Do Surgical Patients Benefit from Perioperative Gabapentin/Pregabalin? A Systematic Review of Efficacy and Safety

Elina M. Tiippana, MD*

Katri Hamunen, MD, PhD*

Vesa K. Kontinen, MD, PhD*#

Eija Kalso, MD, PhD*#

BACKGROUND: Gabapentin and pregabalin have antiallodynic and antihyperalgesic properties useful for treating neuropathic pain. These properties may also be beneficial in acute postoperative pain. In this study we evaluated randomized, controlled trials examining the analgesic efficacy, adverse effects, and clinical value of gabapentinoids in postoperative pain.

METHODS: A systematic search of Medline, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) databases yielded 22 randomized, controlled trials on perioperative administration of gabapentinoids for postoperative pain relief.

RESULTS: Pain relief was better in the gabapentin groups compared with the control groups. The opioid-sparing effect during the first 24 h after a single dose of gabapentin 300–1200 mg, administered 1–2 h preoperatively, ranged from 20% to 62%. The combined effect of a single dose of gabapentin was a reduction of opioid consumption equivalent to 30 ± 4 mg of morphine (mean ± 95% CI) during the first 24 h after surgery. Metaregression analysis suggested that the gabapentin-induced reduction in the 24-h opioid consumption was not significantly dependent on the gabapentin dose. Gabapentin reduced opioid-related adverse effects, such as nausea, vomiting, and urinary retention (number-needed-to-treat 25, 6, and 7, respectively). The most common adverse effects of the gabapentinoids were sedation and dizziness (number-needed-to-harm 35 and 12, respectively).

CONCLUSIONS: Gabapentinoids effectively reduce postoperative pain, opioid consumption, and opioid-related adverse effects after surgery. Conclusions about the optimal dose and duration of the treatment cannot be made because of the heterogeneity of the trials. Studies are needed to determine the long-term benefits, if any, of perioperative gabapentinoids.

(Anesth Analg 2007;104:1545–56)

The current concept of multimodal postoperative analgesia is mainly based on the combination of opioids, nonsteroidal antiinflammatory drugs (NSAIDs) or paracetamol, small-dose ketamine, and perioperative administration of local anesthetics. The use of opioids may be limited by adverse effects, such as nausea, vomiting, excessive sedation, pruritus, and urinary retention, the incidences of which have been reported to be 25%, 20%, 3%, 15%, and 23%, respectively (1). Interventional techniques such as epidural analgesia are effective but require additional work and carry the potential risk of serious complications. NSAIDs are associated with damage to gastrointestinal mucosa, bleeding, renal toxicity, allergic reactions, and heart failure. Cyclooxygenase-2 selective NSAIDs may have prothrombotic properties, increasing the risk of stroke and myocardial ischemia. Ketamine is psychotogenic. A drug that has analgesic properties, opioid-sparing effects, possibly reduces opioid tolerance, relieves anxiety, and is not associated with the adverse effects typical for the traditional analgesics would be an attractive adjuvant for perioperative analgesia.

Gabapentin was introduced as an antiepileptic drug in 1993. It has been extensively used to treat painful neuropathies in patients with diabetic polyneuropathy, postherpetic neuralgia, and neuropathic pain in general (2). The mechanism of action of gabapentin and its successor, pregabalin is likely mediated by binding to the 21 subunits of the presynaptic voltage-gated calcium channels, which are upregulated in the dorsal root ganglia and spinal cord after surgical trauma. Gabapentin may produce antinociception by inhibiting calcium influx via these channels, and subsequently inhibiting the release of excitatory neurotransmitters (e.g., substance P, calcitonin

From the *Pain Clinic, Department of Anaesthesia and Intensive Care Medicine, Helsinki University Central Hospital; and #Department of Pharmacology, Institute of Biomedicine, University of Helsinki, Helsinki, Finland.

Accepted for publication February 13, 2007.

Supported by the Helsinki University Central Hospital Research Funds.

Address correspondence to Elina Tiippana and reprint requests to Eija Kalso, MD, Pain Clinic, Department of Anaesthesia and Intensive Care Medicine, Helsinki University Central Hospital, P.O. Box 340, FIN-00029 HUS, Helsinki, Finland. Address e-mail to elina.tiippana@hus.fi or eija.kalso@helsinki.fi.

DOI: 10.1213/01.ane.0000261517.27532.80

gene-related peptide) from the primary afferent nerve fibers in the pain pathway. Bioavailability of gabapentin varies inversely with dose. The peak plasma level is achieved 3 h after ingestion of a single 300 mg capsule. Gabapentin is not metabolized and is eliminated unchanged in the urine with an elimination half-life of 5–9 h. Because of the lack of hepatic metabolism and low protein binding, gabapentin has no known clinically relevant drug interactions (3). However, gabapentin has saturable absorption within the usual dosing. Pregabalin has a more favorable pharmacokinetic profile, including dose-independent absorption (4,5).

Gabapentin has antiallodynic and antihyperalgesic properties with only a minor effect on normal nociception (6). It reduces the hyperexcitability of dorsal horn neurons induced by tissue injury (7,8). Central sensitization of these neurons is important in chronic neuropathic pain, but also occurs after trauma and surgery. Reduction in central sensitization by an antihyperalgesic drug like gabapentin may reduce acute postoperative pain. Gabapentin may also prevent opioid tolerance (9). Both gabapentin and pregabalin have anxiolytic properties (10–13).

In recent years, gabapentin has been introduced as an adjunct in the multimodal approach to managing acute postoperative pain. Initial studies have been encouraging. However, before it can be recommended for routine clinical use more data on efficacy, dosing, adverse effect profile, ideal timing, and duration of treatment to reduce acute postoperative pain and to prevent chronic postoperative pain are needed. The aim of this systematic review was to evaluate the available literature examining the analgesic efficacy, adverse effects, and clinical utility of gabapentinoids in postoperative pain management.

METHODS

This review was performed according to the standards described in "The Quality of Reporting of Meta-analyses" (QUOROM) statement (14).

Literature Search

A systematic search was performed in the following databases: Medline (from 1966), PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) using the following words: "gabapentin or pregabalin or gabapentinoids or Lyrica or Neurontin" and "postoperative pain." To identify additional trials, Pfizer Corporation was contacted and reference lists of reports and reviews were checked. Abstracts or unpublished observations were not considered for inclusion. Authors were not contacted for original data. There was no language restriction. The last search was performed in September 2006.

Inclusion and Exclusion Criteria

All randomized, placebo- or active-controlled clinical trials described as double-blind and restricted to humans were included. All studies had a minimum of 10 patients in each study group as recommended by L'Abbé et al. (15). The intervention considered by this review was treatment with gabapentin or pregabalin given orally, in any dose, during the perioperative period.

Data Extraction

The following items were collected on the data extraction form: 1) publication details, 2) patient population, number of patients, age, gender, surgical procedure, 3) description of intervention, 4) design, study duration and follow-up, 5) intra- and postoperative analgesics, 6) outcome measures, 7) analgesic outcome results and 8) withdrawals and adverse effects. This was performed independently by two investigators (E.T, K.H.) and reviewed by the others (E.K, V.K.). Also the sources of funding were checked to determine if the trial was sponsored by the pharmaceutical industry and, if so, whether this was reported, as recommended by the CONSORT statement (16). Study quality (randomization/allocation concealment; details of blinding measures; withdrawals and dropouts) was evaluated using the three-item (1–5) Oxford Quality Scale (17). Validity was evaluated using the five-item (1–16) Oxford Pain Validity Scale (18). Scorings were performed independently by two reviewers (E.T, K.H.). In case of discrepancy, a third reviewer (E.K.) was consulted and consensus was reached by discussion.

Data Handling and Analysis

The three main outcome measures were pain scores, total analgesic consumption for the first 24 h, and treatment side effects. Quantitative analysis was performed for the opioid consumption on studies in which a single, perioperative dose of gabapentin was given, the duration of the postoperative observation period was at least 24 h, and the opioid consumption data were given as means, with indication of variance. For the statistical analysis, fentanyl and tramadol consumption values were scaled to arbitrary "morphine equivalent" units, using 100:1 and 1:10, respectively, as the conversion factors. The meta-analysis was calculated with the Comprehensive Meta Analysis program, version 2.2.027 (Biostat, Englewood, NJ). Based on high clinical heterogeneity across the studies, including different types of surgery, differences in anesthesia, opioids, and adjunctive analgesics, the random effects model was chosen. The significance level was set at 0.05. Different gabapentin doses (19) and dosing times (20) in a single study were handled as subgroups within the study. The studies were combined using the random effects model assuming a common among-study variance component across subgroups. A possible dose-response on the opioid-sparing effect of a single-dose of gabapentin was analyzed using metaregression (Comprehensive Meta Analysis, version 2.2.027, Biostat) after a single

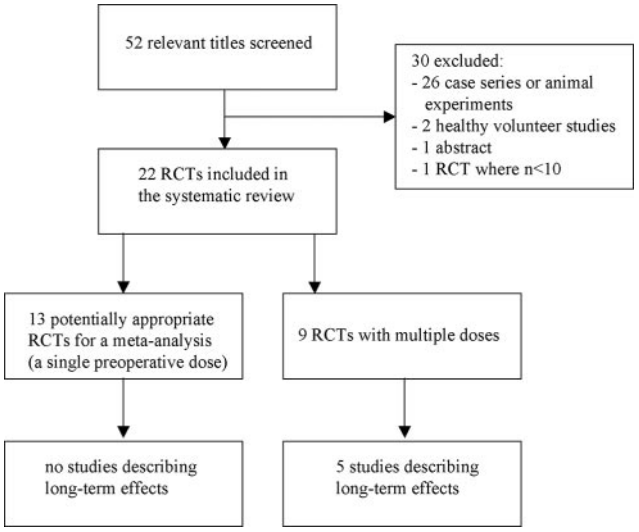

Figure 1. Flow diagram of the review. RCT = randomized, controlled trials.

300–1200 mg preoperative dose of gabapentin 1–2 h before surgery for the first 24 h. Pain intensity difference between the control and gabapentin groups (PIDc-g) was calculated by deducting the pain intensity in the treatment group from the value in the control group at different time points. The number-needed-to-treat was calculated for the reduction of the incidence of nausea, vomiting, and urinary retention caused by gabapentin in comparison to placebo, using the pooled raw data method. The number-needed-to-harm was calculated for the increase of the incidence of sedation and dizziness caused by gabapentin in comparison with placebo during the 24-h follow-up after a single 1200 mg dose of gabapentin administered 1–2 h preoperatively, using the pooled raw data method.

RESULTS

The searches identified 52 possible titles, of which 30 were excluded (Fig. 1). Twenty-six of these were not clinical trials. Two studies examined healthy volunteers (7,21) and one was an abstract (22). In a small pilot study about gabapentin and postoperative delirium, there were only nine patients in the gabapentin group. This study did not meet the inclusion criteria (23). A total of 22 randomized, controlled, double-blind clinical trials of perioperative administration of gabapentin or pregabalin for postoperative pain relief were identified (10,19,20,24–42). All studies are presented in Table 1. A more detailed description of all studies is presented in the Appendix available on the journal's website (http://anesthesia-analgesia.org). A total of 1909 patients were studied, 786 received gabapentin, and 99 received pregabalin (30). The patients' ages ranged from 18 to 74 yr. There were 1265 women and 509 men. In three studies gender was not reported. Gabapentin doses ranged from 300 to 1200 mg. In the pregabalin study the dose was 50 or 300 mg. Thirteen of the studies were single-dose trials and nine examined multiple dosing of gabapentin or pregabalin. The duration of the trials varied between 4 h and 10 days. In the only trial in which pregabalin was studied (30), it was administered postoperatively after dental surgery. Pregabalin 300 mg was better than ibuprofen regarding the patients' satisfaction with pain relief and duration of analgesia. A combination of gabapentin and rofecoxib was given in one treatment arm, which was not included in the present analysis (31).

Two studies disclosed partial pharmaceutical industry sponsorship (26,30). Pfizer provided the medication in another study (25). Two studies received funding independent from the pharmaceutical industry (10,31) and in the other studies the source of funding was not reported. There were no differences in the positive and negative outcomes between the sponsored and independent studies.

The PIDc-g at rest and on movement during the first 24 h after a single 1200 mg dose of gabapentin administered 1–2 h before surgery are presented in Figure 2. There was wide variation in pain at rest after different types of surgery. Pain on movement after a single preoperative dose of gabapentin was studied in only two trials (24,38). After hysterectomy (38) the PIDc-g was greatest in the early postoperative phase and it decreased after 12 h. The difference was not so clear after thyroidectomy (24), in which pain on movement was measured after swallowing.

Five of 22 studies reported the time to first analgesic request as an outcome (10,27,28,36,40). Two of these studies (10,40) found a difference favoring gabapentin 1200 mg over placebo. A meta-analysis was considered inappropriate because of clinical heterogeneity of the studies.

The opioid-sparing effect during the first 24 h after a single preoperative dose of gabapentin 300–1200 mg, administered 1–2 h before surgery, ranged from 20% to 62%. Figure 3 shows the results of the meta-analysis of the opioid-sparing effect. The combined effect of a single dose of gabapentin on opioid consumption was equivalent to reduction of 30 ± 4 mg of morphine (mean ± 95% CI) consumed during the first 24 h after the surgery. Heterogeneity among the studies was significant ($Q = 93$, $df = 11$, $P < 0.0001$). The dose of gabapentin did not seem to be an important source of the heterogeneity. In metaregression, the gabapentin-induced reduction in the 24-h opioid consumption was not significantly dependent on the gabapentin dose (data not shown).

Long-term effects were reported in five trials (Table 2). The number of patients ranged from 46 to 103 per study. Administration of gabapentin continued 2–10 days after surgery. Follow-up times varied from 1 to 6 mo. Three studies were of abdominal hysterectomies and two of mastectomies. Four of five studies investigating the long-term effects found a significant difference in acute pain favoring gabapentin in comparison to placebo. Two of these studies found a difference in

Table 1. Randomized, Double-Blind, Controlled Studies of Gabapentin/Pregabalin in Postoperative Pain

Reference	*n*, active/ control	Age (yr)	Male/ Female	Surgical procedure	Study duration and follow-up	Dosing, active/control	Intraoperative analgesics	Postoperative analgesics	Main results	QS/ OPVS
Al-Mujadi 2006 (24)	37/35	32–64	19/53	Thyroidectomy	24 h	GBP 1200 mg or PL 2 h preop.	Fentanyl at induction	Morphine 3 mg iv every 5 min if needed	VAS/rest and movement lower with GBP vs PL; total morphine consumption reduced 48% with GBP	5/14
Dierking 2004 (25)	39/32	26–73	0/71	Abdominal hysterectomy	24 h	GBP 1200 mg or PL 1 h preop, then GBP 600 mg or PL 8, 16, 24 h after initial dose	Remifentanil infusion	Morphine at skin closure, PCA-morphine postop.	PCA-morphine consumption reduced 32% with GBP vs PL; VAS: NS	5/14
Dirks 2002 (26)	31/34	52–69	0/65	Radical mastectomy with axillary dissection	4 h	GBP 1200 mg or PL 1 h preop.	Remifentanil infusion	Alfentanil at skin closure, PCA-morphine	VAS/rest: NS; VAS/movement: reduced at 2 h and 4 h postop; PCA-morphine consumption reduced 48% with GBP vs PL	5/14
Fassoulaki 2002 (27)	22/21/24	35–54	0/67	Lumpectomy or mastecto-my with axillary dissection	10 days, follow-up 3 mo (phone interview)	GBP 400 mg t.i.d. or mexiletine 200 mg t.i.d. or PL, for 10 days postop, 1st dose on evening before surgery	None	Propoxy phene + para-cetamol im 24 h, codeine + paracetamol po 2–10 pod on demand	VAS/rest: reduced on 3rd pod with GBP and mexiletine; VAS/ movement: reduced on 2–5 pod (mexil. vs GBP: NS); codeine + paracetamol consumption reduced on 2–10 pod (mexil. vs GBP: NS)	4/12
Fassoulaki 2005 (28)	23/23	41–57	0/46	Radical mas-tectomy or lumpectomy with axillary dissection	8 days, follow-up by interviews 3 and 6 mo	GBP 400 mg 4 times, 1st dose on evening before surgery continued until 8th pod plus 20 g EMLA cream from the day of surgery until 3rd pod plus ropivacaine intra operatively, or PL	Not reported	Paracetamol im in PACU as needed, codeine + paracetamol po in the ward as needed	VAS/rest: reduced with treatment 0 h, 1, 3 and 5 pod; VAS/movement: reduced with treatment 0 h, 1–3 and 8 pod; chronic pain and analgesic use at home less with treatment after 3 mo; NS after 6 mo; fewer patients requiring analgesics in PACU with treatment; rescue analgesic con sumption reduced with treatment	5/12
Fassoulaki 2006 (29)	25/28	36–48	0/53	Abdominal hysterectomy for benign disease (Pfannenstiel incision)	5 pod, follow-up 1 mo (phone interview)	GBP 400 mg every 6 h starting at 12:00 PM the day before surgery continuing for 5 days, or PL	Not reported	PCA-morphine for 48 h, then paracetamol 500 mg + code ine 30 mg tab lets on demand	VAS/rest and movement: NS; 1 mo after sur-gery more pts in PL group (81%) vs GBP group (36%) had pain in surgical area and intensity of pain decreased in GBP group; analgesic consumption in acute phase and after 1 mo: NS	5/14

Table 1. (continued)

Reference	*n*, active/control	Age (yr)	Male/Female	Surgical procedure	Study duration and follow-up	Dosing, active/control	Intraoperative analgesics	Postoperative analgesics	Main results	QS/OPVS
Gilron 2005 (31)	23/29/27/24	34–55	0/103	Abdominal hysterectomy	72 h postop, follow-up 30 days (contact by phone on 30 pod)	GBP 600 mg t.i.d. or rofecoxib 50 mg/d or GBP 600 mg t.i.d. + rofecoxib 50 mg/d or PL started 1 h before surgery continuing 72 h	Fentanyl bolus during first 30 min iv-morphine 30 min before end of surgery	PCA-morphine which was discontinued when no longer needed, then morphine po every 3 h as needed	GBP + rofecoxib better analgesia than single GBP (but not rofecoxib) for pain at movement; GBP + rofecoxib better analgesia than either single agent; all 3 treatments reduced PCA-morphine consumption but more with GBP + rofecoxib	5/13
Hill 2001 (30)	49/50/49/50	18–54	82/116	Removal of third molar teeth	8 h observation a diary at home 12 h postdose	Pregabalin 50 mg or 300 mg or ibuprofen 400 mg or PL postop. when pain at least mode rate	Local anesthesia with mepivacaine or prilocaine without vasoconstrictor	Study discontinued when rescue anal gesics given	Pregabalin 300 mg superior to PL and pregabalin 50 mg on all outcome measures; pregabalin 50 mg vs PL: NS; ibuprofen superior to PL; duration of analgesia longer with pregabalin 300 mg vs PL and ibuprofen	3/12
Menigaux 2005 (10)	20/20	23–39	27/13	Arthroscopic anterior cruciate ligament repair using hamstring autograft	48 h	GBP 1200 mg or PL 1–2 h before surgery	Remifentanil infusion, morphine iv 30 min before end of surgery	PCA-morphine, ketoprofen po	Max knee flexions more extensive with GBP; VAS during 1st h postop. lower with GBP, then NS; time to first analgesic request longer with GBP; total PCA-morphine consumption 58% lower with GBP vs PL	5/14
Mikkelsen 2006 (32)	22/27 (study terminated prematurely)	18–53	16/33	Elective tonsillectomy	5 days postop, a diary at home	GBP 1200 mg 1 h before surgery, then 600 mg 2 times on the day of operation, then 600 mg 3 times for 5 days, or PL. Both groups received rofecoxib 50 mg preop. and then daily	Propofol and sufentanil supplemented with alfentanil	Ketobemidone 2.5 mg as escape drug, morphine 2.5 mg iv on request in the PACU; rofecoxib 50 mg daily for both groups	Pain scores (VRS) at rest or during swallo wing: NS; ketobemidone consumption reduced in the 1st 24 h postop.	5/13
Pandey 2004 (33)	153/153/153	30–54	151/308	Laparoscopic cholecystectomy	24 h	GBP 300 mg or tramadol 100 mg po or PL 2 h preop.	Not reported	Fentanyl on demand	VAS with GBP reduced 0–24 h postop. vs PL and tramadol at all time points except 0–6 h; fentanyl consumption reduced 37% with GBP vs PL	3/12

Table 1. (continued)

Reference	*n*, active/control	Age (yr)	Male/Female	Surgical procedure	Study duration and follow-up	Dosing, active/control	Intraoperative analgesics	Postoperative analgesics	Main results	QS/OPVS
Pandey 2004 (34)	28/28	28–50	38/18	Single-level lumbar disc surgery	24 h	GBP 300 mg or PL 2 h before surgery	Not reported	Fentanyl boluses on demand	VAS/rest lower with GBP vs PL at all time points; fentanyl consumption 35% lower with GBP vs PL	5/14
Pandey 2005 (19)	20/20/20/20/20	28–54	67/33	Single-level lumbar disc surgery	24 h	GBP 300/600/900/1200 mg or PL 2 h before surgery	Not reported	PCA-fentanyl	VAS lower at all time points with GBP 300 mg vs PL; VAS lower with GBP 600, 900 and 1200 mg vs 300 mg; increasing dose over 600 mg did not decrease VAS; fentanyl consumption less with GBP vs PL and increasing the dose over 600 mg did not decrease fentanyl consumption	5/13
Pandey 2005 (20)	20/20/20	29–55	41/19	Open donor nephrectomy	24 h	GBP 600 mg 2 h before surgery or 600 mg after incision or PL	Fentanyl boluses	PCA-fentanyl	VAS lower with pre- and postincisional GBP vs PL at all time points; fentanyl consumption less (33%–39%) with both GBP groups vs PL; pre- vs postincisional GBP:NS	5/13
Radhakrishnan 2005 (35)	30/30	29–53	40/20	Lumbar laminectomy and discectomy for nerve root compression	8 h	GBP 400 mg or PL the night before surgery, another 2 h before induction	Fentanyl boluses, lignocaine 1%	PCA-morphine	VRS/rest and movement: NS; total PCA-morphine consumption: NS	4/10
Rorarius 2004 (36)	38/37	42–50	0/75	Vaginal hysterectomy with or without laparoscopic assistance	20 h	GBP 1200 mg or oxazepam 15 mg 2, 5 h preop.	Fentanyl bolus at induction and before start of surgery	PCA-fentanyl	VAS/rest reduced during 2 h postop; then NS; PCA-fentanyl consumption reduced 41% with GBP vs oxazepam during 20 h postop.	5/15
Tuncer 2005 (37)	15/15/15	20–55	Not reported	Major orthopedic surgery	4 h	GBP 800 mg or 1200 mg or PL 1 h before surgery	Fentanyl bolus	PCA-morphine	VAS/rest: NS; morphine consumption 46% lower with GBP 800 and 1200 mg vs PL and lower with GBP 1200 mg vs 800 mg	2/7
Turan 2004 (38)	25/25	40–60	0/50	Abdominal hysterectomy (Pfannenstiel incision)	24 h	GBP 1200 mg or PL 1 h preop.	Not reported	PCA-tramadol	VAS/lying and sitting reduced at all time points; PCA-tramadol consumption reduced 36% with GBP vs PL	4/11

Table 1. (continued)

Reference	*n*, active/ control	Age (yr)	Male/ Female	Surgical procedure	Study duration and follow-up	Dosing, active/control	Intraoperative analgesics	Postoperative analgesics	Main results	QS/ OPVS
Turan 2004 (39)	25/25	37–57	28/22	Lumbar discectomy or spinal fusion surgery	24 h	GBP 1200 mg or PL 1 h preop.	Remifentanil infusion	Morphine iv before awakening, PCA-morphine postop.	VAS reduced at 1, 2, 4 h postop; PCA- morphine consumption reduced 62% with GBP vs PL	4/11
Turan 2004 (40)	25/25	20–36	Not reported	Ambulatory nasal septal surgery or endoscopic sinus surgery	24 h	GBP 1200 mg or PL 1 h before surgery	Local anesthesia (Lidocain 2% with adrenalin) + fentanyl bolus	Diclofenac im on demand	VRS at 45 and 60 min and VAS postop. lower with GBP vs PL; time to first analgesic request longer with GBP vs PL; intraop. fentanyl and postop. diclofenac consumption lower with GBP vs PL	4/11
Turan 2005 (41)	20/20	25–74	Not reported	Lower limb surgery (scar revision, skin graft, combination)	72 h	GBP 1200 mg or PL 1 h before surgery and at 9:00 on the 1 and 2 pod	Fentanyl 3–5 min before incision, epidural bolus of bupivacaine + fentanyl 30 min before end of surgery.	PCEA with bupivac + fentanyl; after this paracetamol po as needed	VRS reduced with GBP vs PL at 1, 4, 8, 12, 16 h; AUC for pain scores different for 24 h but not 72 h; PCEA requirements reduced with GBP at 24, 48, 72 h and paracetamol consumption less with GBP	5/14
Turan 2006 (42)	25/25/25/25	35–66	0/100	Abdominal hysterectomy (Pfannenstiel incision)	72 postop. contacted on pod 7 and 3 mo after surgery	GBP 1200 mg or rofecoxib 50 mg or combination (GBP + rofec) or PL 1 h before surgery and on the 1 and 2 pod at 9:00	Fentanyl 3–5 min before incision, morphine 2 mg iv before discontinuing anesthetics	PCA-morphine; after this paracetamol 500 mg + codeine 30 mg po as needed	VRS/rest lower with GBP, rofecoxib and GBP + rofecoxib vs PL at 4, 8, 16, 20 h and with GBP and combination at 12 and 24 h; VRS/movement lower with GBP and combination at 4 h, with rofecoxib, GBP and combination at 8 h and with rofecoxib and GBP at 20 h vs PL; PCA-morphine consumption reduced in all analgesic treatment groups vs PL; pain after 3 mo: NS	4/11

VAS = visual analogue scale; NS = not significant; GBP = gabapentin; PL = placebo; PACU = postanesthesia care unit; pod = postoperative day; OPVS = Oxford Pain Validity Scale; QS = Quality Scale; PCEA = patients controlled epidural analgesia.

Only statistically significant differences are mentioned.

chronic pain, whereas the other two did not (Table 2). Fassoulaki et al. (27) found more burning pain 1 mo after mastectomy in the placebo group compared with that in the perioperative gabapentin group. In another trial (28) mastectomy patients were treated with perioperative gabapentin, EMLA cream, and intraoperative ropivacaine or placebo. A significant reduction of the total incidence of pain and analgesic consumption in the treatment group compared with placebo group was found at 3 mo after surgery, but the difference disappeared by 6 mo. Fassoulaki et al. (29) also reported less pain in the surgical area and reduced pain intensity with perioperative gabapentin 1 mo after abdominal hysterectomy. In this trial there

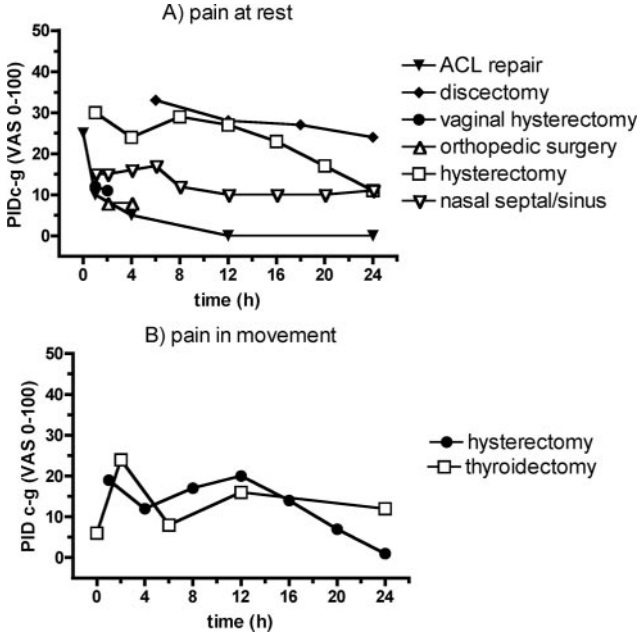

Figure 2. Pain intensity difference between the control and gabapentin groups (PIDc-g) at rest (panel A) and on movement (panel B) on VAS 0–100 during 24 h observation after a single 1200 mg dose 1–2 h before surgery. Each line represents the difference in the pain intensities between the two groups as a function of time. ACL = anterior cruciate ligament.

was no difference in acute pain between the active treatment and placebo groups.

Adverse Effects

Five studies provided data on nausea (265 patients), 4 on vomiting (215 patients), 3 on sedation (140 patients), 4 on dizziness (190 patients), and 2 on urinary retention (100 patients) during 20–24 postoperative hours after a single dose of gabapentin 1200 mg administered 1–2 h before surgery. When all data were combined, the numbers-needed-to-treat to prevent nausea, vomiting, or urinary retention were 25, 6, and 7, respectively. The numbers-needed-to-harm for gabapentin to produce excessive sedation or dizziness were 35 and 12, respectively. There were no significant differences in any other adverse effects reported in the original trials.

Anxiolytic Effects

Two trials reported anxiolytic properties of gabapentin. Menigaux et al. (10) measured anxiety on a visual analog scale (VAS) 1–2 h after premedication with gabapentin and found significantly lower preoperative VAS anxiety scores in the gabapentin group compared with placebo. According to Rorarius et al. (36), 15 mg of oxazepam was more effective in relieving preoperative anxiety than 1200 mg of gabapentin.

DISCUSSION

The aim of this systematic review was to assess the analgesic efficacy, adverse effects and clinical value of gabapentin and pregabalin in postoperative pain management. Pain relief was significantly better in the gabapentin groups compared with the control group. The opioid-sparing effect during the first 24 h after a single preoperative dose of gabapentin 300–1200 mg administered 1–2 h before surgery ranged from 20% to 62%. When single gabapentin dose studies were combined, gabapentin treatment reduced opioid consumption by 30 ± 4 mg of morphine equivalents during the first 24 postoperative hours. However, heterogeneity among the studies was significant. Gabapentin also reduced opioid-related adverse effects, such as nausea, vomiting, and urinary retention. Adverse effects related to gabapentin were negligible. Although it is a clinically relevant variable, time to first analgesic request was only reported in few studies.

In the first review of gabapentin and pregabalin in postoperative pain (43), there was a significant reduction in analgesic requirements and pain during the first 24 h in six of seven studies, without major adverse effects. A review of gabapentin in acute and chronic pain (44) concluded that there is no role for gabapentin in the management of acute pain, but the statement was based on one study (26). Seib and Paul (45) reported decreased pain scores and analgesic consumption in the first 24 h after surgery, but could not demonstrate a significant reduction in adverse effects. Hurley et al. (46) showed that perioperative administration of gabapentin decreased both pain intensity scores and opioid consumption for up to 24 h. Gabapentin was associated with a modest increase in sedation, but with no other adverse effects (46). A review of 16 studies by Ho et al. (47) demonstrated that a single preoperative dose of gabapentin (1200 mg or less) reduced pain intensity, opioid consumption, and opioid-related adverse effects such as vomiting and pruritus for the first 24 h postoperatively. After this, six more randomized, controlled trials (RCTs) have been published.

In the trials included in the present analysis pain on movement was measured in only 13 of 22 trials (59%). A significant difference favoring gabapentin was found in 9 of 13 studies. It is possible that gabapentin could be particularly useful in movement-related pain after surgical trauma because of its ability to prevent central neuronal sensitization. It can be speculated that measuring VAS scores on movement would be more informative than measuring them only at rest. The pain intensity and type of surgery seem to be important sources for the clinical heterogeneity across the studies in this review.

The opioid-sparing effect was not related to the gabapentin dose in our meta-analysis. This may be due to the small number of doses and significant clinical heterogeneity among the currently available studies. In one RCT, increasing the dose from 300 mg

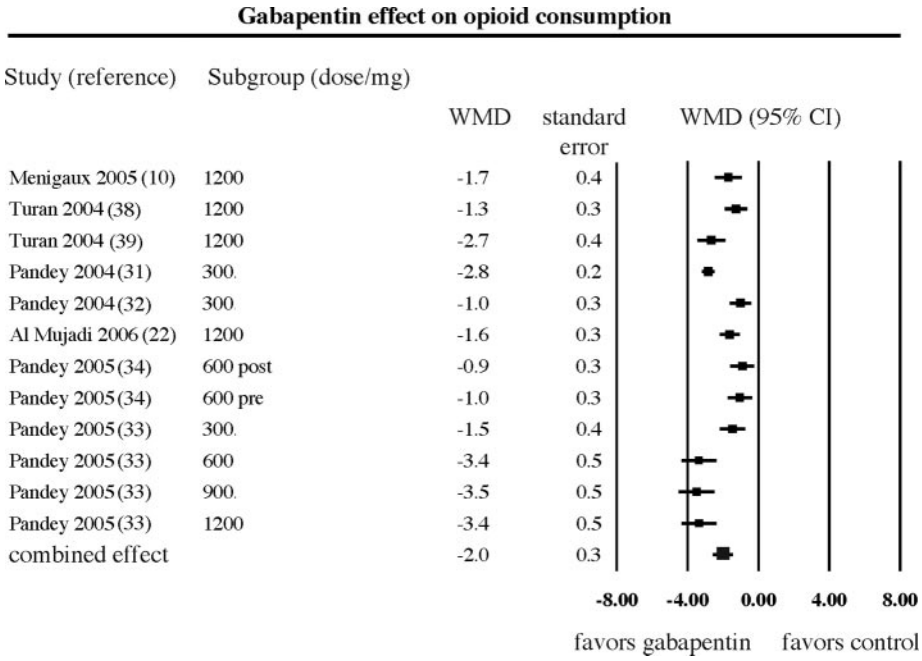

Figure 3. Effect of preoperative gabapentin on postoperative opioid consumption. A meta-analysis was performed for the opioid consumption in studies in which a single preoperative dose of gabapentin was given, the duration of the postoperative observation period was at least 24 h, and opioid consumption data were given as means with indication of variance. For the meta-analysis, fentanyl and tramadol consumption values were converted to arbitrary "morphine equivalent" units, using ratios of 100:1 and 1:10, respectively (for details of the meta-analysis, see the Methods section). For each study and gabapentin dose, the WMD of the opioid consumption with standard error is tabulated. The rectangles indicate the WMD with the 95% CI illustrated with a horizontal line. The vertical lines show the scale for WMD from −8 to 0 (favoring gabapentin) and from 0 to +8 (favoring control treatment). The combined effect (using random effects model) of gabapentin on the opioid consumption (with 95% CI) is indicated with the large rectangle in the bottom line.

to 600–1200 mg improved the analgesic and opioid-sparing effect of gabapentin, but there were no significant differences between the effects of the higher doses (19). This could either indicate lack of a dose–response relationship or a ceiling effect. Conversely, experience from treating chronic pain and epilepsy with gabapentin indicates that initiating gabapentin treatment with high doses causes clinically relevant sedation and dizziness during the first days of the treatment (48). It is unclear why these effects have not been reported in the perioperative setting.

There were 1265 women (71%) and 509 men (29%). In three trials, gender was not reported. Nine trials studied only women (hysterectomies or mastectomies). Rosseland and Stubhaug found a striking effect of gender on the intensity of acute pain after knee arthroscopy (49) with women reporting more pain in the early postoperative period. They expressed concern that the gender difference was ignored as a confounding factor in pain trials. In our review, there was only one study in which a gender difference in pain intensity and opioid consumption was reported (33). Pandey et al. studied patients undergoing laparoscopic cholecystectomy, in which men and women were evenly distributed among gabapentin and placebo groups. They found that, in the placebo group, pain intensity at 12–24 h postoperatively was significantly higher in women than in men. Fentanyl requirements were also significantly higher in women. These findings should be considered when interpreting previous RCTs and planning new pain trials.

In recent years, there has been growing interest in adjuvant drugs that have an opioid-sparing effect. NSAIDs have been shown to decrease opioid-related adverse effects, such as postoperative nausea, vomiting, and sedation (50), but they have well-known disadvantages such as gastrointestinal bleeding and renal complications. Paracetamol (acetaminophen), which is considered to be quite safe, also decreases morphine consumption, but it has no effect on the incidence of morphine-related adverse effects after major surgery (51). Ketamine is effective in reducing morphine requirements and postoperative nausea and vomiting, but has adverse effects of its own (52). Dextromethorphan, a weak *N*-methyl-D-aspartate-antagonist, also has opioid-sparing effects (53). However, the authors of these two reviews emphasize the heterogeneity of their data, and the results should be interpreted with caution. The present review indicates that gabapentin and pregabalin have a clinically significant opioid-sparing effect with less opioid-related adverse effects. The adverse-effect profiles of gabapentin and pregabalin compare favorably with other adjuvant analgesics.

Chronic pain is common after operations such as amputation, inguinal hernia surgery, breast surgery, gallbladder surgery, and lung surgery. For example

Table 2. Studies on Long-term Effects of Gabapentin (1–3 mo Follow-Up)

Reference	*n*, active/control	Surgical procedure	Dosing of GBP	Effect on acute pain	Effect on chronic pain
Fassoulaki 2002 (27)	22/21/24	Lumpectomy or mastectomy with axillary dissection	400 mg t.i.d. for 10 days starting on the evening before surgery	VAS/rest: reduced on 3rd pod with GBP and mexiletine; VAS/movement reduced on 2–5 pod; codeine + paracetamol consumption reduced on 2–10 pod	Total incidence of pain, abnormal sensations and analgesic requirements after 3 mo: NS; burning pain increased in the PLC group (GBP 1/22, mexiletine 1/20, PLC 7/24, $P = 0.033$)
Fassoulaki 2005 (28)	23/23	Radical mastectomy or lumpectomy with axillary lymph node dissection	400 mg 4 times for 8 days starting on the evening before surgery	VAS/rest and movement reduced with treatment vs PLC; fewer pts requiring analgesics in PACU with treatment; rescue analgesic consumption reduced with treatment	3 mo: total incidence of pain in the treatment group was 45% vs PLC group 82% ($P = 0.028$); analgesic requirements: treatment 0/22 vs PLC 5/22; 6 mo: NS
Gilron 2005 (31)	23/29/27/24	Abdominal hysterectomy	600 mg t.i.d.for 72 h starting 1 h before surgery	GBP + rofecoxib: better analgesia compared with GBP alone (but not compared with rofecoxib) for pain on movement; GBP + rofecoxib: better analgesia than with either agent alone; all 3 treatments reduced PCA-morphine consumption but more with GBP + rofecoxib	1 mo: NS
Turan 2006 (42)	25/25/25/25	Abdominal hysterectomy	1200 mg 1 h before surgery and on the 1 and 2 pod	VRS/rest and movement lower with GBP, rofecoxib and GBP + rofecoxib vs PLC; PCA-morphine consumption was reduced in all analgesic treatment groups vs PLC	3 mo: NS
Fassoulaki 2006 (29)	25/28	Abdominal hysterectomy for benign disease	400 mg 4 times for 5 days starting the day before surgery	NS	1 mo: less pain in surgical area with GBP (36%) vs PLC (81%), $P = 0.002$, and pain intensity less with GBP ($P = 0.003$)

VAS = visual analogue scale; VRS = verbal rating scale; PACU = postanesthesia care unit; GBP = gabapentin; PLC = placebo; NS = not significant; pod = postoperative day. Only statistically significant differences are mentioned.

postthoracotomy pain syndrome may have an incidence of more than 50% (54). In our review, long-term pain was studied in only five trials (27–29,31,42) and all patients were women. Fassoulaki et al. found a significant difference in chronic pain favoring gabapentin in their three trials (27–29), but Gilron et al. (31) and Turan et al. (42) reported no significant benefit to gabapentin in preventing chronic pain. There was wide variation in the number of patients (46–103) and duration of treatment (2–10 days). Only a few studies have explored the effects of other than classical analgesics (opioids, NSAIDs, local anesthetics) on the prevention of chronic postsurgery pain. Reuben et al. treated patients undergoing breast cancer surgery with venlafaxine, an antidepressant that increases the synaptic availability of both serotonin and noradrenalin. The treatment was started preemptively the night before surgery and was continued for up to 2 wk (55). No beneficial effect of venlafaxine was found on either acute postoperative pain or analgesic consumption, but there was a significant reduction in the incidence of postmastectomy pain at 6 mo. The comparable efficacy of various drugs (e.g., venlafaxine versus gabapentin) in the prevention of chronic pain is still unclear. Optimal dosing and duration of administration also need further investigation. It would also be important to determine whether gabapentin could prevent or attenuate postamputation phantom limb pain, postthoracotomy pain syndrome, or other common chronic pain states attributable to surgery.

In conclusion, gabapentin and pregabalin are effective in reducing pain intensity, opioid consumption and opioid-related adverse effects after surgery. Gabapentin and pregabalin have very few adverse effects of their own. Because of the heterogeneous data of these studies, no conclusions about the optimal dose and duration of the treatment can be drawn. The efficacy of gabapentinoids in preventing chronic pain needs to be elucidated in future studies.

REFERENCES

1. Dolin SJ, Cashman JN. Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritis, and urinary retention. Evidence from published data. Br J Anaesth 2005;95:584–91.
2. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524–34.
3. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002;57:451–62.
4. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004;45:13–18.
5. Guay DR. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? Am J Geriatr Pharmacother 2005;3:274–87.
6. Iannetti GD, Zambreanu L, Wise RG, et al. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proc Natl Acad Sci USA 2005;102:18195–200.
7. Werner MU, Perkins FM, Holte K, et al. Effects of gabapentin in acute inflammatory pain in humans. Reg Anesth Pain Med 2001;26:322–8.
8. Gilron I. Is gabapentin a "broad-spectrum" analgesic? Anesthesiology 2002;97:537–9.
9. Gilron I, Biederman J, Jhamandas K, Hong M. Gabapentin blocks and reverses antinociceptive morphine tolerance in the rat paw-pressure and tail-flick tests. Anesthesiology 2003;98:1288–92.
10. Menigaux C, Adam F, Guignard B, et al. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100:1394–9.
11. Pollack MH, Matthews J, Scott EL. Gabapentin as a potential treatment for anxiety disorders. Am J Psychiatry 1998;155:992–3.
12. Chouinard G, Beauclair L, Belanger MC. Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders. Can J Psychiatry 1998;43:305.
13. Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 2005;62:1022–30.
14. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896–900.
15. L'Abbé LA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987;107:224–33.
16. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol 2001;1:2.
17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality or reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
18. Smith LA, Oldman AD, McQuay HJ, Moore RA. Teasing apart quality and validity in systematic reviews: an example from acupuncture trials in chronic neck and back pain. Pain 2000;86:119–32.
19. Pandey CK, Navkar DV, Giri PJ, et al. 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.
20. Pandey CK, Singhal V, Kumar M, et al. Gabapentin provides effective postoperative analgesia whether administered preemptively or post-incision. Can J Anaesth 2005;52:827–31.
21. Dirks J, Petersen KL, Rowbotham MC, Dahl JB. Gabapentin suppresses cutaneous hyperalgesia following heat-capsaicin sensitization. Anesthesiology 2002;97:102–7.
22. Gregg AK, Francis S, Sharpe P, Rowbotham DJ. Analgesic effect of gabapentin premedication in laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial [abstract]. Br J Anaesth 2001;87:174P.
23. Leung JM, Sands LP, Rico M, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology 2006;67:1251–3.
24. Al-Mujadi H, A-Refai AR, Katzarov MG, et al. Preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery. Can J Anaesth 2006;53:268–73.
25. Dierking G, Duedahl TH, Rasmussen ML, et al. Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial. Acta Anaesthesiol Scand 2004;48:322–7.
26. Dirks J, Fredensborg BB, Christensen D, et al. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97:560–4.
27. 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.
28. 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.
29. Fassoulaki A, Stamatakis E, Petropoulos G, et al. Gabapentin attenuates late but not acute pain after abdominal hysterectomy. Eur J Anaesthesiol 2006;23:136–41.
30. Hill CM, Balkenohl M, Thomas DW, et al. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001;5:119–24.
31. Gilron I, Orr E, Tu D, et al. A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. Pain 2005;113:191–200.

32. Mikkelsen S, Hilsted KL, Andersen PJ, et al. The effect of gabapentin on post-operative pain following tonsillectomy in adults. Acta Anaesthesiol Scand 2006;50:809–15.
33. Pandey CK, Priye S, Singh S, et al. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004;51:358–63.
34. Pandey CK, Sahay S, Gupta D, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Can J Anaesth 2004;51:986–9.
35. Radhakrishnan M, Bithal PK, Chaturvedi A. Effect of preemptive gabapentin on postoperative pain relief and morphine consumption following lumbar laminectomy and discectomy: a randomized, double-blinded, placebo-controlled study. J Neurosurg Anesthesiol 2005;17:125–8.
36. Rorarius MG, Mennander S, Suominen P, et al. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain 2004;110:175–81.
37. Tuncer S, Bariskaner H, Reisli R, et al. Effect of gabapentin on postoperative pain: a randomized, placebo-controlled clinical study. Pain Clin 2005;17:95–9.
38. Turan A, Karamanlioglu B, Memis D, et al. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg 2004;98:1370–3.
39. Turan A, Karamanlioglu B, Memis D, et al. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004;100:935–8.
40. Turan A, Memis D, Karamanlioglu B, et al. The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery. Anesth Analg 2004;99:375–8.
41. Turan A, Kaya G, Karamanlioglu B, et al. Effect of oral gabapentin on postoperative epidural analgesia. Br J Anaesth 2006;96:242–6.
42. Turan A, White PF, Karamanlioglu B, et al. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006;102:175–81.
43. Dahl JB, Mathiesen O, Moiniche S. "Protective premedication": an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004;48:1130–6.
44. Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. Cochrane Database Syst Rev 2005;20:CD005452.
45. Seib R, Paul J. Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can J Anaesth 2006;53:461–9.
46. Hurley RW, Cohen SP, Williams KA, et al. The analgesic effects of perioperative gabapentin on postoperative pain: A meta-analysis. Reg Anesth Pain Med 2006;31:237–47.
47. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain—a systematic review of randomized controlled trials. Pain 2006;126:91–101.
48. Backonja M, Glanzman RL. Gabapentin dosing neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther 2003;25:81–104.
49. Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. Pain 2004;112:248–53.
50. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005;102:1249–60.
51. Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005;94:505–13.
52. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review [Cochrane review]. Acta Anaesthesiol Scand 2005;49:1405–28.
53. Duedahl TH, Romsing J, Moiniche S, Dahl JB. A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. Acta Anaesthesiol Scand 2006;50:1–13.
54. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93:1123–33.
55. Reuben S, Makari-Judson G, Lurie S. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. J Pain Symptom Manage 2004;27:133–9.