The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis

Hance Clarke, MSc, MD, FRCPC,*†‡ Robert P. Bonin, PhD,§ Beverley A. Orser, MD, PhD, FRCPC,†‡ Marina Englesakis, BA MLIS,‖ Duminda N. Wijeysundera, MD, PhD, FRCPC,*‡¶# and Joel Katz, PhD**

BACKGROUND: Many clinical trials have demonstrated the effectiveness of gabapentin and pregabalin administration in the perioperative period as an adjunct to reduce acute postoperative pain. However, very few clinical trials have examined the use of gabapentin and pregabalin for the prevention of chronic postsurgical pain (CPSP). We (1) systematically reviewed the published literature pertaining to the prevention of CPSP (≥2 months after surgery) after perioperative administration of gabapentin and pregabalin and (2) performed a meta-analysis using studies that report sufficient data. A search of electronic databases (Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, IPA, and CINAHL) for relevant English-language trials to June 2011 was conducted.

METHODS: The following inclusion criteria for identified clinical trials were used for entry into the present systematic review: randomization; double-blind assessments of pain and analgesic use; report of pain using a reliable and valid measure; report of analgesic consumption; and an absence of design flaws, methodological problems or confounders that render interpretation of the results ambiguous. Trials that did not fit the definition of preventive analgesia and did not assess chronic pain at 2 or more months after surgery were excluded.

RESULTS: The database search yielded 474 citations. Eleven studies met the inclusion criteria. Of the 11 trials, 8 studied gabapentin, 4 of which (i.e., 50%) found that perioperative administration of gabapentin decreased the incidence of chronic pain more than 2 months after surgery. The 3 trials that used pregabalin demonstrated a significant reduction in the incidence of CPSP, and 2 of the 3 trials also found an improvement in postsurgical patient function. Eight studies were included in a meta-analysis, 6 of the gabapentin trials demonstrated a moderate-to-large reduction in the development of CPSP (pooled odds ratio [OR] 0.52; 95% confidence interval [CI], 0.27 to 0.98; $P = 0.04$), and the 2 pregabalin trials found a very large reduction in the development of CPSP (pooled OR 0.09; 95% CI, 0.02 to 0.79; $P = 0.007$).

CONCLUSIONS: The present review supports the view that perioperative administration of gabapentin and pregabalin are effective in reducing the incidence of CPSP. Better-designed and appropriately powered clinical trials are needed to confirm these early findings.

The development of chronic postsurgical pain (CPSP) is an unfortunate consequence of surgery that adversely impacts the patient's quality of life. Efforts to prevent the establishment of CPSP include perioperative administration of a variety of drugs. We systematically reviewed the published literature pertaining to the prevention of CPSP after perioperative interventions using gabapentin and pregabalin. After defining preventive analgesia we present the results of the systematic review and meta-analysis, followed by a discussion of the results, including the limitations of the current literature and future directions for clinical trials. Finally, we provide an overview of recent basic science studies that suggest novel mechanisms that may be responsible for some of the behavioral properties of gabapentin and pregabalin.

The factors that influence the transition from acute postoperative pain to CPSP have yet to be elucidated. CPSP has been defined as pathological pain that persists for longer than 2 months after surgery.[1] Several patient-related and surgical factors have been linked to the development of CPSP.[2] The most consistent patient factor is the presence and/or intensity of preoperative and postoperative pain.[3–5] Because moderate to severe postoperative pain is a frequent occurrence after surgery,[6] novel drugs such as gabapentin and pregabalin in addition to traditional opioids are administered with the aim of providing superior pain relief at rest and with movement, reducing opioid consumption and reducing analgesic-related adverse effects.[7–9] If drugs, such as gabapentin and pregabalin, can prevent the establishment of surgery-induced central sensitization and can decrease postoperative pain,[10–12] then these drugs, given

Author affiliations are listed at the end of the article.

Accepted for publication December 15, 2011.

Study funding information is listed at the end of the article.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Hance Clarke, MSc, MD, FRCPC, Department of Anesthesia and Pain Management, Toronto General Hospital, 200 Elizabeth Street, Eaton North 3 EB 317, Pain Research Unit, Toronto, ON M5G 2C4, Canada. Address e-mail to hance.clarke@utoronto.ca.

during the perioperative period, may also play a role in preventing the transition of acute pain to chronic pain.[13,14]

Neuropathic pain, which is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system,[15] has been implicated as a major contributor to the development of CPSP.[2,16] Given that both gabapentin and pregabalin are front-line treatments for patients suffering from established chronic neuropathic pain,[17,18] it is plausible that these drugs, when used in the perioperative setting, may be of benefit in reducing the incidence and/or intensity of chronic pain.

PREVENTIVE ANALGESIA

Preventive analgesia has evolved from preemptive analgesia by shifting the focus from blocking solely noxious preoperative stimuli[12,19–21] to a broader conceptualization involving blocking noxious stimuli across the entire perioperative period.[13,14,22] A preventive analgesic effect is demonstrated when postoperative pain and/or analgesic consumption is reduced in relation to an intervention, as long as the effect is observed at a time that exceeds the expected clinical duration of action of the target drug. We have defined a preventive analgesic effect as one that is demonstrated when postoperative pain and/or analgesic use are reduced beyond 5.5 half-lives of the target drug.[12,13,22] This requirement ensures that the observed effects are not direct analgesic effects.[12,13]

GABAPENTIN (NEURONTIN, PFIZER, INC.) AND PREGABALIN (LYRICA, PFIZER, INC.)

Gabapentin, a structural analog of γ-aminobutyric acid (GABA), was initially used as an anticonvulsant in the late 1980s. Clinically, gabapentin demonstrated poor efficacy as an anticonvulsant.[23] The antinociceptive properties of this drug, along with the advantage of producing only mild side effects, made gabapentin an attractive therapeutic option for pain specialists who used other anticonvulsants with significant adverse events (i.e., carbamazepine) for chronic pain conditions.[23] By the late 1990s, gabapentin had become a first-line treatment for patients who suffered from chronic neuropathic pain.[24,25] In recent years, gabapentin has been used widely as an adjunct for the treatment of acute postsurgical pain. Several meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain.[26–28]

Pregabalin is structurally similar to gabapentin and was also marketed primarily for epilepsy and neuropathic pain. Pregabalin (S-[+]-3-isobutylgaba) was designed as a lipophilic GABA analog substituted at the 3′ position to facilitate diffusion across the blood–brain barrier.[29,30] Pregabalin has also been found to be effective at reducing acute postoperative pain.[10,31–36]

Studies have reported the effects of the gabapentinoids in the prevention of CPSP. We systematically reviewed the published, clinical trials pertaining to the prevention of CPSP (≥2 months after surgery) after perioperative interventions using gabapentin and pregabalin.

METHODS

Search Strategy

A search strategy was developed using the Medline database and subsequently translated into the remaining databases. The following databases were searched: Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts (IPA, accessed via the OvidSP platform) and Cumulative Index to Nursing & Allied Health Literature (CINAHL, accessed via the EbscoHost platform). The search strategy contained 3 components: pregabalin or gabapentin terms, including generic and trade names, chemical abstract service (CAS) registry numbers, MeSH or Emtree or text words; preemptive, preventive, or perioperative terms, using MeSH or Emtree or text words; and finally, chronic pain terms, using MeSH or Emtree or text words (Appendix 1). These 3 components were combined using the Boolean operator, "AND," to obtain the intersection of the 3 sets; the results were limited to human subjects and English-language articles. All databases were searched in their entirety to the end of June 2011; however, the Embase database was limited to searches from 2006 to 2011.

Inclusion Criteria

All clinical trials were evaluated according to the following inclusion criteria for entry into the present review: randomized assignment of patients to treatment groups; double-blind assessments of pain and analgesic use; report of pain using a reliable and valid measure; report of analgesic consumption; and an absence of design flaws, methodological problems, or confounders that render interpretation of the results ambiguous.[22] Trials that did not fit the definition of preventive analgesia[14] and did not assess chronic pain at 2 or more months after surgery were excluded.

Data Extraction

Two reviewers (H.C. and J.K.) independently reviewed the abstracts of each reference identified by the above search strategy, independently evaluated each included study for content, and completed a data extraction table that included relevant data. Studies were included if both reviewers agreed that the studies met the inclusion criteria.

Assessment of the Methodological Quality and Risk of Bias

Two reviewers (H.C. and J.K.) independently assessed the methodological quality of the included trials according to the Delphi criteria list.[38] The Delphi list identifies 9 criteria for quality assessment (Table 1).

Statistical Analysis

Meta-analysis was used to calculate pooled effects of gabapentin or pregabalin on the development of chronic pain at 3 to 6 months after surgery. For cases in which a study reported the rates of chronic pain development of chronic pain at both 3 and 6 months, we included only 6-month event rates in the statistical analysis. Summary effects were expressed as pooled odds ratios (OR) with associated 95% confidence intervals (CI). Initially, statistical heterogeneity was assessed using the I^2 statistic,[39,40] which describes the proportion of total variation explained by between-studies variation instead of chance. Higher I^2 statistics imply more heterogeneity between studies than would be expected by chance alone. In the presence of low heterogeneity ($I^2 \leq 25\%$), pooled ORs were calculated under the fixed-effects model; otherwise, the random-effects

Table 1. Methodological Quality Assessment

Study	Randomization	Treatment allocation concealed?	Similar groups at baseline?	Specified eligibility criteria?	Outcome assessor blinded?	Care provider blinded?	Patient blinded?	Point estimates of variability for primary outcome measures?	Intention-to-treat analysis for postoperative outcomes?	Total quality score/9
Amr et al. (2010)[46]	Y	Y	Y	Y	Y	Y	Y	N	N	7
Buvanendran et al. (2010)[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Brogly et al. (2008)[50]	Y	Y	Y	Y	Y	?	Y	N	N	6
Burke et al. (2010)[34]	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Clarke et al. (2009)[49]	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Fassoulaki et al. (2002)[51]	Y	Y	Y	Y	Y	Y	Y	N	N	7
Fassoulaki et al. (2005)[52]	Y	Y	Y	Y	Y	Y	Y	N	N	7
Moore et al. (2011)[45]	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Pesonen et al. (2011)[53]	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Sen et al. (2009)[48]–hysterectomy	Y	Y	Y	Y	Y	?	Y	Y	N	7
Sen et al. (2009)[47]–hernia	Y	Y	Y	Y	Y	Y	Y	Y	N	8

Note: The listed criterion are taken from the Delphi consensus for quality assessment of randomized clinical trials. A higher score indicates higher study quality. ? = Not reported; N = No; NA = not applicable; Y = Yes.

model was used. In addition, a subgroup analysis based on the drug administered was performed, with a statistical test-of-interaction being used to assess for subgroup differences. Finally, funnel plots[41] and the test of Harbord et al.[42] were used to test for any publication bias.

Statistical significance was defined by a 2-sided P value <0.05, and all analyses were performed using Stata Version 11.2 (StataCorp Inc., College Station, TX). Our review complies with the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[43,44]

RESULTS

Search Results

The database search yielded 474 citations, of which 64 studies were retrieved and examined; 11 studies met the inclusion criteria (Fig. 1).[31,34,45–53]

Assessment of Methodological Quality

Table 1 summarizes the assessment of methodological quality of the 11 clinical trials. All studies were double-blind, randomized, controlled trials with specified eligibility criteria listed. Outcome assessors were blinded in all studies. Only 1 study reported an intention-to-treat analysis for postoperative outcomes.[31]

Study Characteristics

The 11 studies are summarized in Table 2. The studies examined the preventive effects of gabapentin or pregabalin on CPSP (≥2 months after surgery) and were published between October 2002 and June 2011. A total of 930 patients were included in the trials. The sample sizes ranged from $n = 30$ to $n = 240$, with a median of $n = 50$. The surgical populations studied were as follows: breast surgery,[46,51,52] total knee arthroplasty,[31] total hip arthroplasty,[49] cesarean delivery,[45] thyroidectomy,[50] cardiac surgery,[53] lumbar discectomy,[34] inguinal herniorraphy,[47] and abdominal hysterectomy.[48] Eight trials studied the effects of gabapentin,[45–52] and 3 trials studied the effects of pregabalin[31,34,53] on the prevention of pain that persisted for at least 2 months after surgery.

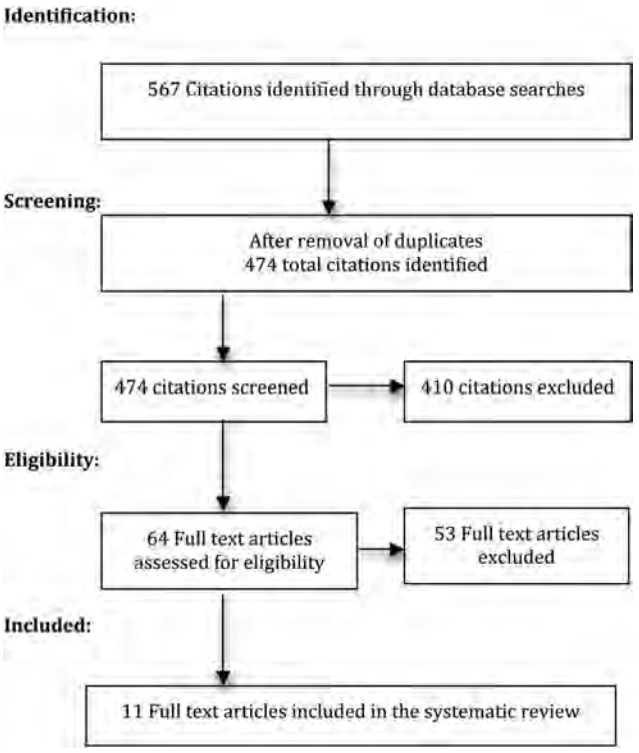

Figure 1. Selection process for systematic review.

The clinical heterogeneity is considerable among the 11 trials presented in this systematic review and meta-analysis. The studies using gabapentin varied with respect to the dosing regimen and the perioperative administration. Five of the 8 gabapentin studies administered a single preoperative dose of gabapentin,[45,47–50] 3 studies used a single preoperative dose of 1200 mg,[47,48,50] and the 2 other studies used a single 600-mg preoperative dose.[45,49] The remaining 3 studies started gabapentin administration before surgery and continued either 1200 mg of gabapentin daily for 8 or 10 days,[51,52] or 300 mg for 10 days postoperatively.[46] Finally, the pregabalin studies were also variable with respect to the timing and

Table 2. Study Characteristics

Study	Design and sample	Intervention	Outcome measuresintravenous	Measurement time points
Amr et al. (2010)[46]	Date: NR Design: 3 group RCT *N* = 150 (Ven: *n* = 50; Gpn: *n* = 50; C: *n* = 50) Sample characteristics: Low-risk patients ASA 1 and 2 scheduled for either partial or radical mastectomy Mean age (SD): Ven = 45 years (6); Gpn = 43 years (5); C = 44 years (8)	Perioperative intervention RCT: Breast surgery F: (G1) oral Ven 37.5 mg/day started the night before surgery and continued for 10 days (G2) oral Gpn 300 mg/day started the night before surgery and continued for 10 days (G3) placebo	Primary outcome: Postop opioid consumption Secondary outcomes: Pain scores perioperatively and daily until 10 days postop Chronic pain outcomes	T1 = daily pain scores and opioid consumption until postop day 10 T2 = 6 months postop
Brogly et al. (2008)[50]	Date: May–November 2006 Design: RCT *N* = 50 (Gpn: *n* = 22; C: *n* = 21) Sample characteristics: ASA I–III patients scheduled for total or partial thyroidectomy without lymph node dissection Mean age (range): Gpn = 49 (18–63) C = 49 (25–72)	Perioperative intervention RCT: effect of Gpn after thyroid surgery with SCPB F: (G1) oral Gpn 1200 mg given 2 hours before surgery (G2) placebo All patients received a SCPB	Primary outcome: Postop rescue analgesic use after thyroidectomy with SCPB Secondary outcomes: Chronic neuropathic pain outcomes	T1 = 0–24 hours postop T2 = 6 months postop
Burke et al. (2010)[34]	Date: NR Design: RCT *N* = 40 (Pregab: *n* = 20; C: *n* = 20) Sample characteristics: Low-risk (ASA 1 and 2) patients with chronic lumbar sacral radiculopathy undergoing elective lumbar discectomy Mean age: Pregab = 37 years (7.8); C = 41 years (12.4)	Perioperative intervention RCT: Effect of Pregab on pain and functional outcomes 3 months after discectomy F: (G1) oral Pregab 300 mg given 90 minutes before surgery followed by 150 mg at 12 and 24 hours postoperatively (G2) placebo	Primary outcome: Change in pain intensity as measured by a visual analogue scale ([VAS], 0–100 mm) from the preoperative assessment to the 3- month follow-up Secondary outcomes: Preoperative anxiolysis, disability measures, health- related quality-of-life measures, quantitative sensory testing assessments (i.e., pain sensation thresholds), and DNA analysis of CGH1 and OPRM1	T1 = baseline T2 = 24 hours postop T3 = 3 months postop
Buvanendran et al. (2010)[31]	Date: August 2006 to August 2007 Design: RCT *N* = 240 (Pregab: *n* = 120; C: *n* = 120) Sample characteristics: ASA I–III patients scheduled for total knee arthroplasty Mean age: Pregab = 64 years (8.3); C = 63.3 years (8.9)	Perioperative intervention RCT: Effect of Pregab on pain after total knee arthroplasty F: (G1) oral Pregab 300 mg before surgery and pregab 50–150 mg daily and for 14 days after total knee arthroplasty (G2) placebo	Primary outcome: A reduction in the incidence of neuropathic pain at 6 months for the Pregab-treated group Secondary outcomes: Pain scores perioperatively. Opioid consumption and adverse events Active knee flexion 3 days postop, sleep disturbance	T1 = perioperative to postop day 3 T2 = 1 month postop T3 = 3 months postop T4 = 6 months postop
Clarke et al. (2009)[49]	Date: May 2006 to April 2008 Design: 3 group RCT *N* = 126 (Preop Gpn: *n* = 38; postop Gpn: *n* = 38; C: *n* = 38) Sample characteristics: ASA I–III patients scheduled for total primary hip arthroplasty Mean age (SD): Preop Gpn = 58.9 years (9.4); postop Gpn = 60.4 years (8.1); C = 61.3 years (10.7)	Perioperative intervention RCT: Gpn after total hip arthroplasty F: (G1) preemptive oral Gpn 600 mg given 2 hours before surgery (G2) oral Gpn 600 mg given in PACU immediately after surgery (G3) placebo All patients received a robust perioperative multimodal pain regimen that consisted of acetaminophen, celecoxib, dexamethasone, and spinal anesthesia	Primary outcome: Opioid consumption and pain scores at rest and with movement to 48 hours Secondary outcomes: Incidence and severity of chronic pain 6 months post surgery. Psychosocial Questionnaire Hip Arthroplasty Pain questionnaire, Neuropathic Pain Scale, The Hospital Anxiety and Depression Scale	T1 = 48 hours postop T2 = 6 months postop

(*Continued*)

Table 2. (Continued)

Study	Design and sample	Intervention	Outcome measuresintravenous	Measurement time points
Fassoulaki et al. (2002)[51]	Date: NR Design: 3 group RCT *N* = 75 (Mexil: *n* = 21; Gpn: *n* = 22; C: *n* = 24) Sample characteristics: Low-risk patients ASA 1 and 2 scheduled for breast cancer surgery Mean age (SD) Mexil = 46 years (5); Gpn = 42 years (7); C = 45 years (10)	Perioperative intervention RCT: Breast surgery F: (G1) oral Mexil 600 mg/day started the night before surgery and continued for 10 days (G2) oral Gpn 1200 mg/day started the night before surgery and continued for 10 days (G3) placebo	Primary outcomes: Supplemental analgesic consumption until postop day 10. Pain scores at rest and with movement until postop day 10 Secondary outcomes: Incidence and severity of chronic pain 3 months postsurgery. The use of supplemental analgesics 3 months after surgery	T1 = periop to postop day 10 T2 = 3 months postop
Fassoulaki et al. (2005)[52]	Date: March 2001 to January 2004 Design: RCT *N* = 50 (Gpn: *n* = 25; C: *n* = 25) Sample characteristics: Low-risk patients ASA 1 and 2 scheduled for breast cancer surgery Mean age (SD): Gpn = 49 years (8.4); C = 48 years (8.1)	Perioperative intervention RCT: Effect of multimodal analgesia and Gpn on acute and chronic pain after breast cancer surgery F: (G1) Gpn 400 mg every 6 hours, starting the evening before surgery (18:00) and continued until the eighth postop day. 20 g of EMLA cream (2.5% of lidocaine and 2.5% of prilocaine) was applied to the wound area from the day of surgery until the third postop day. Intraoperatively, irrigation of the brachial plexus and the third, fourth, and fifth intercostal spaces were performed with 10 mL of 0.75% ropivacaine (G2) placebo	Primary outcomes: Supplemental analgesic consumption until postop day 8. Pain scores at rest and with movement until postop day 8 Secondary outcomes: Incidence and severity of chronic pain 3 and 6 months postsurgery. The use of supplemental analgesics 3 and 6 months after surgery	T1 = periop to postop day 10 T2 = 3 months postop T3 = 6 months postop
Moore et al. (2011)[45]	Date: November 2007 to November 2008 Design: RCT *N* = 46 (Gpn: *n* = 23; C: *n* = 23) Sample characteristics: Low-risk patients ASA 1 and 2 undergoing elective caesarian delivery Mean age (SD): Gpn = 35 years (5); C = 34 years (6)	Perioperative intervention RCT: Effect of Gpn after elective caesarian delivery F: (G1) oral Gpn 600 mg given 2 hours before surgery (G2) placebo	Primary outcomes: Postop pain scores at rest and with movement 24 hours after surgery Secondary outcomes: Supplemental analgesics and side effects 24 hours after surgery. Incidence and severity of chronic pain 3 months postsurgery	T1 = 24 hours postop T2 = 3 months postop
Pesonen et al. (2011)[53]	Date: April 2008 to September 2009 Design: RCT *N* = 70 (Pregab: *n* = 35; C: *n* = 35) Sample characteristics: elderly patients ≥75 years of age scheduled to undergo primary CABG with CPB or single-valve repair or replacement with CPB Mean age: Pregab = 79.5 years (75–89); C = 69.6 years (75–91)	Perioperative intervention RCT: effect of Pregab on elderly patients after cardiac surgery F: (G1) oral Pregab 150 mg before surgery and Pregab 75 mg twice daily and for 5 days after cardiac surgery (G2) placebo	Primary outcomes: Mean parenteral oxycodone consumption until 48 hours after surgery Secondary outcomes: Pain scores, sedation, confusion, and nausea and vomiting rates after surgery. Incidence and severity of chronic pain 1 and 3 months postsurgery	T1 = 48 hours postop T2 = 1 month postop T3 = 3 months postop

(*Continued*)

Table 2. (Continued)

Study	Design and sample	Intervention	Outcome measuresintravenous	Measurement time points
Sen et al. (2009)[48]	Date: NR Design: 3 group RCT Design: 3 group RCT *N* = 60 (Ket: *n* = 20; Gpn: *n* = 20; C: *n* = 20) Sample characteristics: Women undergoing total abdominal hysterectomy Mean age (SD): Ket = 46 years (6); Gpn = 47 years (7); C = 46 years (7)	Perioperative intervention RCT: A comparison of intraoperative ketamine infusion to preemptive Gpn for total abdominal hysterectomy F: (G1) Ket 0.3 mg/kg intravenous bolus before incision and 0.05 mg/kg/h infusion until the end of surgery (G2) oral Gpn 1200 mg given 1 hour before surgery (G3) placebo	Primary outcome: Pain scores in the supine and sitting positions until 24 hours after surgery Secondary outcomes: Intravenous patient-controlled analgesia morphine consumption up to 24 hours after surgery. Incidence and severity of incisional pain 1, 3, and 6 months postsurgery	T1 = 24 hours postop T2 = 1 month postop T3 = 3 months postop T3 = 3 months postop T4 = 6 months postop
Sen et al. (2009)[47]	Date: November 2007 to November 2008 Location: Istanbul, Turkey Design: RCT *N* = 59 (Gpn: *n* = 30; C: *n* = 29) Sample characteristics: Low-risk patients ASA 1 male patients undergoing inguinal hernia repair Mean age (SD): Gpn = 24 years (5.5); C = 24 years (5.3)	Perioperative intervention RCT: Effect of Gpn after inguinal herniorrhaphy F: (G1) oral Gpn 1200 mg given 1 hour before surgery (G2) placebo	Primary outcomes: Postop pain scores at rest and with movement 24 hours after surgery Secondary outcomes: Supplemental analgesics and side effects 24 hours after surgery. Incidence and severity of chronic pain 1, 3, and 6 months postsurgery	T1 = 24 hours postop T2 = 1 month postop T3 = 3 months postop T4 = 6 months postop

ASA = American Society of Anesthesiologists; CABG = coronary artery bypass graft; C = control; CPB = cardiopulmonary bypass; EMLA = eutectic mixture of local anesthetics; F = frequency of treatment; G1 = group 1; G2 = group 2; G3 = group 3; Gpn = gabapentin; Ket = ketamine; Mexil = mexiletine; NR = not recorded; Postop = postoperative; Pregab = pregabalin; Preop = preoperative; RCT = randomized controlled trial; SCPB = superficial cervical plexus block; SD = standard deviation; T = time point; Ven = venlafaxine; VAS = visual analogue scale.

dosing administered. Two studies gave a 300-mg preoperative dose and either continued the drug for 2 more doses (150 mg at 12 hours and 24 hours after surgery)[34] or continued a regimen of 50 to 150 mg of pregabalin daily for 2 weeks after surgery.[31] The third pregabalin trial gave a single preoperative dose of 150 mg followed by 75 mg of pregabalin twice daily for 5 days after surgery.[53]

Eight of the included trials[31,45,46,49–53] reported sufficient data for inclusion in a meta-analysis, the results of which are presented in Figure 2. There was moderate overall statistical heterogeneity (I^2 = 36.6%), which was explained in part by the specific drug administered. Specifically, heterogeneity was lower within the subgroups of gabapentin (I^2 = 30.5%) and pregabalin studies (I^2 = 0%). There was statistical evidence (P = 0.05) of different effects across the 2 subgroups (Fig. 2). Notably, funnel plots of the 8 studies included in the meta-analysis suggest a publication bias (Fig. 3); this raises the possibility that several negative trials of gabapentin or pregabalin have not been published. This possibility of publication bias was supported by formal statistical testing that bordered on significance (P = 0.051).

Preventive Effects of Gabapentin on CPSP

Of the 8 gabapentin trials, 4[47,48,50,52] reported that the perioperative use of gabapentin resulted in a lower incidence of pain and/or lower analgesic requirements at long-term follow-up (≥2 months after surgery) (Table 3). Brogly et al.[50] administered 1200 mg of gabapentin (n = 25) or placebo (n = 25) 2 hours before total thyroidectomy surgery. Patients also received superficial cervical plexus blocks; a significant difference in opioid consumption or pain scores was not observed during the first 24 hours after surgery.[50] Using the neuropathic pain diagnostic questionnaire (DN2) as a diagnostic tool, Brogly et al.[50] found that 30% (7 of 24) of patients reported neuropathic pain in the placebo group in comparison with 4% (1 of 23) of gabapentin-treated patients at 6 months after surgery.

Using a similar design (i.e., 1200 mg gabapentin (n = 30) 1 hour before inguinal herniorrhaphy with spinal anesthesia), Sen et al.[47] reported that patients who received gabapentin had less intense pain at 1, 3, and 6 months after surgery. The gabapentin-treated patients reported less interruption with their activities of daily living 1 month postsurgery.[47]

In another study by Sen et al.,[48] 40 women were randomly assigned to receive placebo (n = 20) versus intraoperative ketamine until the end of surgery (n = 20) versus 1200 mg gabapentin 1 hour before total abdominal hysterectomy. Patients who received gabapentin had lower pain scores and consumed fewer opioids in the acute postoperative period (24 hours). The incidence of incisional pain and pain intensity at 1, 3, and 6 months after surgery was significantly lower in the gabapentin group than in the ketamine and control groups.[48]

Finally, Fassoulaki et al.[52] found a reduction in pain and analgesic consumption using a multimodal analgesic regimen, which involved 50 women who underwent breast cancer surgery and were randomly assigned to receive 1200 mg gabapentin (for 8 postoperative days) starting the evening before surgery, a eutectic mixture of local anesthetic cream (for 3 postoperative days), and ropivacaine in the wound (at wound closure) (n = 25) and were compared with placebo

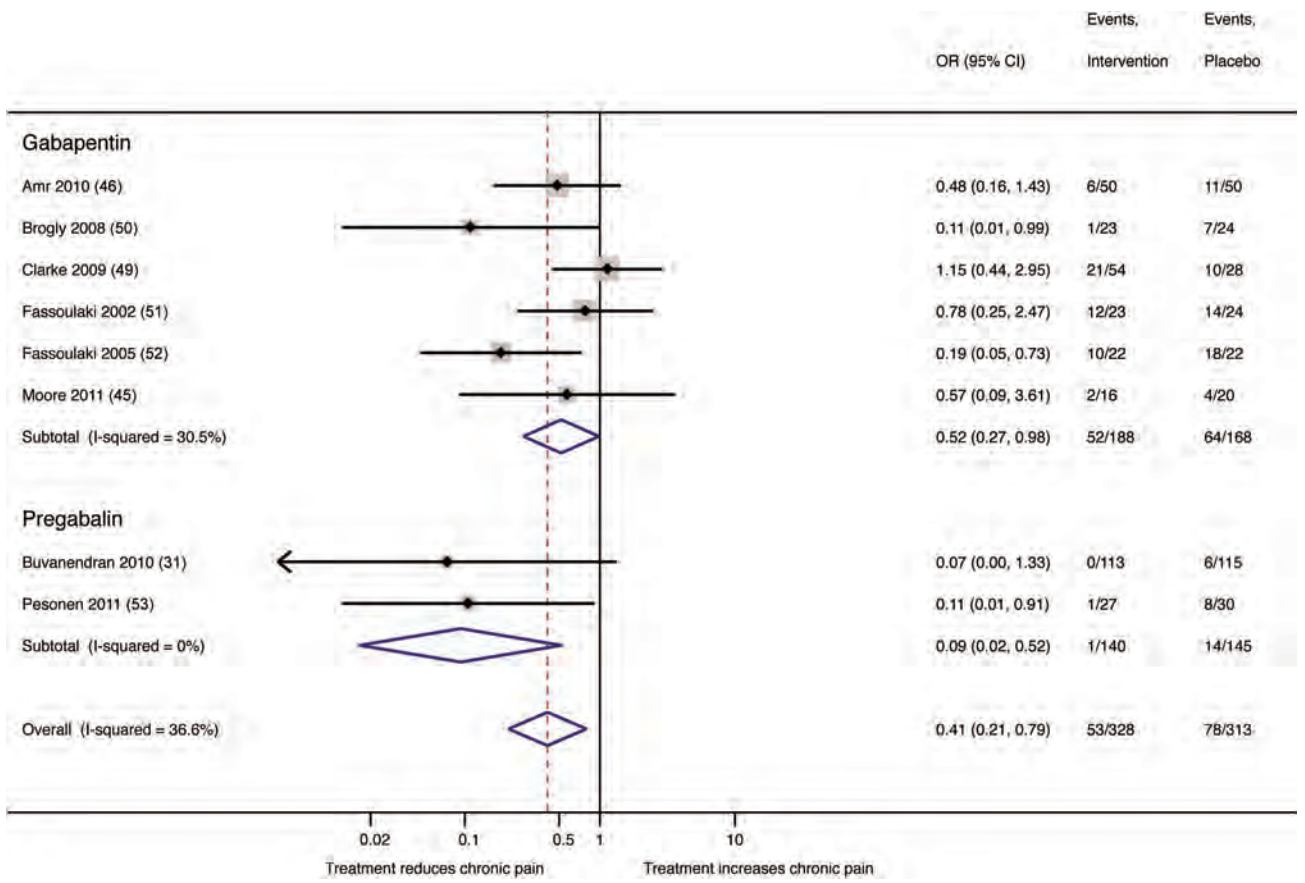

Figure 2. Effects of gabapentin or pregabalin on the development of chronic pain at 3 to 6 months after surgery, stratified by the specific drug administered. The pooled effect is expressed as a pooled odds ratio (OR) with associated 95% confidence intervals (CI). The shaded squares represent point estimates in individual randomized controlled trials. The area of each square correlates with its contribution towards the pooled summary estimates. Horizontal lines denote 95% CIs. The open diamonds represent the pooled estimates for all studies, as well as the 2 subgroups. The statistical heterogeneity, as measured by the I^2 statistic, was 36.6% for the overall analysis, 30.5% for the gabapentin subgroup, and 0% for the pregabalin subgroup. There was borderline statistical evidence ($P = 0.05$) of a difference between the pooled estimates in the gabapentin and pregabalin subgroups.

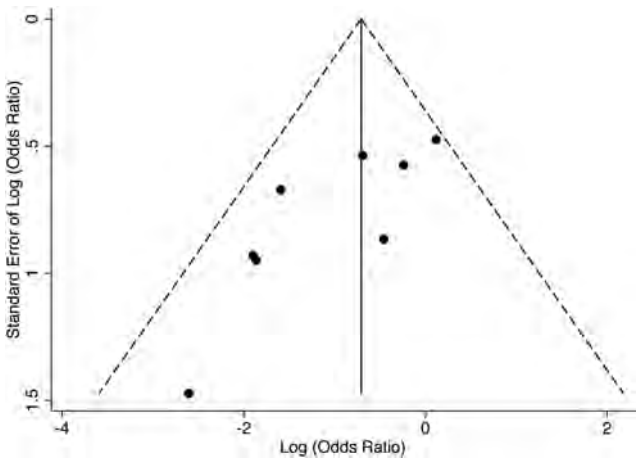

Figure 3. Funnel plot to assess for publication bias. Funnel plot[41] of the effect size from each study (expressed as the natural logarithm of the odds ratio) against a measure of result precision from each trial (expressed as the SE of the log odds ratio). The asymmetry of the plot was suggestive of publication bias, which was further confirmed through formal testing ($P = 0.051$) using the method of Harbord et al.[42]

($n = 25$).[52] The group that received the multimodal analgesic regimen used significantly less paracetamol and adjunctive pain medications than did controls; they also reported lower pain scores at rest and with movement on early postoperative days. At 3 months after surgery, the patients who were in the multimodal analgesia group reported a significantly lower incidence of chronic pain (82% versus 45%) and used fewer supplemental analgesics (23% versus 0%) than did patients who received only placebo. Six months after surgery, 57% of control patients complained of chronic pain in comparison with 30% in the treatment group; however, this was not a statistically significant finding.

The remaining 4 studies reported no effect of gabapentin on pain or supplemental analgesic use more than 2 months after surgery[45,46,49,51] (Table 3). A closer examination of 2 of the negative gabapentin studies[46,51] showed that, although there was no difference in the incidence or severity of CPSP after breast cancer surgery at the 3-month and 6-month follow-ups, both studies found that patients who received gabapentin reported less burning pain at these time points. Table 4 shows the odds ratios comparing placebo-treated patients with gabapentin- or pregabalin-treated patients with respect to the

Table 3. Postoperative Results for Specified Outcomes

Outcome	Study	Quality/ Delphi score	$\alpha 2\delta$ agent/ preventive effects	Postoperative outcome results*($P < 0.05$)
Chronic postsurgical pain	Amr et al. (2010)[46]	7	Gabapentin, no	Venlafaxine demonstrated a greater preventive effect with respect to decreasing chronic pain versus placebo-treated patients (i.e., less burning and stabbing/pricking pain) at 6 months. Patients who received gabapentin reported less burning than control patients
	Brogly et al. (2008)[51]	6	Gabapentin, yes	Significantly more patients in the placebo group (7 out of 24, 30%) fit the DN2 criterion for chronic neuropathic pain than did the patients who received gabapentin after thyroid surgery with SCPB (1 out of 23, 4.3%) 6 months after surgery
	Burke et al. (2010)[34]	8	Pregabalin, yes	Results demonstrated that the (mean ± SD) decrease in the VAS pain score at 3 months was greater in patients who received pregabalin (37.6 ± 19.6 mm) than those who received placebo (25.3 ± 21.9 mm) ($P = 0.08$)
	Buvanendran et al. (2010)[31]	9	Pregabalin, yes	Neuropathic pain was absent in the treatment group (0%) versus placebo (8.7%) 3 months after total knee arthroplasty surgery and again 0% in the treatment group versus 5.2% in the placebo group 6 months after surgery
	Clarke et al. (2009)[49]	8	Gabapentin, no	6 months after total hip athroplasty surgery, the incidence and severity of chronic postsurgical pain was similar in all groups
	Fassoulaki et al. (2002)[51]	7	Gabapentin, no	3 months after surgery, the incidence of chronic pain, its severity, and the need for supplemental analgesics were not affected by either intervention. There was a report of increased "burning" pain in the control group versus the other 2 groups
	Fassoulaki et al. (2005)[52]	7	Gabapentin and multimodal regimen, yes	3 and 6 months after surgery, 18 of 22 (82%) and 12 of 21 (57%) of the controls reported chronic pain versus 10 of 22 (45%) and 6 of 20 (30%) in the treatment group. A significant difference was evident at 3 months, but not 6 months
	Moore et al. (2011)[45]	8	Gabapentin, no	3 months after surgery, the incidence of chronic pain, its severity, and the need for supplemental analgesics were similar between groups
	Pesonen et al. (2011)[53]	8	Pregabalin, yes	At 3 months after surgery, patients in the placebo group (23%) experienced non-zero pain significantly more often than patients in the pregabalin group (4%)
	Sen et al. (2009)[48]	7	Gabapentin, yes	The severity of incisional pain was significantly less in the gabapentin-treated group at 1, 3, and 6 months
	Sen et al. (2009)[47]	8	Gabapentin, yes	The severity of incisional pain was significantly less in the gabapentin-treated group at 1, 3, and 6 months
Self-report measures of disability/ physical function	Amr et al. (2010)[46]	7	Gabapentin N/A	No self-report measures of disability performed
	Brogly et al. (2008)[50]	6	Gabapentin N/A	No self-report measures of disability performed
	Burke et al. (2010)[34]	8	Pregabalin, yes	The Roland Morris disability score at 3 months was significantly lower in patients who received pregabalin (2.7 ± 2.4) than in those who received placebo (5.6 ± 4.8)
	Buvanendran et al. (2010)[31]	9	Pregabalin, yes	The KOOS–PS knee function score (0–100) was improved in patients who received perioperative pregabalin (12.4 ± 5.5) versus placebo patients with chronic pain (49.0 ± 16.2) and an age-matched nonchronic pain placebo cohort (25.7 ± 7.2)

(*Continued*)

Table 3. (Continued)

Outcome	Study	Quality/ Delphi score	$\alpha 2\delta$ agent/ preventive effects	Postoperative outcome results*($P < 0.05$)
	Clarke et al. (2009)[49]	8	Gabapentin, no	No difference between groups: "To what extent does your hip arthroplasty site pain interfere with your everyday activities?" Pain intensity was also similar in both groups at 6 months with bending knees to 90 degrees
	Fassoulaki et al. (2002)[51]	7	Gabapentin N/A	No self-report measures of disability performed
	Fassoulaki et al. (2005)[52]	7	Gabapentin and multimodal regimen N/A	No self-report measures of disability performed
	Moore et al. (2011)[45]	8	Gabapentin, no	Only 1 patient in each group reported that pain limited his or her daily function
	Pesonen et al. (2011)[53]	8	Pregabalin, yes	No self-report measures of disability performed
	Sen et al. (2009)[48]	7	Gabapentin, yes	Daily activities were significantly less affected in the gabapentin-treated patients at 1 and 3 months after surgery, but not at 6 months. Unfortunately, data were not provided, and the magnitude of this difference cannot be determined
	Sen et al. (2009)[47]	8	Gabapentin, no	A smaller number of patients in the gabapentin-treated group reported an impairment in daily activities 1 month after surgery. No difference was seen at 3 and 6 months after surgery
Functional outcome measurement	Buvanendran et al. (2010)[31]	9	Pregabalin, yes	Patients treated with pregabalin had greater active knee flexion 30 days after surgery
Significant side effects	Buvanendran et al. (2010)[31]	9	Pregabalin, yes	Patients who received 300 mg of pregabalin preoperatively followed by 50–150 mg of pregabalin BID experienced greater postoperative sedation and confusion
	Moore et al. (2011)[45]	8	Gabapentin, no	Patients receiving gabapentin were more likely to report their sedation as severe (19%) than patients receiving placebo (0%) within the first 24 hours postoperatively
	Pesonen et al. (2011)[53]	8	Pregabalin, yes	The CAM–ICU confusion test score was significantly reduced in the placebo group on the first day after extubation

BID = twice a day; CAM–ICU = the Confusion Assessment Method for Intensive Care Unit Patients; DN2 = Neuropathic Pain Diagnostic Questionnaire; KOOS–PS = Knee Osteoarthritis Outcome Score—Physical Function short form; N/A = not applicable; SCPB = superficial cervical plexus block; VAS = visual analogue scale.

outcomes presented in 6 of the 8 gabapentin trials. Among the 6 studies that could be included in meta-analysis, gabapentin caused a moderate-to-large reduction in the development of CPSP (pooled OR 0.52; 95% CI, 0.27 to 0.98; $P = 0.04$).

Preventive Effects of Pregabalin on CPSP

Three studies examined the preventive effects of perioperative pregabalin administration on the incidence and intensity of CPSP (Tables 2 and 3).[31,34,53] All 3 studies showed significant preventive analgesic effects in that there was a reduced incidence of pain and/or lower analgesic requirements at long-term follow-up, ≥2 months after surgery. Buvanendran et al.[31] randomized patients to receive a 300-mg preoperative dose of pregabalin followed by a 14-day twice-a-day (BID) regimen of pregabalin (50 mg to 150 mg) or placebo after total knee arthroplasty.[31] The Leeds Assessment of Neuropathic Symptoms and Signs[54] was used to diagnose the presence of chronic neuropathic pain at 3 and 6 months after surgery. The results showed that 8.7% and 5.2% of placebo-treated patients experienced chronic neuropathic pain 3 and 6 months after surgery, respectively. In contrast, not a single patient in the pregabalin-treated group was diagnosed with chronic neuropathic pain at either follow-up.[31]

Burke and Shorten[34] randomly assigned patients to receive either pregabalin (300 mg at 90 minutes preoperatively and 150 mg at 12 and 24 hours postoperatively) ($n = 20$) or placebo ($n = 20$) at corresponding times in a double-blind manner while undergoing lumbar discectomy. The primary outcome measure was a change in the intensity of pain as measured by a visual analog scale from the preoperative assessment to 3-month follow-up. Visual analog scale pain scores were lower at 3 months (37.6 ± 19.6 mm) in treated patients than in controls (25.3 ± 21.9 mm).[34]

Pesonen et al. randomly assigned 75 elderly patients (all 75 years or older) to receive either 150 mg of pregabalin before surgery and 75 mg of pregabalin BID for 5 postoperative days or placebo.[53] Elderly patients in this study who received pregabalin consumed fewer supplemental analgesics in the acute hospital period and had lower confusion assessment scores on postoperative day 1. The incidence of pain during movement was significantly lower in the pregabalin group 3 months after surgery.[53] Table 4 presents the odds ratios for the outcomes reported in the 3 pregabalin trials. Within the 2 studies that could be included in the meta-analysis, pregabalin caused a very large reduction in the development of CPSP (pooled OR 0.09; 95% CI, 0.02 to 0.79; $P = 0.007$).

Table 4. Odds Ratios for Reported Outcomes Comparing Placebo-Treated Patients with Gabapentin- or Pregabalin-Treated Patients

Study*	Outcome	Odds ratio (95% CI)	*P* value	Interpretation
Amr et al.[46]	Incidence of CPSP at 6 months	0.48 (0.16–1.43)	0.187	Gabapentin-treated at no lower risk than placebo-treated
Brogly et al.[50]	Number of Patients with DN2 score ≥3 at 6 months	0.11 (0.01–0.99)	0.048	Gabapentin-treated at lower risk than placebo-treated
Burke et al.[34]	Number of patients achieving a good outcome on the RMDQ	0.15 (0.03–0.85)	0.031	Pregabalin-treated at lower risk of poor functional outcome than placebo-treated
Buvanendran et al.[31]	CPSP at 3 months (S–LANS score >12)	0.04 (0.003–0.76)	0.032	Pregabalin-treated at lower risk than placebo-treated
	CPSP at 6 months (S–LANS score >12)	0.07 (0.00–1.33)	0.077	Pregabalin-treated at no lower risk than placebo-treated
Clarke et al.[49]	CPSP at 6 months	1.15 (0.44–2.95)	0.779	Gabapentin-treated at no lower risk than placebo-treated
Fassoulaki et al.[51]	Incidence of chronic pain at 3 months	0.78 (0.25–2.47)	0.671	Gabapentin-treated at no lower risk than placebo-treated
	Incidence of burning pain at 3 months	0.11 (0.01–1.03)	0.054	Gabapentin-treated at no lower risk than placebo-treated
Fassoulaki et al.[52]	CPSP at 3 months	0.19 (0.04–0.72)	0.015	Gabapentin-treated at lower risk than placebo-treated
	CPSP at 6 months	0.19 (0.05–0.73)	0.084	Gabapentin-treated at lower risk than placebo-treated
Moore et al.[45]	CPSP at 3 months	0.57 (0.09–3.61)	0.552	Gabapentin-treated at no lower risk than placebo-treated
Pesonen et al.[53]	CPSP at 3 months	0.11 (0.01–0.91)	0.041	Pregabalin-treated at lower risk than placebo-treated

CI = confidence interval; CPSP = chronic post surgical pain; DN2 = Neuropathic Pain Diagnostic Questionnaire; RMDQ = Roland Morris Disability Questionnaire; S–LANS = Leeds Assessment of Neuropathic Symptoms and Signs pain scale.
*Data from Sen et al.[47,48] not shown in published article nor supplied upon request.

Functional Outcomes and Disability Assessment

Six of the 11 trials included a long-term functional outcome measure or disability assessment.[31,34,45,47–49] These studies used self-report questionnaires to measure the impact of perioperative gabapentin and pregabalin on daily function in the long-term. The 4 gabapentin trials assessed this outcome by asking the patients, "What impact does pain currently have on your daily activities?"[45,47–49]

Four of the 6 trials found that perioperative gabapentin/pregabalin administration improved long-term functional outcomes. Two gabapentin trials reported that a single 1200-mg dose of gabapentin was associated with improved daily functioning 1 month after inguinal herniorrhaphy[47] and 1 and 3 months after total hysterectomy.[48] Two pregabalin trials[31,34] used valid and reliable tools to measure postoperative functional disability. Three months after lumbar discectomy the Roland Morris disability score was significantly lower in the patients who received perioperative pregabalin (2.7 ± 2.4) than in those who received placebo (5.6 ± 4.8).[34] Using scores from the Knee Osteoarthritis Outcome Score—Physical Function Short-form (KOOS–PS),[55] Buvanendran et al.[31] reported that patients who were diagnosed with chronic pain at 6 months (all placebo treated) had significantly worse KOOS–PS knee scores (49 ± 16.2) than did pregabalin-treated patients (12.4 ± 5.5). The KOOS–PS knee scores of the pregabalin-treated patients were also significantly better when compared with an age-matched nonchronic pain placebo cohort (25.7 ± 7.2).[31]

The remaining 2 gabapentin trials[45,49] reported that a single 600-mg dose of gabapentin did not affect functional outcomes or disability 3 and 6 months after surgery.

DISCUSSION

We systematically reviewed the published literature on the development of CPSP (≥2 months after surgery) after perioperative gabapentin or pregabalin administration. Our search yielded 11 trials published between 2002 and 2011. Of the 11 trials published, 8 were perioperative gabapentin trials, 4 of which (i.e., 50%) found that gabapentin decreased the incidence of chronic pain that persisted for more than 2 months after surgery. All pregabalin trials (3 of 3) demonstrated that pregabalin decreased the incidence of CPSP, and 2 of those trials also found an improvement in postsurgical patient function. These findings in individual trials were confirmed by our meta-analysis, which found that gabapentin and pregabalin caused an overall moderate-to-large reduction in CPSP.

The randomized controlled trials included in this systematic review are of moderate to high quality (mean Delphi score = 7.5/9). Fifty percent of the gabapentin trials and 100% of the pregabalin trials demonstrated a preventive effect with respect to the incidence/intensity of chronic postsurgical pain. This is compelling, but early, evidence suggesting that the reduction in CPSP may be linked to the perioperative administration of these medications. However, there are several shortcomings in the literature reviewed.

All 11 trials had small sample sizes and appeared to be underpowered for the secondary outcomes related to the incidence and severity of CPSP. The trial by Burke and Shorten[34] is the only one that powered the study, a priori, to detect an effect on chronic postoperative pain 3 months after surgery.[34] Importantly, and in contrast to the other 10 studies, Burke and Shorten[34] studied the magnitude of the change from preoperative persistent lumbar back pain to

CPSP as a function of the drug intervention. The other 10 trials used patients without preexisting pain, and reported the effects of the intervention in relation to the incidence and severity of CPSP without an appropriate power calculation for this endpoint.

Overall, the meta-analysis found very promising pooled effects of gabapentin and pregabalin; the magnitude of these effects, especially with respect to pregabalin given the limited number of studies (OR 0.09), may be clinically implausible. In addition, our analysis found that publication bias might have exaggerated the reported benefits of gabapentin and pregabalin. Consequently, this meta-analysis, while promising, should not be viewed as definitive.

Of the 8 gabapentin trials included in this review, 5 of the studies used single-dose gabapentin 1 to 2 hours before surgery.[45,47–50] The 3 trials that used 1200 mg gabapentin before surgery all reported that gabapentin reduced the incidence and severity of chronic pain.[47,48,50] The 2 trials that used a single 600-mg gabapentin administration 2 hours before surgery failed to show any reduction in the incidence or severity of CPSP at 3 and 6 months after surgery.[45,49] This is limited evidence to suggest that using a high preoperative dose of gabapentin (i.e., 1200 mg) is more effective than using low preoperative doses for the prevention of CPSP. Gabapentin at higher doses in the preoperative period may have a greater effect on blunting the peripheral and central sensitization processes that occur during surgery.

Of the 3 remaining gabapentin studies (all the studies continued gabapentin into the postoperative time period), only 1[52] demonstrated a significant pain reduction that persisted for 2 or more months after surgery. It has been well documented that the absorption profile of gabapentin in humans is inconsistent due to the active and saturable α-amino acid transport system.[56] Thus, the bioavailability of any given dose varies from 35% to 90%.[56] Without plasma samples, one cannot confirm therapeutic drug concentrations of gabapentin; no trial identified in this systematic review tested plasma levels to confirm therapeutic levels. The results from this systematic review suggest that pregabalin may have a more promising and effective role in the prevention of CPSP syndromes, given its more reliable absorption profile ($\geq$90% bioavailability of a single dose). Finally, although the results from this review suggest that higher doses of the α-2-δ ligands may produce greater antinociceptive efficacy, higher doses also unreliably increase somnolence and confusion in the clinical setting.[57,58] It is not uncommon to have patients who have been given 1200 mg of gabapentin 1 to 2 hours before surgery present in the postoperative care unit completely awake, while others are almost completely somnolent.

The factors involved in the development of CPSP are not well understood. Several observational studies have outlined highly variable rates of CPSP after total knee arthroplasty,[59] total hip arthroplasty,[59,60] cardiac surgery,[61] mastectomy,[62] inguinal hernia,[63] cholecystectomy,[64] and thoracotomy[65,66] populations. Future studies need to elaborate on the impact that CPSP syndromes have on patient function. To that end, recommendations have been made for the assessment of core measures and domains in clinical trials focused on chronic pain.[67] These recommendations include psychological, emotional, and physical variables in addition to those routinely assessed in perioperative anesthesia trials (i.e., pain incidence and severity, and analgesic consumption). Assessment of additional domains of physical function and the experience of pain during those functional activities may help to identify patient-related factors, which may impact the recovery process after surgery; these factors may also be associated with the development of CPSP.

Multimodal analgesic regimens involve the use of different classes of analgesic drugs to provide superior pain relief at rest and with movement, reduce opioid consumption, and reduce analgesic-related adverse effects.[68] Using multimodal perioperative acute pain strategies (i.e., different classes of medications that act on different nociceptive afferent and efferent pathways in the perioperative setting) has become the standard of care for many surgical populations.[68] These strategies have demonstrated good acute pain reductions and opioid sparing in the short term.[69,70] More data that assess these regimens at preventive endpoints are needed. One study in this review compared a comprehensive multimodal perioperative regimen to placebo and found that patients treated with the multimodal regimen had a decreased incidence and severity of CPSP and used less supplemental analgesics at 3 and 6 months.[52] The obvious limitation with this study and other similar studies is the inability to determine to what extent each medication affected the transition to chronic pain.

The field of human pain genetics is in its infancy. One review summarized the rapidly accumulating evidence from animal models of CPSP and studies in human twins, which showed that chronic pain was a complex heritable trait.[2] Several studies have recently reported on polymorphisms in certain genes that predispose carriers to transition to pain chronicity.[71–73] Burke and Shorten[34] attempted to link their findings to known human genetic polymorphisms associated with pain. They did not report significant associations with GCH1 or OPRM1 in the 38 patients followed. However, there were several shortcomings to the genetic data presented, including too few patients, the absence of a detailed description of the assays/methods used with respect to gene mapping, and appropriate input from genetic statisticians. This information is essential for future researchers attempting to replicate and validate positive genetic findings.

Novel Postulated Mechanisms of Action of Gabapentinoids

The proposed mechanism of action of gabapentin and pregabalin is believed to be the selective inhibitory binding to the $\alpha 2\delta$ subunit of voltage-dependent calcium channels in activated neurons.[74] The binding of gabapentin to the $\alpha 2\delta$ subunit reduces the expression of voltage-dependent calcium channels.[75] A point mutation in the $\alpha 2\delta$ type 1 subunit (R217A) prevents the binding of gabapentin to the calcium channel.[76] The analgesic properties of both gabapentin and pregabalin are greatly reduced in mice expressing this point mutation.[77] The mutation also prevents the ability of gabapentin to reduce calcium channel expression.[75]

Several lines of evidence suggest that this high-affinity site contributes to, but may not fully account for, the analgesic

properties of gabapentin. The increased expression of the α2δ subunit that occurs in animal models of hyperalgesia is not a prerequisite for the short-term analgesic actions of gabapentin.[78] In addition, a comparison of the antinociceptive properties of gabapentin and stereoisomeric analogues of gabapentin revealed a stereospecific analgesic effect of some but not all of the gabapentin analogues;[79] but surprisingly, some of the gabapentin analogues with high affinity for the α2δ subunit did not have antinociceptive properties.

Some evidence suggests that the α2δ subunit also regulates synaptogenesis through mechanisms that are independent of Ca^{2+} channel function.[80] Specifically, the α2δ subunit is a receptor for thrombospondins, proteins that are secreted by astrocytes and promote synapse formation.[81] Gabapentin disrupts the interaction between thrombospondins and the α2δ subunit, resulting in decreased synapse formation.[80] The disruption of α2δ subunit-mediated synaptogenesis by gabapentin may also contribute to the analgesic effects of gabapentin and pregabalin, particularly for the treatment of chronic pain.

Gabapentin and pregabalin have been proposed to act through a wide variety of mechanisms beyond inhibiting the actions of the α2δ subunit protein. Gabapentin inhibits glutamate release, increases the activity of *N*-methyl-D-aspartate receptors, inhibits the activity of voltage-gated sodium channels, and enhances the activity of voltage-gated potassium channels.[82] Additionally, prolonged exposure to gabapentin can increase the amplitude of a tonic inhibitory GABAergic conductance[83] that may regulate pain processes.[84] However, it remains to be determined whether these mechanisms contribute to the analgesic effects of gabapentin and pregabalin.

CONCLUSIONS

Our systematic review found promising results for gabapentin with respect to the reduction of CPSP. Commonalities among the 4 positive studies should be explored in future trials given that there appears to be emerging basic science data to support its plausibility with respect to the prevention of CPSP. The 3 pregabalin trials included in this systematic review reported even greater promise in preventing the conversion from acute pain to CPSP. The improved absorption profile of pregabalin may be a primary reason for its improved efficacy. The study of the antecedent patient-related factors that may also predict the development of CPSP is important, and future studies should expand current outcome domains. Appropriate measures of psychological and physical functioning should be included, along with measures of chronic pain incidence and severity. Given the limited number of studies identified in our review, the clinical heterogeneity of the trials identified, and the suggestion that a publication bias may be present, future well-designed, appropriately powered studies are needed to clarify whether gabapentin and pregabalin have a perioperative role in the prevention of CPSP.

AUTHOR AFFILITATIONS

From the *Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Ontario, Canada; †Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; ‡Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada; §Centre de Recherche Universite' Laval Robert-Giffard, Universite' Laval, Que'bec, Canada; ‖Library and Information Services, University Health Network, Toronto, Ontario, Canada; ¶Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada; #Institute of Health Policy Management and Evaluation, University of Toronto; **Department of Psychology and School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada.

STUDY FUNDING

Hance Clarke is supported by a Canadian Institutes of Health Research PhD Fellowship Award. Hance Clarke and Duminda Wijeysundera are supported by Merit Awards from the Department of Anesthesia at the University of Toronto. Duminda Wijeysundera is supported by a Clinician Scientist Award from the Canadian Institutes of Health Research. Joel Katz is supported by a Canada Research Chair in Health Psychology at York University.

APPENDIX 1. Search Terms

Pregabalin or gabapentin-related terms	Perioperative/preemptive/preventive and related terms
Pregabalin	exp perioperative care/
lyrica	intraoperative care/
Gabapentin	postoperative care/
60142-96-3.rn. (registry number)	preoperative care/
neurontin	exp Anesthesia Recovery Period/
((alpha adj2 delta) or (alpha2delta.mp) AND exp Calcium channel blockers/	perioperat*
	peri-operat*
	peroperat*
	postop*
Chronic pain-related terms	post-op*
exp chronic diseases/ AND exp pain/	preoperat*
(chronic* adj4 pain*)	pre-operat*
	intraoperat*
	intra-operat*
	(before adj2 surgery)
	(before adj2 operat*4)
	(prior adj2 surgery)
	(prior adj2 operat*4)
	operation?
	operative*
	(surgery or surgeries or surgeon? or surgical*)
	su.fs. (surgery floating subheading)
	exp surgical procedures, operative/
	exp Anesthesiology/
	anesthes*
	anaesthes*
	exp Anesthesia/
	anesthe*.jn,in. (journal or institution)
	anaesthe*.jn,in. (journal or institution)
	preincision?
	pre-incision?
	postincision?
	post-incision?
	preemptive*
	pre-emptive*
	preventive*

DISCLOSURES

Name: Hance Clarke, MSc, MD, FRCPC.
Contribution: This author designed and conducted the research study and wrote the manuscript.
Attestation: Hance Clarke has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Robert P. Bonin, PhD.
Contribution: This author helped to write the manuscript.
Attestation: Robert P. Bonin has approved the final manuscript.
Name: Beverley A. Orser, MD, PhD, FRCPC.
Contribution: This author designed and conducted the research study and wrote the manuscript.
Attestation: Beverley Orser has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Marina Englesakis, BA, MLIS.
Contribution: This author designed and conducted the research study and wrote the manuscript.
Attestation: Marina Englesakis has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Duminda N. Wijeysundera, MD, PhD, FRCPC.
Contribution: This author designed and conducted the research study and wrote the manuscript.
Attestation: Duminda N. Wijeysundera has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Joel Katz, PhD.
Contribution: This author designed and conducted the research study and wrote the manuscript.
Attestation: Joel Katz has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Spencer S. Liu, MD.

REFERENCES

1. Macrae W, Davies H. Chronic post surgical pain. In: Crombie IK, Linton S, Croft P, Von Knorff M, LeResche L, eds. Epidemiology of Pain. Washington, DC: IASP Press, 1999:125–42
2. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009;9:723–44
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25
4. Katz J. Pain begets pain—predictors of long-term phantom limb pain and post-thoracotomy pain. Pain Forum 1997;6: 140–4
5. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93:1123–33
6. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003;97:534–40
7. Gilron I, Milne B, Hong M. Cyclooxygenase-2 inhibitors in postoperative pain management: current evidence and future directions. Anesthesiology 2003;99:1198–208
8. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg 2005;100:475–80
9. Menigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100:1394–9
10. Mathiesen O, Jacobsen LS, Holm HE, Randall S, Adamiec-Malmstroem L, Graungaard BK, Holst PE, Hilsted KL, Dahl JB. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008;101:535–41
11. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004;51:358–63
12. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of *N*-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004;98: 1385–400
13. Clarke H, Woodhouse L, Kennedy D, Stratford P, Katz J. Strategies aimed at preventing chronic post-surgical pain: comprehensive peri-operative pain management after total joint replacement surgery. Physiother Can 2011;63:289–304
14. Katz J, Clarke H, Seltzer Z. Preventive analgesia: quo vadimus? Anesth Analg 2011;113:1242–53
15. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. Pain 2008;137:473–7
16. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Ann Rev Neurosci 2009;32:1–32
17. Ifuku M, Iseki M, Hidaka I, Morita Y, Komatus S, Inada E. Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy. Pain Med 2011;12:1112–6
18. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 2009;374:1252–61
19. Katz J. Pre-emptive analgesia: evidence, current status and future directions. Eur J Anaesthesiol Suppl 1995;10:8–13
20. Kissin I. Preemptive analgesia: terminology and clinical relevance. Anesth Analg 1994;79:809–10
21. Wall PD. The prevention of postoperative pain. Pain 1988;33:289–90
22. Katz J, Clarke H. Preventive analgesia and beyond: current status, evidence, and future directions. In: Macintyre PE, Rowbotham DJ, Howard R, eds. Clinical Pain Management: Acute Pain. 2nd ed. London: Hodder Arnold Ltd., 2008:154–98
23. Guay DR. Update on gabapentin therapy of neuropathic pain. Consult Pharm 2003;18:158–70, 173–8
24. Laird MA, Gidal BE. Use of gabapentin in the treatment of neuropathic pain. Ann Pharmacother 2000;34:802–7
25. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, Coderre T, Morley-Forster PK, Stinson J, Boulanger A, Peng P, Finley GA, Taenzer P, Squire P, Dion D, Cholkan A, Gilani A, Gordon A, Henry J, Jovey R, Lynch M, Mailis-Gagnon A, Panju A, Rollman GB, Velly A. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag 2007;12:13–21
26. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain—a systematic review of randomized controlled trials. Pain 2006;126:91–101
27. Peng PW, Wijeysundera DN, Li CC. Use of gabapentin for perioperative pain control—a meta-analysis. Pain Res Manag 2007;12:85–92
28. Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can JAnaesth 2006;53:461–9
29. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007;105:1805–15
30. Field MJ, Oles RJ, Lewis AS, McCleary S, Hughes J, Singh L. Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 1997;121:1513–22
31. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesth Analg 2010;110:199–207

32. Mathiesen O, Rasmussen ML, Dierking G, Lech K, Hilsted KL, Fomsgaard JS, Lose G, Dahl JB. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand 2009;53:227–35
33. Ittichaikulthol W, Virankabutra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S. Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy: a randomized, double-blind trial. J Med Assoc Thai 2009;92:1318–23
34. Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg 2010;110:1180–5
35. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. Aesthet Surg J 2008;28:421–4
36. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. Obes Surg 2010;20:1678–81
37. Deleted in proof.
38. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235–41
39. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58
40. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60
41. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34
42. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006;25:3443–57
43. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700
44. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535
45. Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. Anesth Analg 2011;112:167–73
46. Amr YM, Yousef AAA-M. Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clin J Pain 2010;26:381–5
47. Sen H, Sizlan A, Yanarates O, Senol MG, Inangil G, Sucullu I, Ozkan S, Dagli G. The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol 2009;26:772–6
48. Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G, Turan A. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg 2009;109:1645–50
49. Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J, Katz J, Kay J. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. Acta Anaesthesiol Scand 2009;53:1073–83
50. Brogly N, Wattier JM, Andrieu G, Peres D, Robin E, Kipnis E, Arnalsteen L, Thielemans B, Carnaille B, Pattou F, Vallet B, Lebuffe G. Gabapentin attenuates late but not early postoperative pain after thyroidectomy with superficial cervical plexus block. Anesth Analg 2008;107:1720–5
51. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95:985–91
52. Fassoulaki A, Triga A, Melemeni A, Sarantopoulos C. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anesth Analg 2005;101:1427–32
53. Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth 2011;106:873–81
54. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. J Pain 2005;6:149–58
55. Perruccio AV, Stefan Lohmander L, Canizares M, Tennant A, Hawker GA, Conaghan PG, Roos EM, Jordan JM, Maillefert JF, Dougados M, Davis AM. The development of a short measure of physical function for knee OA KOOS—Physical Function Shortform (KOOS-PS)—an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:542–50
56. Cheng JK, Chiou LC. Mechanisms of the antinociceptive action of gabapentin. J Pharmacol Sci 2006;100:471–86
57. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, Singh U, Singh PK. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol 2005;17:65–8
58. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009;108:1140–5
59. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. Pain 2011;152:566–72
60. Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H. Chronic pain following total hip arthroplasty: a nationwide questionnaire study. Acta Anaesthesiol Scand 2006;50:495–500
61. Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WC, Chambers WA. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. Pain 2003;104:265–73
62. Bruce J, Poobalan AS, Smith WC, Chambers WA. Quantitative assessment of chronic postsurgical pain using the McGill Pain Questionnaire. Clin J Pain 2004;20:70–5
63. Aasvang E, Kehlet H. Surgical management of chronic pain after inguinal hernia repair. Br J Surg 2005;92:795–801
64. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. Scand J Gastroenterol 2005;40:1358–64
65. Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011;55:60–8
66. Guastella V, Mick G, Soriano C, Vallet L, Escande G, Dubray C, Eschalier A. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. Pain 2011;152:74–81
67. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19
68. Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. Anesthesiol Clin North Am 2005;23:185–202
69. Clarke H, Pereira S, Kennedy D, Gilron I, Katz J, Gollish J, Kay J. Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. Pain Res Manag 2009;14:217–22
70. Horlocker TT, Kopp SL, Pagnano MW, Hebl JR. Analgesia for total hip and knee arthroplasty: a multimodal pathway featuring peripheral nerve block. J Am Acad Orthop Surg 2006;14:126–35

71. Costigan M, Belfer I, Griffin RS, Dai F, Barrett LB, Coppola G, Wu T, Kiselycznyk C, Poddar M, Lu Y, Diatchenko L, Smith S, Cobos EJ, Zaykin D, Allchorne A, Shen PH, Nikolajsen L, Karppinen J, Mannikko M, Kelempisioti A, Goldman D, Maixner W, Geschwind DH, Max MB, Seltzer Z, Woolf CJ. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain 2010;133:2519–27
72. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006;12:1269–77
73. Nissenbaum J, Devor M, Seltzer Z, Gebauer M, Michaelis M, Tal M, Dorfman R, Abitbul-Yarkoni M, Lu Y, Elahipanah T, delCanho S, Minert A, Fried K, Persson AK, Shpigler H, Shabo E, Yakir B, Pisante A, Darvasi A. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res 2010;20:1180–90
74. Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin—calcium channel alpha2-delta [Cavalpha2-delta] ligands. Pain 2009;142:13–6
75. Mich PM, Horne WA. Alternative splicing of the Ca2+ channel beta4 subunit confers specificity for gabapentin inhibition of Cav2.1 trafficking. Mol Pharmacol 2008;74:904–12
76. Wang M, Offord J, Oxender DL, Su TZ. Structural requirement of the calcium-channel subunit alpha2delta for gabapentin binding. Biochem J 1999;342:313–20
77. Field MJ, Cox PJ, Stott E, Melrose H, Offord J, Su TZ, Bramwell S, Corradini L, England S, Winks J, Kinloch RA, Hendrich J, Dolphin AC, Webb T, Williams D. Identification of the alpha2-delta-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. Proc Natl Acad Sci USA 2006;103:17537–42
78. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, Yaksh TL. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci 2001;21:1868–75
79. Urban MO, Ren K, Park KT, Campbell B, Anker N, Stearns B, Aiyar J, Belley M, Cohen C, Bristow L. Comparison of the antinociceptive profiles of gabapentin and 3-methylgabapentin in rat models of acute and persistent pain: implications for mechanism of action. J Pharmacol Exp Ther 2005;313:1209–16
80. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E, Chakraborty C, Mulinyawe SB, Annis DS, Huberman AD, Green EM, Lawler J, Dolmetsch R, Garcia KC, Smith SJ, Luo ZD, Rosenthal A, Mosher DF, Barres BA. Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. Cell 2009;139:380–92
81. Christopherson KS, Ullian EM, Stokes CC, Mullowney CE, Hell JW, Agah A, Lawler J, Mosher DF, Bornstein P, Barres BA. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell 2005;120:421–33
82. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006;6:108–13
83. Cheng VY, Bonin RP, Chiu MW, Newell JG, MacDonald JF, Orser BA. Gabapentin increases a tonic inhibitory conductance in hippocampal pyramidal neurons. Anesthesiology 2006;105:325–33
84. Bonin RP, Labrakakis C, Eng DG, Whissell PD, Koninck YD, Orser BA. Pharmacological enhancement of delta-subunit-containing GABA(A) receptors that generate a tonic inhibitory conductance in spinal neurons attenuates acute nociception in mice. Pain 2011;152:1317–26