologic

quality and summary estimates of the outcome measures were also extracted. When the data were only available in a diagram or graphic format, the information was extracted using an open-access software (WebPlotDigitizer 4.1).[61] Publications written in languages other than English were translated by a healthcare professional fluent in the language of interest or using an online translator.[62–64]

Risk of Bias Assessment

The risk of bias of included trials was evaluated using the Cochrane's risk of bias tool.[65] Two reviewers (M.V. and X.S.) independently assessed the risk of bias for each included trial, and a third reviewer (A.F.T.) was consulted in case of disagreement. The overall methodologic quality of each trial was reported using the worst score obtained across the seven domains.

Data Synthesis and Statistical Analyses

Pain intensity measurement scores were collected using a scale from 0 (no pain) to 100 (worst imaginable pain) points. When scores were not presented in a 100-point scale format, they were converted (mean and SD) using the appropriate ratio.[43] The minimal clinically important difference between groups for acute pain intensity has been established to be 10 points on a 100-point scale[66] and is independent of pain severity.[67] A difference of 20 to 30 points represents an "appreciable" analgesic effect, while a 50-point difference represents a "substantial" effect.[43,68] For comparison of opioid administration, all doses of opioids were converted into intravenous milligrams of morphine equivalents using data from recent recommendations.[69] Intravenous morphine was assumed to be twice as potent as oral morphine administration.

The analyses were conducted with Review Manager, version 5.3.5 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) using random-effects models and the Mantel–Haenszel method for dichotomous data and the inverse variance method for continuous data. Pooled continuous data are presented as mean differences, and pooled dichotomous data are presented as risk ratios with a 95% CI. The presence of statistical heterogeneity was assessed with the I^2 statistic. An I^2 greater than 50% was considered to represent substantial heterogeneity.[54] Subgroup and sensitivity analyses were defined *a priori* to evaluate known or potential sources of heterogeneity.[70–72] The subgroup analyses were the type of funding, the type of drug (pregabalin *vs.* gabapentin), the dosage regimen (high dose [at least 300 mg/day for pregabalin and at least 900 mg/day for gabapentin] *vs.* low dose [less than 300 mg/day for pregabalin and less than 900 mg/day for gabapentin]), the postoperative care pathway (inpatient *vs.* ambulatory), use with regular opioids (rather than on demand), and the risk of bias. Additional exploratory subgroup analyses were performed on postoperative acute pain at the 12-h assessment. Sources of heterogeneity were interpreted through the overall and subgroup I^2 statistic and with the test for subgroup differences.[73] The potential presence of publication bias was explored using funnel plots when 10 or more trials were reported for a given outcome. To evaluate the clinical significance of the analgesic effect, the probability of experiencing an effect greater than the minimally important difference (10 of 100 points) in the gabapentinoids group was compared with the control group using risk difference.[74–76] Sensitivity analyses were carried out for an appreciable (20 to 30 of 100) and substantial (50 of 100) difference in pain intensity in accordance with the method favored by the Outcome Measures in Rheumatology (OMERACT) group.[43]

Strength of Evidence and Trial Sequential Analysis

The strength of evidence was evaluated for each outcome according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group statement using the GRADEpro guideline development tool (McMaster University, 2015, developed by Evidence Prime, Inc., Canada).[44] The GRADE approach involved grading the quality of the evidence on a continuum from high, moderate, low, or very low for each outcome based on a structured approach. This grading was performed in duplicate independently by two reviewers (M.V. and X.S.). To limit a potential type 1 error and inform future research, a trial sequential analysis was performed on our primary outcome using the TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark, 2011).[77,78] The available data were used to calculate the required information size and the O'Brien–Fleming α-spending boundaries function to calculate the cumulative Z-score. All calculations were based on 5% α and 80% power with a two-tailed test.

Results

Study Identification and Selection

We identified 6,795 citations from our search strategy, from which 322 trials (N = 28,465 participants) met our inclusion criteria and were included in our systematic review. Of these, 281 trials (N = 24,682 participants) reported quantitative data and could therefore be included in our meta-analysis (fig. 1). None of the unpublished trials were eligible for inclusion (research reports 720-04378, 720-04455, 720-04471, and 720-04483).[57]

Trial Characteristics

Of the 322 trials included in this systematic review, most trials were written in English, while four were written in Persian,[79–82] five in Turkish,[83–87] one in Polish,[88] two in Korean,[89,90] two in Spanish,[91,92] and one in French.[93] The source of funding was not mentioned for 58% of the trials (187 trials; 15,019 participants) and came from the pharmaceutical industry for 7% of trials (22 trials; 2,873 participants).

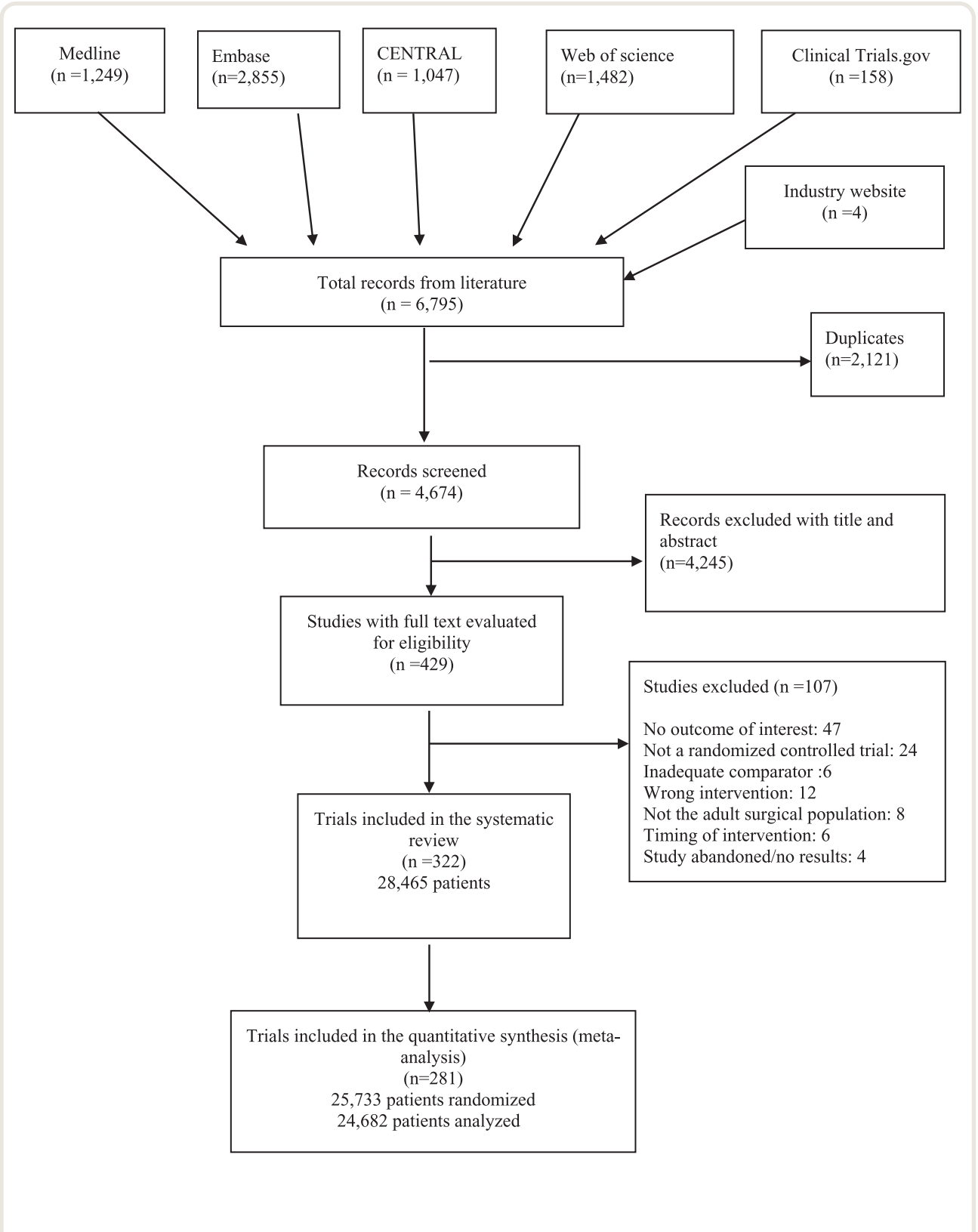

Fig. 1. Flow diagram of trials

In this 281-trial meta-analysis, 27% (73 trials; 6,549 participants) were performed in patients undergoing orthopedic or spinal surgeries; 23% (64 trials; 5,589 participants) were performed in patients undergoing nonendoscopic abdominal surgeries; 15% (39 trials; 3,758 participants) were performed in patients undergoing endoscopic abdominal surgeries; 10% (32 trials; 2,431 participants) were performed in patients undergoing ophthalmologic, maxillofacial, oral, and ear, nose and throat surgeries; 7% (24 trials; 1,686 participants) were performed in patients undergoing plastic, peripheral vascular or breast surgeries; 6% (23 trials; 1,512 participants) were performed in patients undergoing thoracic or cardiac surgeries; 1% (2 trials; 173 participants) were performed in neurosurgeries; and 10% (24 trials; 2,564 participants) were performed in patients undergoing miscellaneous types of surgeries (Supplemental Digital Content 2, etable 1, http://links.lww.com/ALN/C410). Of all the eligible trials, 52% of trials evaluated gabapentin (146 trials; 5,800 participants), 43% of trials evaluated pregabalin (122 trials; 4,228 participants), and 5% evaluated both drugs (13 trials; 421 participants). Only 6% of the trials (18 trials; 1,403 participants) were presented only in abstract form. Gabapentinoids were administered as a single dose in 68% of trials (192 trials; 15,189 participants), while multiple doses were administered in 31% of trials (87 trials; 9,333 participants). Gabapentinoids were administered before surgery in 71% of trials (198 trials; 15,675 participants), after surgery in 4% of trials (12 trials; 806 participants), and at both time periods in 25% of trials (71 trials; 8,201 participants; Supplemental Digital Content 2, etable 1, http://links.lww.com/ALN/C410). Regarding the type of coanalgesia, regional analgesia was used in 9% of trials (25 trials; 2,408 participants), regional analgesia was not used in 84% of trials (236 trials; 20,470 participants), and in 7% of trials (20 trials; 1,804 participants) the information was not mentioned. Four trials included only patients with a previous diagnosis of chronic pain condition.[94–97] The authors' responses contributed to the data on pain,[98] delirium,[99] and ataxia.[100]

Risk of Bias Assessment

The overall risk of bias was unclear for 62% of trials (n = 174 of 281), low for 11% of trials (n = 32 of 281), and high for 27% of trials (n = 75 of 281) included in our meta-analysis (Supplemental Digital Content 3, etable 2, http://links.lww.com/ALN/C411). For blinded assessment of postoperative acute pain at any time point, 46% of the trials (n = 79 of 173) were at high or unclear risk of bias (Supplemental Digital Content 4, efig. 2, http://links.lww.com/ALN/C412).

Primary Outcome: Postoperative Acute Pain Intensity at 6, 12, 24, 48, and 72 h

A slightly lower postoperative pain intensity was observed at 6, 12, 24, and 48 h with gabapentinoids administration but not at 72 h (table 1 and Supplemental Digital Content 4, efigs. 3 to 7, http://links.lww.com/ALN/C412). This effect was not clinically significant ranging below the minimally important difference (10 points out of 100) for each time point. The effect was not different with the type of drugs (gabapentin or pregabalin; table 2) and was consistent for all subgroup analyses. Trials at low risk of bias showed consistently no effect or a smaller effect on pain intensity compared with trials at high or unclear risk of bias (Supplemental Digital Content 5, etables 3 to 7 and 22, http://links.lww.com/ALN/C413). There was a significant statistical heterogeneity between trials, which was partly attributable to the type of coanalgesia (regional analgesia *vs.* not) and the risk of bias (low *vs.* high or unclear). The timing of the intervention (preoperative *vs.* postoperative), the type of pain assessment (at rest *vs.* dynamic), the dosage regimen, and the type of comparator (analgesic effect *vs.* no analgesic effect *vs.* both) were not identified as factors contributing to the heterogeneity. In an exploratory analysis, additional subgroup analyses showed consistent findings, including surgeries potentially associated with pronociceptive mechanisms. Gabapentinoids were associated with a slightly greater probability of experiencing an analgesic effect of more than 10 points out of 100 of their postoperative pain scores at 6, 12, and 24 h, but no significant difference was found at 48 and 72 h (table 3). The proportion of participants achieving an effect greater than 20 points out of 100 of their pain scores was small and limited to the very early phase and absent for an effect greater than 30 points out of 100, the definition used for what is considered an appreciable analgesic effect. No difference in the probability of experiencing substantial analgesic effect was observed in any subgroups (table 3).

Secondary Outcomes

Postoperative Subacute Pain Intensity (between 4 and 12 Weeks Postoperative). A slightly lower postoperative subacute pain intensity was observed (mean difference, −6; 95% CI, −9 to −3; I^2 = 98%; 18 trials; 1,392 participants) with gabapentinoids use (table 1 and Supplemental Digital Content 4, efig. 8, http://links.lww.com/ALN/C412). This effect was also not clinically significant. The observed statistical heterogeneity was not explained by the type of drug (gabapentin or pregabalin; Supplemental Digital Content 5, etable 8, http://links.lww.com/ALN/C413).

Incidence of Postoperative Chronic Pain (between 3 and 12 Months Postoperative). Gabatentinoids were not associated with the risk of development of postoperative chronic pain (risk ratio, 0.89; 95% CI, 0.74 to 1.07; I^2 = 42%; 27 trials; 3,198 participants). The results were consistent according to the type of drug (pregabalin *vs.* gabapentin), the dosage regimen, and whether single or multiple administrations were given (table 1 and Supplemental Digital Content 5, etable 9, http://links.lww.com/ALN/C413).

Cumulative Dose of Opioids Administered within 24, 48, and 72 h after Surgery. The amount of opioids administered (intravenous morphine equivalent) at 24 h was slightly lower

Table 1. Summary Estimates from Meta-analyses with the Assessment of the Statistical Heterogeneity and the Quality of the Evidence

Outcomes	Number of Trials	Number of Patients: Gabapentinoids	Number of Patients: Control	Summary Estimate: Mean Difference or Risk Ratio [95% CI]	I^2, %	Quality of the Evidence: Grades of Recommendation, Assessment, Development, and Evaluation Rating
Postoperative acute pain (100-point scale)*						
6 h	129	5,499	4,710	−10 [−12 to −9]	91	Low†
12 h	130	5,871	5,198	−9 [−10 to −7]	90	Low†
24 h	141	6,593	5,481	−7 [−8 to −6]	88	Low†
48 h	59	3,434	2,778	−3 [−5 to −1]	88	Low†
72 h	32	2,410	1,724	−2 [−4 to 0]	76	Low†
Postoperative subacute pain (100-point scale)	18	650	642	−6 [−9 to −3]	98	Low‡
Postoperative chronic pain	27	1,767	1,431	0.89 [0.74 to 1.07]	42	Moderate§
Postoperative opioid administration, mg of IV morphine equivalent‖						
24 h	117	4,807	4,253	−7.90 [−8.82 to −6.98]	98	Very low#
48 h	24	808	692	−9.79 [−12.81 to −6.78]	93	Very low#
72 h	4	200	173	−29.18 [−46.89 to −11.47]	94	Very low#
Length of stay (h)						
Postanesthesia care unit	10	512	383	−0.01 [−0.09 to 0.07]	73	Low†
Intensive care unit	6	184	184	0.14 [−3.49 to 3.78]	0	Low†
Hospital	17	1,359	1,104	2.96 [0.28 to 5.63]	62	Moderate§
Adverse events						
Ataxia or fall	14	1,228	1,107	1.31 [0.88 to 1.95]	40	Moderate**
Delirium	4	452	454	1.12 [0.85 to 1.47]	0	Low††
Visual disturbance	54	2,494	2,143	1.89 [1.53 to 2.33]	0	Moderate‡‡
Respiratory depression	42	2,251	2,108	0.79 [0.46 to 1.35]	0	Low§§
Nausea and/or vomiting	187	9,337	7,808	0.77 [0.72 to 0.82]	44	Moderate‡‡
Dizziness	134	6,645	5,409	1.25 [1.12 to 1.39]	39	Low‖‖

*Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h. †One level for potential risk of bias and one level for inconsistency. ‡One level for inconsistency and one level for imprecision. §One level for potential publication bias. ‖Intervals considered for the time point: 24 h, 0 to 24 h; 48 h, 0 to 48 h; and 72 h, 0 to 72 h. #One level for potential risk of bias, one level for indirectness, one level for inconsistency, and one level for potential publication bias. **One level for imprecision. ††Two levels for imprecision. ‡‡One level for potential risk of bias. §§One level for potential risk of bias and one level for imprecision. ‖‖One level for potential risk of bias and one level for potential publication bias.

(mean difference, −7.90 mg; 95% CI, −8.82 to −6.98; I^2 = 98%; 117 trials; 9,060 participants) with the use of gabapentinoids. The mean dose of intravenous morphine equivalent administered in the gabapentinoids group was 25.3 mg compared with 32.6 mg in the control group. Slightly less opioid use was also observed at 48 h (24 trials) and 72 h (4 trials; table 1). For pregabalin, the level of evidence was very low, and one trial reported the use of opioids at 72 h (mean difference, −48.60 mg; 95% CI, −56.39 to −40.81; 80 participants). Statistical heterogeneity between trials was explained mainly by the risk of bias and the type of funding (Supplemental Digital Content 5, etables 10 to 12, http://links.lww.com/ALN/C413).

Persistent Opioid Use. One trial evaluated the risk of persistent opioid use associated with gabapentin *versus* placebo and found no effect (odds ratio, 1.28; 95% CI, 0.28 to 5.87; 410 participants).[101]

Postoperative Lengths of Stay. Gabapentinoids were associated with a longer hospital length of stay (mean difference, 2.96 h; 95% CI, 0.28 to 5.63; I^2 = 62%; 17 trials; 2,463 participants; Supplemental Digital Content 5, etable 13, http://links.lww.com/ALN/C413), but no difference was observed for the length of stay in the intensive care unit or in the postoperative care unit (Supplemental Digital Content 5, etables 13 to 15, http://links.lww.com/ALN/C413).

Adverse Effects. The perioperative use of gabapentinoids was associated with less postoperative nausea and vomiting (risk ratio, 0.77; 95% CI, 0.72 to 0.82; I^2 = 44%; 187 trials; 17,145 participants; Supplemental Digital Content 5, etable 16, http://links.lww.com/ALN/C413). Gabapentinoids were also associated with a greater incidence of dizziness (risk ratio, 1.25; 95% CI, 1.13 to 1.39; I^2 = 39%; 134 trials; 12,054 participants; Supplemental Digital Content 5, etable 17, http://links.lww.com/ALN/C413) and visual disturbance (risk ratio, 1.89; 95% CI, 1.53 to 2.33; I^2 = 0%; 54 trials; 4,637 participants; Supplemental Digital Content 5, etable 18, http://links.lww.com/ALN/C413). Dizziness and visual disturbance were more frequent with pregabalin than with gabapentin (Supplemental Digital Content,

Table 2. Summary Estimates from Meta-analyses with the Assessment of the Statistical Heterogeneity: Subgroup Analyses for the Type of Drug (Gabapentin and Pregabalin)

	Gabapentin				Pregabalin			
Outcomes	Number of Trials	Number of Patients	Summary Estimate (Mean Difference or Risk Ratio [95% CI])	I^2, %	Number of Trials	Number of Patients	Summary Estimate (Mean Difference or Risk Ratio [95% CI])	I^2, %
Postoperative acute pain (100-point scale)*								
6 h	70	5,371	−12 [−15 to −10]	89	56	4,568	−8 [−11 to −6]	92
12 h	71	6,301	−10 [−12 to −8]	83	51	3,988	−8 [−10 to −5]	93
24 h	76	6,355	−7 [−9 to −6]	83	59	5,169	−6 [−8 to −4]	91
48 h	34	3,578	−3 [−6 to −1]	76	24	2,484	−2 [−6 to 1]	92
72 h	15	1,933	−2 [−5 to 2]	78	16	2,051	−2 [−6 to 1]	75
Postoperative subacute pain (100-point scale)	7	588	−5 [−14 to 3]	99	11	804	−6 [−10 to −1]	94
Postoperative chronic pain	13	1,237	0.94 [0.77 to 1.14]	34	14	1,961	0.77 [0.52 to 1.15]	51
Postoperative opioid administration, mg of IV morphine equivalent†								
24 h	68	5,458	−8.58 [−10.04 to −7.12]	98	42	2,937	−7.09 [−8.30 to −5.88]	96
48 h	12	858	−5.46 [−9.60 to −1.33]	80	12	642	−13.46 [−17.98 to −8.94]	95
72 h	2	203	−5.38 [−17.25 to 6.49]	0	1	80	−48.60 [−56.39 to −40.81]	
Length of stay, h								
Postanesthesia care unit	5	584	−0.03 [−0.17 to 0.10]	45	5	311	0.01 [−0.09 to 0.11]	83
Intensive care unit	1	60	−2.40 [−9.69 to 4.89]		5	308	0.98 [−3.20 to 5.17]	0
Hospital	8	1,165	4.11 [−1.64 to 9.87]	62	9	1,298	1.31 [−1.44 to 4.06]	51
Adverse events								
Ataxia or fall	7	1,582	1.14 [0.80 to 1.62]	51	7	753	1.79 [0.74 to 4.30]	34
Delirium	2	774	1.15 [0.87 to 1.51]	0	2	132	0.26 [0.03 to 2.26]	0
Visual disturbance	15	1,715	1.49 [1.14 to 1.95]	0	37	2,742	2.78 [1.97 to 3.92]	0
Respiratory depression	15	1,850	0.79 [0.30 to 2.10]	0	22	2,059	1.09 [0.50 to 2.39]	0
Nausea and/or vomiting	92	8,248	0.77 [0.70 to 0.85]	40	85	7,919	0.76 [0.69 to 0.84]	43
Dizziness	57	4,914	1.05 [0.95 to 1.16]	0	69	6,420	1.47 [1.25 to 1.74]	52

*Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h. †Intervals considered for the time point: 24 h, 0 to 24 h; 48 h, 0 to 48 h; and 72 h, 0 to 72 h.

etables 17 and 18, http://links.lww.com/ALN/C413). Gabapentinoids were not significantly associated with respiratory failure, ataxia/falls, or delirium (Supplemental Digital Content, etables 19 to 21, http://links.lww.com/ALN/C413). The risk of respiratory failure was not different when gabapentinoids were used with opioids (Supplemental Digital Content, etable 19, http://links.lww.com/ALN/C413). Results from two trials showed no effect of gabapentinoids use on opioid-related adverse events.[102,103] Most of these analyses are based on limited sample size (limited number of studies). No trial evaluated the incidence of drug addiction or abuse.

Publication Bias

Visual analysis of the funnel plots suggested a potential publication bias in the reporting of some outcomes (opioid administration, incidence of postoperative chronic pain, and hospital length of stay; Supplemental Digital Content 6, efigs. 22 to 35, http://links.lww.com/ALN/C414).

Trial Sequential Analysis for Postoperative Acute Pain Assessment

The sample size of this systematic review and meta-analysis was much larger than the required information size, suggesting that further research is not required for postoperative pain at 6, 12, 24, and 48 h (Supplemental Digital Content 6, efigs. 36 to 40, http://links.lww.com/ALN/C433). This was further suggested by the Z-curve crossing the trial sequential boundaries before the required information size.

Post Hoc Analysis

A subgroup analysis was conducted to explore the effect of the trial's country of origin on the results.[104] No statistically significant difference was observed between low- to middle-income countries and high-income countries (Supplemental Digital Content 5, etable 22, http://links.lww.com/ALN/C413). The use of gabapentinoids in the context of surgeries associated with potential pronociceptive pain mechanisms was not associated with a better analgesic effect at 12 h.

Table 3. Risk Difference between Gabapentinoids and Control Group in the Proportion of Participants Achieving a Minimally Important Difference of Postoperative Pain Intensity Score at Different Time Points

Timing of Postoperative Pain Intensity Assessment*	Minimally Important Difference Threshold (100-Point Scale)	Gabapentinoids								
		Overall			Gabapentin			Pregabalin		
		No. of Trials	No. of Patients	Summary Estimate Risk Difference [95% CI]	No. of Trials	No. of Patients	Summary Estimate Risk Difference [95% CI]	No. of Trials	No. of Patients	Summary Estimate Risk Difference [95% CI]
6 h	10	129	10,209	−0.26 [−0.31 to −0.20]	70	5,371	−0.30 [−0.37 to −0.23]	56	4,568	−0.21 [−0.30 to −0.12]
	20	129	10,209	−0.14 [−0.16 to −0.12]	70	5,371	−0.20 [−0.22 to −0.17]	56	4,568	−0.12 [−0.14 to −0.10]
	30	129	10,209	0	70	5,371	−0.00 [−0.01 to −0.00]	56	4,568	0
	50	127	10,080	0	70	5,371	0	54	4,439	0
12 h	10	130	11,069	−0.21 [−0.25 to −0.17]	71	6,301	−0.24 [−0.30 to −0.19]	51	3,988	−0.19 [−0.25 to −0.12]
	20	130	11,069	−0.05 [−0.06 to −0.04]	71	6,301	−0.12 [−0.14 to −0.10]	51	3,988	−0.06 [−0.07 to −0.04]
	30	129	10,995	0	71	6,301	0	50	3,914	0
	50	125	10,700	0	69	6,181	0	48	3,739	0
24 h	10	140	12,024	−0.16 [−0.19 to −0.14]	76	6,355	−0.18 [−0.22 to −0.14]	58	5,119	−0.16 [−0.19 to −0.12]
	20	140	12,024	0	76	6,355	−0.01 [−0.01 to −0.00]	58	5,119	0
	30	138	11,840	0	76	6,355	0	56	4,935	0
	50	134	11,486	0	72	6,001	0	56	4,935	0
48 h	10	59	6,212	−0.07 [−0.11 to −0.04]	34	3,578	−0.06 [−0.11 to −0.01]	24	2,484	−0.09 [−0.16 to −0.02]
	20	58	6,141	−0.00 [−0.01 to 0.00]	34	3,578	−0.01 [−0.03 to 0.01]	23	2,413	−0.02 [−0.04 to 0.01]
	30	58	6,141	0	34	3,578	0	23	2,413	0
	50	56	5,946	0	33	3,443	0	22	2,353	0
72 h	10	32	4,134	−0.05 [−0.09 to −0.01]	15	1,933	−0.05 [−0.12 to 0.02]	16	2,051	−0.05 [−0.10 to 0.01]
	20	32	4,134	−0.00 [−0.02 to 0.01]	15	1,933	−0.00 [−0.02 to 0.01]	16	2,051	−0.01 [−0.03 to 0.01]
	30	32	4,134	0	15	1,933	0	16	2,051	0
	50	30	4,016	0	15	1,933	0	14	1,933	0

*Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h.

Quality of the Evidence

The quality of the evidence for the primary outcome, postoperative acute pain, was low. The GRADE ratings for all outcomes are presented in table 1.

Discussion

No clinically significant difference in self-reported postoperative acute pain with the perioperative use of gabapentinoids was observed in this systematic review of randomized controlled trials. This finding was consistent at every time point of evaluation and regardless of the dosage regimen. Importantly, the results were comparable whether pregabalin or gabapentin was used. The probability of achieving a clinically meaningful postoperative analgesic effect with perioperative use of gabapentinoids was, at best, negligible. The opioid-sparing effect was small, not clinically significant, and associated with a greater incidence of visual disturbance and dizziness. Although a lower risk in postoperative nausea or vomiting was observed, it was not associated with the opioid use. No effect on postoperative subacute pain intensity or on the incidence of postoperative chronic pain was observed. The trial sequential analyses also showed that further trials looking at the analgesic effect of gabapentinoids on postoperative acute pain are very unlikely to provide any new evidence. In addition to the observed adverse events, the risk of postoperative ataxia, delirium, respiratory depression, substance abuse disorder, and persistent opioid use could not be assessed or optimally assessed because of the absence of data, the small number of trials, or the imprecision of the summary effect.

The results of this systematic review are consistent with recently published systematic reviews showing a statistically significant lower pain intensity and opioid administration with perioperative use of gabapentin[36] and pregabalin.[35] However, as opposed to previous work, our study did not consider the type of drugs separately, but rather included trials evaluating the use of gabapentin or pregabalin, because those drugs have comparable pharmacologic properties.[41,42,105] This systematic review was designed to conduct a thorough and accurate evaluation of the potential benefits and harms of these drugs with sufficient power to further prevent type II errors previously observed.[106] More importantly, this work shows that despite a statistical difference, the analgesic effect of the perioperative use of gabapentinoids is not clinically significant, because it does not reach the minimally clinically significant difference (10 of 100). Furthermore, the analgesic effect is negligible or absent when considering appreciable (20 to 30 of 100) or substantial (50 of 100) minimally important difference in

pain intensity. Previous systematic reviews concluding on a favorable effect of gabapentinoids for postoperative analgesic effect did not consider whether these observed differences were clinically significant. In the context of perioperative medicine, the use of different time points for pain assessment may lead to conflicting results in absence of consensus on the best timing for the assessment of acute pain. Recent recommendations suggest using several timings of assessment like the ones used in this systematic review.[66] Such an approach allows avoidance of selective reporting or focusing on a single time point when there is no overall effect.

This study also informs the role of gabapentinoids in the prevention of chronic pain, one of the most frequent justifications for using gabapentinoids in the perioperative period.[6] The results of this study show that gabapentinoids do not seem to be effective to prevent postoperative chronic pain, as opposed to the findings of a previous systematic review.[107] The different results were likely related to the exhaustive search strategy and the rigorous methods used.[108,109] The absence of effect on the incidence of postoperative chronic pain was a consistent observation across trials and highlights the gap between current evidence and bedside practices. The effect of gabapentinoids on hospital length of stay and the risk of addiction were also considered, as opposed to previous works that have not evaluated those outcomes.[110]

The results of this review are not congruent with the American Pain Society recommendation for using gabapentinoids in the perioperative period,[22] as well as other societies suggesting that gabapentinoids may be beneficial in surgery associated with pronociceptive pain.[23,111] These recommendations are based on the results of a systematic review evaluating the perioperative use of pregabalin that included 33 trials.[34] Although interesting, this previous systematic review was designed to look at subgroups based on types of surgeries associated with potential pronociceptive pain mechanisms rather than using these subgroups to explain a potential overall effect. Importantly, the definitions used to classify the types of surgeries were based on clinical experience without any solid evidence to justify a theoretical differential effect depending on the type of surgical pain.[112] These findings were not observed in the exploratory subgroup analyses. In fact, a *post hoc* analysis looking at surgeries associated with potential pronociceptive pain mechanisms using the same models showed no effect modification. Furthermore, no effect was observed when performing a pragmatic evaluation of an effect modification in surgeries associated with a high risk of postoperative chronic pain, as well as for the type of surgery.

This systematic review has several strengths. Standardized recommendations were followed, and an electronic peer review process was used to validate the quality and exhaustiveness of our search strategy. Furthermore, a trial sequential analysis was performed and showed an information size seven times the required information size, which suggests that unnecessary trials were conducted, and no further study is required. Finally, the evaluation of clinically relevant outcomes that should be driving clinical practice combined with the evaluation of the proportion of patients achieving a minimally important difference in their pain score showed no clinically meaningful beneficial effect and potential risk of adverse effects.

One important limitation of this study is the risk of bias of the included trials, thus limiting the quality of the evidence of the findings. It is, however, well established that selective reporting and allocation concealment usually overestimate the benefits of an intervention.[113,114] Also, there is residual statistical heterogeneity in this meta-analyses that was not fully explained by our subgroup analyses. This residual inconsistency between trials could be explained by the relative subjectivity of the assessment of pain control. However, pain intensity is one of the most valid, reliable, and patient-centered outcome available currently used to evaluate patient pain and comfort after surgery.[57] More likely, the very large number of relatively small trials included in this systematic review in the absence of large clinical trials may also explain this statistical although not clinical heterogeneity.

Conclusions

In this systematic review, no clinically significant difference in postoperative acute, subacute, and chronic pain was observed with the perioperative use of gabapentinoids, whether gabapentin or pregabalin was used. Gabapentinoids were also associated with a greater incidence of adverse events, namely dizziness and visual disturbance, while other major adverse events such as respiratory depression and addiction are not reported or are underreported. These results do not support the routine use of gabapentin or pregabalin for the management of postoperative pain in adult patients. Additional trials evaluating the effect of the perioperative use of gabapentinoids on postoperative acute pain intensity are also not required.

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Competing Interests

Dr. Anne-Marie Pinard has received consulting fees from Antibody Healthcare Communications (Toronto, Ontario, Canada). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Turgeon: CHU de Québec - Université Laval Research Center, Population Health and Optimal Health Practices Research Unit, 1401, 18e rue, Québec City, Québec G1J 1Z4, Canada. alexis.turgeon@fmed.ulaval.ca. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix. Members of the Canadian Perioperative Anesthesia Clinical Trials (PACT) Group

Al McAuley, M.D.
Alana Flexman, M.D.
Alexis F. Turgeon, M.D., M.Sc.
André Y. Denault, M.D., Ph.D.
Angela Jerath, M.D.
Christopher Prabhakar, M.D.
Colin McCartney, M.D.
Corey Sawchuk, M.D.
Cynthia Yarnold, M.D.
David Boyle, M.D.
David Mazer, M.D.
David Roach, M.D.
Diem Tran, M.D.
Dolores McKeen, M.D.
Doreen Yee, M.D.
Duminda Wijeysundera, M.D., Ph.D.
Edmund Tan, M.D.
Emilie Belley-Côté, M.D., M.Sc.
Eric Jacobsohn, M.D.
Étienne de Médicis, M.D.
Francois M. Carrier, M.D., M.Sc.
Greg Hare, M.D., Ph.D.
Gregory Bryson, M.D.
Hilary Grocott, M.D.
Homer Yang, M.D.
Jason McVicar, M.D.
Jennifer O'Brien, M.D.
Jessica Spence, M.D.
Jim Kim, M.D.
John Murkin, M.D.
Jonathan Gamble, M.D.
Kathryn Sparrow, M.D.
Kim Wong, M.D.
Stuart McCluskey, M.D.
Michael Bautista, M.D.
Michael Law, M.D.
Michael Schmidt, M.D.
Nicola Edwards, M.D.
Peter Choi, M.D.
Philippe Richebe, M.D.
Pierre Beaulieu, M.D.
Rakesh Sondekoppam, M.D.
Ramiro Arellano, M.D.
Richa Dhawan, M.D.
Richard Hall, M.D.
Ron Ree, M.D.
Ronald George, M.D.
Rosaleen Chun, M.D.
Scott Brudney, M.D.
Stephen Kowalski, M.D.
Summer Syed, M.D.
Surita Sidhu, M.D.
Tarit Saha, M.D.
Thomas Mutter, M.D.
Vishal Uppal, M.D.