

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*

ANESTHESIOLOGY 2020; 133:265–79

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

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.

Submitted for publication September 10, 2019. Accepted for publication May 20, 2020. Published online first on June 26, 2020. Corrected on November 13, 2020. From the Population Health and Optimal Health Practices Research Unit, Trauma-Emergency-Critical Care Medicine, CHU de Québec - Université Laval Research Center, Québec City, Québec, Canada (M.V., F.L., C.P., X.S., A.-M.P., G.L., M.-J.C., X.N., A.F.T.); the Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine (M.V., F.L., A.-M.P., G.L., A.F.T.), the Department of Medicine (F.L.), Faculty of Medicine, and the Interdisciplinary Research Centre for Rehabilitation and Social Integration (A.-M.P.), Université Laval, Québec City, Québec, Canada; the Department of Internal Medicine, Section of Critical Care, University of Manitoba, Winnipeg, Manitoba, Canada (R.Z.); and the Department of Haematology and Medical Oncology, Cancer Care Manitoba, Winnipeg, Manitoba, Canada (R.Z.).

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

Copyright © 2020, the American Society of Anesthesiologists, Inc. All Rights Reserved. *Anesthesiology* 2020; 133:265–79. DOI: 10.1097/ALN.0000000000003428

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.

(*ANESTHESIOLOGY* 2020; 133:265–79)

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}

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 difference⁴³ 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). ClinicalTrials.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 scale⁶⁶ 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.

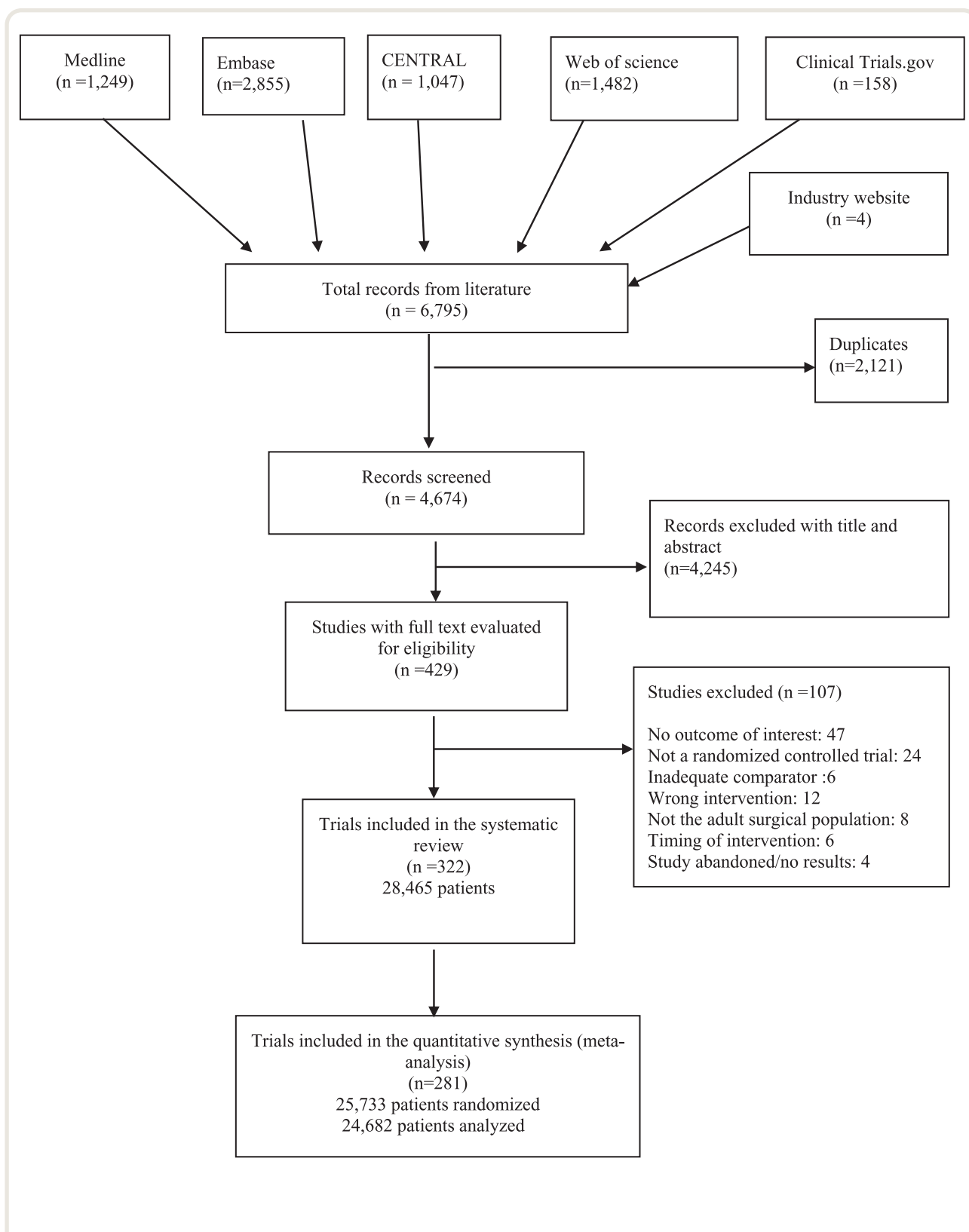
Results

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).



Downloaded from <http://aas2.silverchair.com/anesthesiology/article-pdf/133/2/265/14275/20200800.0-00011.pdf> by guest on 01 March 2024

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, table 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, table 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, table 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, tables 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, table 8, <http://links.lww.com/ALN/C413>).

Incidence of Postoperative Chronic Pain (between 3 and 12 Months Postoperative). Gabapentinoids 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, table 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 Patients			Summary Estimate	I ² , %	Quality of the Evidence Grades of Recommendation, Assessment, Development, and Evaluation Rating
	Number of Trials	Gabapentinoids	Control	Mean Difference or Risk Ratio [95% CI]		
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, one level for imprecision, 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; I² = 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; I² = 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; I² = 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; I² = 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; I² = 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)

Outcomes	Gabapentin				Pregabalin			
	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) ^a								
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 ^b								
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

^aIntervals 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. ^bIntervals 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 gabapentin³⁶ 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-analysis 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.

Acknowledgments

The authors acknowledge Valérie Gingras, B.Sc. (CHU de Québec - Université Laval, Québec City, Québec, Canada), for her help with the search strategy, Mohsen Agharazii, M.D., M.Sc. (Centre Hospitalier Universitaire de Québec-Université Laval, Québec City, Québec, Canada), for the translation of Persian articles, Rasheda Rabani, Ph.D. (George and Fay Yee Center for Healthcare Innovation, University of Manitoba/Winnipeg Regional Health Authority, Winnipeg, Manitoba, and Department Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba), for her help with the trial sequential analysis, and François Chalifour for his help with data extraction.

Research Support

Supported by Foundation Scheme grant No. 354039 from the Canadian Institutes of Health Research (Ottawa, Ontario,

Canada), a research salary support award from the Fonds de la Recherche du Québec–Santé (Montréal, Québec, Canada; to Dr. Lauzier), a New Investigator Award from the Canadian Institutes of Health Research (to Dr. Zarychanski), and a Canada Research Chair in Critical Care Neurology and Trauma from the Canadian Institutes of Health Research (to Dr. Turgeon).

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.

References

- Kammerman PR, Finnerup FN, De Lima L, Haroutounian S, Raja SN, Rice AS, Smith BH, Treede R-D: Gabapentin for Neuropathic Pain. Geneva, Switzerland, World Health Organization. 2016. Available at: https://www.who.int/selection_medicines/committees/expert/21/applications/s2_gabapentin.pdf?ua=1. Accessed June 14, 2020.
- FDA: Approved Labeling: Gabapentin. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020235s036,020882s022,021129s022lbl.pdf. Accessed June 14, 2020.
- FDA: Full prescribing information: Pregabalin. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021446s028lbl.pdf. Accessed June 14, 2020.
- EMA: Summary of Product Characteristics: Lyrica. 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000546/WC500046602.pdf. Accessed June 14, 2020.
- EMA: List of the Names, Pharmaceutical Forms, Strengths of the Medicinal Products, Route of Administration, Marketing Authorisation Holders in the Member States. 2006. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Neurontin_30/WC500009308.pdf. Accessed June 14, 2020.
- Martinez V, Carles M, Marret E, Beloeil H; Regional Anaesthesia and Pain Committee of the French Society of Anaesthesiology and Intensive Care Medicine: Perioperative use of gabapentinoids in France: Mismatch between clinical practice and scientific evidence. *Anaesth Crit Care Pain Med* 2018; 37:43–7
- OpenPrescribing: Prescribing of Pregabalin by All CCGs. 2018. Available at: <https://openprescribing.net/measure/pregabalin/>. Accessed June 14, 2020.
- Johansen ME: Gabapentinoid Use in the United States 2002 through 2015. *JAMA Intern Med* 2018; 178:292–4
- Morrison EE, Sandilands EA, Webb DJ: Gabapentin and pregabalin: Do the benefits outweigh the harms? *J R Coll Physicians Edinb* 2017; 47:310–3
- Goodman CW, Brett AS: Gabapentin and pregabalin for pain: Is increased prescribing a cause for concern? *N Engl J Med* 2017; 377:411–4
- Radley DC, Finkelstein SN, Stafford RS: Off-label prescribing among office-based physicians. *Arch Intern Med* 2006; 166:1021–6
- Wallach JD, Ross JS: Gabapentin approvals, off-label use, and lessons for postmarketing evaluation efforts. *JAMA* 2018; 319:776–8
- Federico CA, Wang T, Doussau A, Mogil JS, Fergusson D, Kimmelman J: Assessment of pregabalin postapproval trials and the suggestion of efficacy for new indications: A systematic review. *JAMA Intern Med* 2019; 179:90–7
- Kong VK, Irwin MG: Gabapentin: A multimodal perioperative drug? *Br J Anaesth* 2007; 99:775–86
- Montastruc F, Loo SY, Renoux C: Trends in first gabapentin and pregabalin prescriptions in primary care in the United Kingdom, 1993–2017. *JAMA* 2018; 320:2149–51
- Throckmorton DC, Gottlieb S, Woodcock J: The FDA and the next wave of drug abuse: Proactive pharmacovigilance. *N Engl J Med* 2018; 379:205–7
- Kharasch ED, Eisenach JC: Wherefore gabapentinoids?: Was there rush too soon to judgment? *ANESTHESIOLOGY* 2016; 124:10–2
- Landefeld CS, Steinman MA: The Neurontin legacy: Marketing through misinformation and manipulation. *N Engl J Med* 2009; 360:103–6
- Goodman CW, Brett AS: A clinical overview of off-label use of gabapentinoid drugs. *JAMA Intern Med* 2019; 179:695–701
- Dirks JP, Petersen KL, Rowbotham MC, Dahl JB: Gabapentin suppresses cutaneous hyperalgesia following heat-capsaicin sensitization. *ANESTHESIOLOGY* 2002; 97:102–7
- Wick EC, Grant MC, Wu CL: Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: A review. *JAMA Surg* 2017; 152:691–7
- Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL: Management of postoperative pain: A clinical practice guideline from the American Pain

- Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016; 17:131–57
23. The European Society of Regional Anaesthesia and Pain Therapy: Prospect. Available at: <https://esraeu-rope.org/prospect/>. Accessed June 14, 2020.
 24. Peng C, Li C, Qu J, Wu D: Gabapentin can decrease acute pain and morphine consumption in spinal surgery patients: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017; 96:e6463
 25. Maitra S, Baidya DK, Bhattacharjee S, Som A: [Perioperative gabapentin and pregabalin in cardiac surgery: A systematic review and meta-analysis]. *Rev Bras Anesthesiol* 2017; 67:294–304
 26. Li S, Guo J, Li F, Yang Z, Wang S, Qin C: Pregabalin can decrease acute pain and morphine consumption in laparoscopic cholecystectomy patients: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017; 96:e6982
 27. Jiang HL, Huang S, Song J, Wang X, Cao ZS: Preoperative use of pregabalin for acute pain in spine surgery: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017; 96:e6129
 28. Fabritius ML, Geisler A, Petersen PL, Wetterslev J, Mathiesen O, Dahl JB: Gabapentin in procedure-specific postoperative pain management: Preplanned subgroup analyses from a systematic review with meta-analyses and trial sequential analyses. *BMC Anesthesiol* 2017; 17:85
 29. Sanders JG, Dawes PJ: Gabapentin for perioperative analgesia in otorhinolaryngology—Head and neck surgery: Systematic review. *Otolaryngol Head Neck Surg* 2016; 155:893–903
 30. Park IJ, Kim G, Ko G, Lee YJ, Hwang SH: Does preoperative administration of gabapentin/pregabalin improve postoperative nasal surgery pain? *Laryngoscope* 2016; 126:2232–41
 31. Han C, Li XD, Jiang HQ, Ma JX, Ma XL: The use of gabapentin in the management of postoperative pain after total knee arthroplasty: A PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016; 95:e3883
 32. Han C, Li XD, Jiang HQ, Ma JX, Ma XL: The use of gabapentin in the management of postoperative pain after total hip arthroplasty: A meta-analysis of randomised controlled trials. *J Orthop Surg Res* 2016; 11:79
 33. Hamilton TW, Strickland LH, Pandit HG: A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. *J Bone Joint Surg Am* 2016; 98:1340–50
 34. Eipe N, Penning J, Yazdi F, Mallick R, Turner L, Ahmadzai N, Ansari MT: Perioperative use of pregabalin for acute pain—a systematic review and meta-analysis. *Pain* 2015; 156:1284–300
 35. Fabritius ML, Strøm C, Koyuncu S, Jæger P, Petersen PL, Geisler A, Wetterslev J, Dahl JB, Mathiesen O: Benefit and harm of pregabalin in acute pain treatment: A systematic review with meta-analyses and trial sequential analyses. *Br J Anaesth* 2017; 119:775–91
 36. Fabritius ML, Geisler A, Petersen PL, Nikolajsen L, Hansen MS, Kontinen V, Hamunen K, Dahl JB, Wetterslev J, Mathiesen O: Gabapentin for post-operative pain management: A systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiol Scand* 2016; 60:1188–208
 37. Mishriky BM, Waldron NH, Habib AS: Impact of pregabalin on acute and persistent postoperative pain: A systematic review and meta-analysis. *Br J Anaesth* 2015; 114:10–31
 38. Arumugam SL, Lau CSM, Chamberlain RS: Use of preoperative gabapentin significantly reduces postoperative opioid consumption: A meta-analysis. *J Pain Res* 2016; 9:631–40
 39. Lam DM, Choi SW, Wong SS, Irwin MG, Cheung CW: Efficacy of pregabalin in acute postoperative pain under different surgical categories: A meta-analysis. *Medicine (Baltimore)* 2015; 94:e1944
 40. Zhang J, Ho KY, Wang Y: Efficacy of pregabalin in acute postoperative pain: A meta-analysis. *Br J Anaesth* 2011; 106:454–62
 41. Sills GJ: The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol* 2006; 6:108–13
 42. Chincholkar M: Analgesic mechanisms of gabapentinoids and effects in experimental pain models: A narrative review. *Br J Anaesth* 2018; 120:1315–34
 43. Busse JW, Bartlett SJ, Dougados M, Johnston BC, Guyatt GH, Kirwan JR, Kwok K, Maxwell LJ, Moore A, Singh JA, Stevens R, Strand V, Suarez-Almazor ME, Tugwell P, Wells GA: Optimal strategies for reporting pain in clinical trials and systematic reviews: Recommendations from an OMERACT 12 workshop. *J Rheumatol* 2015; 42:1962–70
 44. GRADEpro GDT: GRADEpro Guideline Development Tool. 2015. Available at: <https://gradepro.org/>. Accessed August 17, 2019.
 45. Evoy KE, Morrison MD, Saklad SR: Abuse and misuse of pregabalin and gabapentin. *Drugs* 2017; 77:403–26
 46. NHS: Advice for Prescribers on the Risk of the Misuse of Pregabalin and Gabapentin. Public Health England. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385791/PHE-NHS_England_pregabalin_and_gabapentin_advice_Dec_2014.pdf. Accessed June 14, 2020.
 47. Spence D: Bad medicine: Gabapentin and pregabalin. *BMJ* 2013; 347:f6747

48. Smith RV, Havens JR, Walsh SL: Gabapentin misuse, abuse and diversion: A systematic review. *Addiction* 2016; 111:1160–74
49. Moberly T: BMA annual meeting: Pregabalin must be made a controlled drug, BMA says. *BMJ* 2017; 357:j3151
50. Mayor S: Pregabalin and gabapentin become controlled drugs to cut deaths from misuse. *BMJ* 2018; 363:k4364
51. Molero Y, Larsson H, D’Onofrio BM, Sharp DJ, Fazel S: Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: Population based cohort study in Sweden. *BMJ* 2019; 365:l2147
52. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W: Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. *PLoS Med* 2017; 14:e1002396
53. Cairns R, Schaffer AL, Ryan N, Pearson SA, Buckley NA: Rising pregabalin use and misuse in Australia: Trends in utilization and intentional poisonings. *Addiction* 2019; 114:1026–34
54. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors): *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK, John Wiley & Sons, 2019. Available at: <http://handbook.cochrane.org>. Accessed August 14, 2017.
55. Verret M, Lauzier F, Zarychanski R, Savard X, Cossi MJ, Pinard AM, Leblanc G, Turgeon AF: Perioperative use of gabapentinoids for the management of postoperative acute pain: Protocol of a systematic review and meta-analysis. *Syst Rev* 2019; 8:24
56. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C: PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016; 75:40–6
57. California University: Drug Industry Documents. 2008. Available at: <https://www.industrydocumentslibrary.ucsf.edu/drug/results/#q=Neurontin&h=%7B%22hideDuplicates%22%3Atrue%2C%22hideFolders%22%3Atrue%7D&subsite=drug&cache=true&count=606>. Accessed June 14, 2020.
58. Myles PS, Boney O, Botti M, Cyna AM, Gan TJ, Jensen MP, Kehlet H, Kurz A, De Oliveira GS Jr, Peyton P, Sessler DI, Tramèr MR, Wu CL, Myles P, Grocott M, Biccari B, Blazeby J, Boney O, Chan M, Diouf E, Fleisher L, Kalkman C, Kurz A, Moonesinghe R, Wijeyesundera D; StEP–COMPAC Group: Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: Patient comfort. *Br J Anaesth* 2018; 120:705–11
59. Kent ML, Hurley RW, Oderda GM, Gordon DB, Sun E, Mythen M, Miller TE, Shaw AD, Gan TJ, Thacker JKM, McEvoy MD; POQI-4 Working Group: American Society for Enhanced Recovery and Perioperative Quality Initiative-4 Joint Consensus Statement on Persistent Postoperative Opioid Use: Definition, incidence, risk factors, and health care system initiatives. *Anesth Analg* 2019; 129:543–52
60. Hegmann KT, Weiss MS, Bowden K, Branco F, DuBrueler K, Els C, Mandel S, McKinney DW, Miguel R, Mueller KL, Nadig RJ, Schaffer MI, Studt L, Talmage JB, Travis RL, Winters T, Thiese MS, Harris JS; American College of Occupational and Environmental Medicine: ACOEM practice guidelines: Opioids for treatment of acute, subacute, chronic, and postoperative pain. *J Occup Environ Med* 2014; 56:e143–59
61. Rohatgi A: WebPlotDigitizer. Available at: <https://automeris.io/WebPlotDigitizer/images/wpd.png>. Accessed August 15, 2017.
62. Google Translate. Google. 2019. Available at: <https://translate.google.ca/?hl=fr&tab=TT>. Accessed February 22, 2020.
63. Jackson JL, Kuriyama A, Anton A, Choi A, Fournier J-P, Geier A-K, Jacquerioz F, Kogan D, Scholcoff C, Sun R: The accuracy of Google Translate for abstracting data from non-English-language trials for systematic reviews. *Ann Int Med* 2019; 171:677–9
64. Turner K: Google Translate is getting really, really accurate. *Washington Post*. 2016. Available at: www.washingtonpost.com/news/innovations/wp/2016/10/03/google-translate-is-getting-really-really-accurate/?utm_term=.4eb5991f4cfc. Accessed July 9, 2019.
65. Cochrane: The Cochrane Collaboration’s tool for assessing risk of bias. 2010. Available at: http://handbook.cochrane.org/index.htm#chapter_8/8_assessing_risk_of_bias_in_included_studies.htm. Accessed December 17, 2017.
66. Myles PS, Myles DB, Gallagher W, Boyd D, Chew C, MacDonald N, Dennis A: Measuring acute postoperative pain using the visual analog scale: The minimal clinically important difference and patient acceptable symptom state. *Br J Anaesth* 2017; 118:424–9
67. Kelly AM: The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J* 2001; 18:205–7
68. Cooper SA, Desjardins PJ, Turk DC, Dworkin RH, Katz NP, Kehlet H, Ballantyne JC, Burke LB, Carragee E, Cowan P, Croll S, Dionne RA, Farrar JT, Gilron I, Gordon DB, Iyengar S, Jay GW, Kalso EA, Kerns RD, McDermott MP, Raja SN, Rappaport BA, Rauschkolb C, Royal MA, Segerdahl M, Stauffer JW, Todd KH, Vanhove GF, Wallace MS, West C, White RE, Wu C: Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. *Pain* 2016; 157:288–301
69. Nielsen S, Degenhardt L, Hoban B, Gisev N: A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf* 2016; 25:733–7

70. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618–25
71. Ip HY, Abrishami A, Peng PW, Wong J, Chung F: Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. *ANESTHESIOLOGY* 2009; 111:657–77
72. Vedula SS, Bero L, Scherer RW, Dickersin K: Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 2009; 361:1963–71
73. Sedgwick P: Meta-analyses: Heterogeneity and subgroup analysis. *BMJ* 2013; 346:f4040
74. Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH: Pooling health-related quality of life outcomes in meta-analysis: A tutorial and review of methods for enhancing interpretability. *Res Synth Methods* 2011; 2:188–203
75. R: A language and environment for statistical computing. Vienna, Austria
76. Schwarzer G: meta: An R package for meta-analysis. *R News* 2007; 7:40–5
77. TSA software. Copenhagen Trial Unit, 2018
78. Wetterslev J, Thorlund K, Brok J, Gluud C: Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008; 61:64–75
79. Maleh PA, Alijanpour E, Nickbakhsh N, Modarress R, Naghshineh A, Esmaeili M: Effects of gabapentin on postoperative pain following laparoscopic cholecystectomy. *J Mazandaran Univ Med Sci* 2013; 23:29–32
80. Pourfakhr P, Raaefi V, Najafi A, Moharari RS, Etezadi F, Orandi A, Khajavi MR: Evaluation of postoperative analgesic effects of gabapentin and ketorolac after orthognathic surgeries. *Tehran Univ Med J* 2016; 73:812–8
81. Foroozanfard F, Fazel MR, Moraveji AR, Gha M, Abolhasani A: The gabapentin effect on pain morphin consumption after total abdominal hysterectomy. *J Zanjan Univ Med Sci Health Services* 2012; 20:79–89
82. Faraji R, Haryalchi K, Fashkhami F, Pourmarzi D: Comparison of low dose gabapentin and diclofenac efficacy for postoperative pain reduction after abdominal hysterectomy: A randomized clinical trial. *J Guilan Univ Med Sci* 2015; 24:63–9
83. Takmaz SA, Kaymak C, Pehlivan BS, Dikmen B: [Effect of preoperative 900 and 1200 mg single oral dose of gabapentin on postoperative pain relief and tramadol consumption in open cholecystectomy surgery]. *Agri* 2007; 19:32–8
84. Ercan S, Akpek E, Aslim E, Akay T, Dönmez A: The effects of gabapentin on intraoperative cooperation, stress response and postoperative analgesia in patients undergoing carotid endarterectomy with regional anesthesia. *Gogus-Kalp-Damar Anestezi ve Yogun Bakim Dernegi Dergisi* 2014; 20:7–15
85. Koyuncu T, Oğuz G, Akben S, Nas S, Ünver S: [The effects of pregabalin on postoperative pain and opioid consumption used perioperatively in patients undergoing modified radical mastectomy]. *Agri* 2013; 25:169–78
86. Kılıç E, Mızrak A, Göksu S, Cesur M: Preemptive analgesic efficacy of gabapentin and nimesulide in the functional endoscopic sinus surgery [article in Turkish]. *Agri* 2014; 26:73–81
87. Tunç M, Cinar D, Sahin S, Sazak H, Kose SK: The effects of pre-emptive pregabalin on post-thoracotomy pain and epidural analgesia. *Turkish J Thoracic Cardiovasc Surgery* 2014; 22:129–37
88. Przesmycki K, Wiater-Kozioł E, Kotarski J, Czuczwar M, Jaskowiak R, Zabek M, Kołacz A, Fijałkowska M, Kotus M: Effect of pre-emptive pregabalin on pain intensity and morphine requirement after hysterectomy [article in Polish]. *Anestezjol Intens Ter* 2011; 43:14–7
89. Kim SI, Park DY, Ok SY, Kim SC: Effects of preemptive gabapentin on postoperative pain after mastectomy. *Korean J Anesthesiol* 2004; 47:527–31
90. Kang HS, Park HJ, Choi J, Park SJ, Lee SK: The optimal preemptive dose of gabapentin following gynecologic surgery. *Korean J Anesthesiol* 2009; 56:309–12
91. Acín MP, Bono MC, Rodrigo MD, Martínez R, Faci A, Escartín R: Preventive analgesia with pregabalin in mesh hernia repair: Review at 1 year. *Revista de la Sociedad Espanola del Dolor* 2009; 16:215–21
92. Batista JA, Errigo MM: Preoperative gabapentin as adjuvant in the management of acute postoperative pain in abdominal hysterectomy. *Revista de la Sociedad Espanola del Dolor* 2015; 22:200–4
93. Debaecker L, Roosebeke A, Garot M, Andrieu G, Sanders V, Chalons N, Capron B, Wattier JM, Lebuffé G: Administration préopératoire de gabapentine et douleurs résiduelles après chirurgie thyroïdienne: Une étude randomisé double aveugle contre placebo. *Annales francaises d'anesthésie et de reanimation* 2014; 33:A147–8
94. Zarei M, Najafi A, Mansouri P, Sadeghi-Yazdankhah S, Saberi H, Moradi M, Farzan M: Management of postoperative pain after lumbar surgery: Pregabalin for one day and 14 days: A randomized, triple-blinded, placebo-controlled study. *Clin Neurol Neurosurg* 2016; 151:37–42
95. Khurana G, Jindal P, Sharma JP, Bansal KK: Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. *Spine (Phila Pa 1976)* 2014; 39:E363–8
96. Hegarty DA, Shorten GD: A randomised, placebo-controlled trial of the effects of preoperative pregabalin on pain intensity and opioid consumption following lumbar discectomy. *Korean J Pain* 2011; 24:22–30
97. Burke SM, Shorten GD: Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. *Anesth Analg* 2010; 110:1180–5

98. Mardani-Kivi M, Mobarakeh MK, Keyhani S, Motlagh KH, Ekhtiari KS: Is gabapentin effective on pain management after arthroscopic anterior cruciate ligament reconstruction?: A triple blinded randomized controlled trial. *Arch Bone Jt Surg* 2013; 1:18–22
99. Borde DP, Futane SS, Asegaonkar B, Apsingekar P, Khade S, Khodve B, Puranik M, George A, Joshi S: Effect of perioperative pregabalin on postoperative quality of recovery in patients undergoing off-pump coronary artery bypass grafting (OPCABG): A prospective, randomized, double-blind trial. *J Cardiothorac Vasc Anesth* 2017; 31:1241–5
100. Monks DT, Hoppe DW, Downey K, Shah V, Bernstein P, Carvalho JCA: A perioperative course of gabapentin does not produce a clinically meaningful improvement in analgesia after cesarean delivery: A randomized controlled trial [randomized controlled trial; research support, non-U.S. gov't]. *ANESTHESIOLOGY* 2015; 123:320–6
101. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J, Efron B, Clay D, Sharifzadeh Y, Ruchelli G, Goodman S, Huddleston J, Maloney WJ, Dirbas FM, Shrager J, Costouros J, Curtin C, Carroll I: Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: A randomized clinical trial. *JAMA Surg* 2017; 13:13
102. YaDeau JT, Lin Y, Mayman DJ, Goytizolo EA, Alexiades MM, Padgett DE, Kahn RL, Jules-Elysee KM, Ranawat AS, Bhagat DD, Fields KG, Goon AK, Curren J, Westrich GH: Pregabalin and pain after total knee arthroplasty: A double-blind, randomized, placebo-controlled, multidose trial. *Br J Anaesth* 2015; 115:285–93
103. Yadeau JT, Paroli L, Kahn RL, Jules-Elysee KM, Lasala VR, Liu SS, Lin E, Powell K, Buschiazio VL, Wukovits B, Roberts MM, Levine DS: Addition of pregabalin to multimodal analgesic therapy following ankle surgery: A randomized double-blind, placebo-controlled trial. *Reg Anesth Pain Med* 2012; 37:302–7
104. Panagiotou OA, Contopoulos-Ioannidis DG, Ioannidis JP: Comparative effect sizes in randomised trials from less developed and more developed countries: Meta-epidemiological assessment. *BMJ* 2013; 346:f707
105. Alles SRA, Smith PA: The anti-allodynic gabapentinoids: Myths, paradoxes, and acute effects. *Neuroscientist* 2017; 23:40–55
106. Tiippana EM, Hamunen K, Kontinen VK, Kalso E: Do surgical patients benefit from perioperative gabapentin/pregabalin?: A systematic review of efficacy and safety. *Anesth Analg* 2007; 104:1545–56
107. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeyesundera DN, Katz J: The prevention of chronic postsurgical pain using gabapentin and pregabalin: A combined systematic review and meta-analysis. *Anesth Analg* 2012; 115:428–42
108. Davies HT, Crombie IK, Tavakoli M: When can odds ratios mislead? *BMJ* 1998; 316:989–91
109. Deeks J: When can odds ratios mislead?: Odds ratios should be used only in case-control studies and logistic regression analyses. *BMJ* 1998; 317:1155–6
110. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, Antrobus J, Huang J, Scott M, Wijk L, Acheson N, Ljungqvist O, Dowdy SC: Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations—Part II. *Gynecol Oncol* 2016; 140:323–32
111. Aubrun F, Nouette-Gaulain K, Fletcher D, Belbachir A, Beloeil H, Carles M, Cu villon P, Dadure C, Lebuffe G, Marret E, Martinez V, Olivier M, Sabourdin N, Zetlaoui P: Revision of expert panel's guidelines on postoperative pain management. *Anaesth Crit Care Pain Med* 2019; 38:405–11
112. Doleman B, Lund JN, Williams JP: Is analysis of pregabalin outcomes by surgical pain model evidence based? *Pain* 2016; 157:504–5
113. Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC: Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol* 2007; 36:847–57
114. Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG: Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to published articles. *JAMA* 2004; 291:2457–65

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 Wijesundera, 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.