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REVIEW ARTICLES

EDITOR'S CHOICE

Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis

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Editor's key points

- The authors reviewed the evidence for the use of pregabalin for pain relief in the perioperative period.
- They found a significant positive effect (in terms of improved pain scores, opioid-sparing and reduction in nausea, vomiting, and pruritus), but a slight increase in some side-effects.

Summary. We performed this systematic review to assess the analgesic efficacy of perioperative pregabalin. Subgroup analyses and meta-regression were performed to assess the impact of individual dose and frequency of pregabalin administration on analgesic efficacy. We included 55 studies. When all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 h compared with placebo {mean difference [95% confidence interval (CI)]=−0.38 (−0.57, −0.20), −0.47 (−0.76, −0.18), and −8.27 mg morphine equivalents (−10.08, −6.47), respectively}. Patients receiving pregabalin had less postoperative nausea and vomiting and pruritus compared with placebo [relative risk (RR) (95% CI)=0.62 (0.48, 0.80) and 0.49 (0.34, 0.70), respectively]. Sedation, dizziness, and visual disturbance were more common with pregabalin compared with placebo [RR (95% CI)=1.46 (1.08, 1.98), 1.33 (1.07, 1.64), and 3.52 (2.05, 6.04), respectively]. All doses of pregabalin tested (≤75, 100–150, and 300 mg) resulted in opioid sparing at 24 h after surgery. There were no significant differences in acute pain outcomes with pregabalin 100–300 mg between single preoperative dosing regimens and those including additional doses repeated after surgery. Data were insufficient to reach conclusions regarding persistent pain, but limited data available from two studies suggested that pregabalin might be effective for the reduction of neuropathic pain. In conclusion, this review suggests that pregabalin improves postoperative analgesia compared with placebo at the expense of increased sedation and visual disturbances.

Keywords: meta-analysis; postoperative pain; pregabalin

Pregabalin is a γ-aminobutyric acid analogue that binds to $\alpha_2\delta$ subunits of the voltage-gated calcium channels.[1] It reduces the excitability of the dorsal horn neurones after tissue damage.[2] The use of pregabalin for the management of postoperative pain is off-label, and therefore, there are no dosing guidelines for this indication. For other indications, the recommended starting dose is 150 mg day^{-1} in two to three divided doses, increased within 1 week to 300 mg day^{-1} with a maximum recommended dose of 600 mg day^{-1}.[2] Studies investigating the perioperative use of pregabalin used doses ranging from 50 to 300 mg and daily doses ranging from 50 to 750 mg. The efficacy of perioperative administration of pregabalin was investigated in previous meta-analyses,[3–5] with all showing better postoperative analgesia with pregabalin. Those meta-analyses grouped studies based on the total daily dose of pregabalin. Zhang and colleagues[5] reported that pregabalin doses of <300 and ≥300 mg day^{-1} reduced 24 h opioid consumption but not pain scores after surgery. Engelman and Cateloy[4] grouped the analysis over a wide time-frame (6 h–7 days after surgery) according to the daily dose of pregabalin (50–150, 225–300, and 600–750 mg) and reported that the lowest effective dose for reducing postoperative analgesic consumption was 225–300 mg with no reduction in pain scores. Since doses were reported in those meta-analyses as total daily dose, it is not clear if the individual dose or frequency of administration of pregabalin affect outcome. For instance, it is not clear from those reviews if individual single doses lower than 225–300 mg have analgesic efficacy or if twice daily dosing of a particular dose of pregabalin would be more effective than single preoperative administration of the same dose. Some studies have investigated the impact of pregabalin on preoperative anxiety, but this was not addressed in those previous meta-analyses. More than 30 studies investigating perioperative pregabalin administration on acute pain outcomes have been published after the publication of those reviews, which included 11[5] and 18[4] studies. In addition, while one previous meta-analysis[3] assessed the impact of the perioperative administration of pregabalin on chronic pain, it included only three studies.[6–8] Seven other studies[9–15] addressing persistent pain after pregabalin administration have since been published.

Therefore, we performed this systematic review to provide an updated meta-analysis of the impact of pregabalin

administration on postoperative pain scores and opioid consumption and investigate whether those outcomes differ according to individual pregabalin dose, frequency of administration, type of anaesthesia, or type of surgery. Secondary aims were to assess the impact of pregabalin administration on anxiety scores and persistent pain, and provide an updated meta-analysis of the side-effects of pregabalin administration.

Methods

We followed the recommendations of the PRISMA statement.[16]

We searched MEDLINE (1966–2014), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (1947–2014), and CINAHL for randomized controlled trials (RCTs) that compared pregabalin with control in patients undergoing surgery. Databases were searched using the term 'pregabalin' combined with the MESH terms: 'Pain, postoperative', 'Postoperative period', 'Pain, acute', 'Pain, chronic', 'Opioids', and 'Analgesics, opioid'. The search was performed without language restriction. The last literature search was done on March 31, 2014. We also searched the bibliographies of retrieved articles for additional studies. Reviews, abstracts, letters to the editor, and retrospective studies were not included. Articles were included if pregabalin was administered before operation and pain scores, opioid consumption, incidence of persistent pain, and/or time to first analgesia were reported. We excluded studies where pregabalin administration was initiated after operation, the endpoints of interest were not reported or if a placebo group was not included.

The articles meeting the inclusion criteria were assessed separately by two authors (B.M.M. and N.H.W.) using the risk of bias table suggested by the Cochrane Collaboration.[17] A data collection sheet was created and two authors (B.M.M. and N.H.W.) extracted data on:

(i) Patients: type of surgery, type of anaesthesia, and number of patients.
(ii) Interventions: pregabalin dose and frequency of administration.
(iii) Comparison: control group regimen.
(iv) Outcomes: (a) acute pain outcomes: pain scores at rest and during movement, opioid consumption, and duration of post-anaesthesia care unit (PACU) and hospital stay, (b) preoperative anxiety scores, (c) adverse effects: nausea, vomiting, sedation, dizziness, confusion, headache, visual disturbance, pruritus, difficulty passing urine, dry mouth, fatigue, and request for rescue antiemetics, and (d) persistent pain: pain scores and incidence of persistent pain.

Data presented in graphs were requested from the authors. If authors did not respond, data were extracted from the graph. Discrepancies between the two authors were resolved by discussion with the third author (A.S.H.).

The primary outcomes of this meta-analysis were pain scores and opioid consumption at 2 and 24 h. Secondary outcomes were duration of PACU and hospital stay, incidence of persistent pain at 1, 3, 6, and 12 months, preoperative anxiety scores, and side-effects.

Analyses performed for the research questions and synthesis of data

Acute pain outcomes

In studies involving different doses of pregabalin, we combined all pregabalin doses for the main analysis assessing the impact of pregabalin administration on postoperative pain scores and opioid consumption. Visual analogue scale (VAS) scores for pain reported as 0–100 was converted to the 0–10 scale for analysis (0, no pain; 10, worst possible pain). Opioids were converted to morphine equivalents (ME) for analysis using a conversion factor of 3:1 for oxycodone,[18] 0.15:1 for parenteral hydromorphone,[18] 10:1 for fentanyl,[18] 20:1 for codeine,[18] 10:1 for tramadol,[5] and 1:1 for both ketobemidone[19] and piritramide.[20] If ketorolac was the only analgesic used, it was converted to ME using a conversion factor of 3:1.[21] If results were not reported at the time points specified in this analysis, those recorded close to those time points were used instead.

To evaluate different pregabalin dosing regimens, we performed subgroup analyses for pain scores and opioid consumption at 2 h after operation according to the individual dose of pregabalin administered before surgery ($\leq$75, 100–150, and 300 mg). For pain scores and opioid consumption at 24 h, we performed a subgroup analysis according to the dose and frequency of administration of pregabalin comparing the three dose levels ($\leq$75, 100–150, and 300 mg) and single *vs* multiple dosing at each dose level. Single dosing refers to studies that administered a single preoperative dose of pregabalin, while multiple dosing refers to studies that used at least one postoperative dose of pregabalin in addition to the preoperative dose or administered more than one preoperative dose. We also performed sensitivity analyses according to the type of surgery and type of anaesthesia (general *vs* regional) for the primary outcomes of pain scores and opioid consumption at 2 and 24 h. To evaluate predictors that could impact our primary outcomes, we also performed a meta-regression using pregabalin dose, type of surgery, and type of anaesthesia (general or regional) as predictors for the 2 h outcomes. The frequency of administration of pregabalin (single *vs* multiple dosing) was used as an additional predictor for 24 h outcomes.

Preoperative anxiety

We pooled preoperative anxiety scores after administration of pregabalin compared with placebo. VAS scores for anxiety reported as 0–100 were converted to the 0–10 scale for analysis.

Side-effects of perioperative pregabalin administration

We pooled adverse effects after administration of pregabalin compared with placebo. If an event rate was reported over multiple time intervals instead of the entire duration of the study, the highest recorded incidence over the duration of the study was used in the analysis. Sedation was defined as scores 3–6 on the Ramsay sedation scale (1, patient is anxious and

agitated or restless; 2, patient is co-operative, oriented, and tranquil; 3, patient responds to commands only; 4, patient exhibits brisk response to light glabellar tap or loud auditory stimulus; 5, patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus; 6, patient exhibits no response), 2–5 on the five-point scale (1, completely awake; 2, awake but drowsy; 3, asleep but responsive to verbal commands; 4, asleep but responsive to tactile stimulus; 5, asleep and not responsive to any stimulus), and 2–4 on the four-point scale (1, awake; 2, mild sedation; 3, sleepy but rousable; and 4, very sleepy), while severe sedation was considered for scores 4–6, 4–5, and 3–4 on the Ramsay, five-point scale, and four-point scale, respectively. In studies investigating sedation on the four-point scale (none, mild, moderate, and severe), sedation was defined as any sedation (mild, moderate, or severe). If sedation was not reported, somnolence or drowsiness was used instead for the analysis.

Persistent pain

We compared the incidence of persistent pain at 1, 3, 6, and 12 months after surgery after pregabalin *vs* placebo administration. We also compared pain scores at 1 and 3 months after surgery between pregabalin and placebo.

Continuous data were summarized as mean difference (MD) with 95% confidence interval (CI). If the 95% CI included a value of 0, we considered that the difference between pregabalin and placebo was not statistically significant. Dichotomous data were summarized as relative risk (RR) with 95% CI. If the 95% CI included a value of 1, we considered the difference not statistically significant. If the pooled results were not statistically significant and the CIs included values that exceeded a 30% difference in the pregabalin group compared with the control group, we considered that no conclusion could be derived from the pooled results due to the wide CIs. Analyses were performed using the Review Manager (RevMan), Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, and Comprehensive Meta-Analysis Software (version 3.0). A random effects model (which assumes that the effects being estimated in the different studies are not identical, but follow some distribution) was used.[17] We assessed heterogeneity using the I^2-test. Heterogeneity was assumed to be present if the I^2 was >50%. Forest plots were used to graphically represent and evaluate treatment effects. Subgroup analysis was performed using the *Q*-test. We assessed for publication bias for the primary outcomes using the Egger's test.[22] We also performed a sensitivity analysis for the primary outcomes after removing papers with an unclear or high risk of bias. To exclude a small study effect, we compared the results of the random effects and fixed effect models for our primary outcomes. We assessed the proportion of the total variance explained by each of the covariates (R^2) included in the meta-regression (pregabalin dose, frequency of administration, type of anaesthesia, and type of surgery) for the primary outcomes. Meta-regression was performed using the method of moments.

Results

Six hundred and ninety-five studies were assessed for inclusion in this review (Fig. 1). Fifty-five studies[6–15 23–67] with 4155 patients (2270 received pregabalin and 1885 served as control) were included in the final analysis. Additional data from 16 studies[13–15 24–27 36 37 40–42 46 48 50 57] were provided by the authors. Forty-nine studies investigated acute pain,[7–11 13–15 23–29 31–57 59 61–64 66 68] and 10 chronic pain.[6–15] The characteristics of the included studies are shown in Table 1. The risk of bias of the included studies is shown in Table 2.

Primary outcomes

Pain scores

Pain scores at 2 h Pain scores at rest at 2 h (Fig. 2) were investigated in 33[9–11 13–15 24 27 28 34–38 40–44 46 49 51–57 61–63 66 68] studies and during movement in 14[9–11 13 14 29 36 37 40–42 44 51 57] studies. Pooled results showed a statistically significant reduction in pain scores at rest [MD (95% CI)=−0.81 (−1.07, −0.51, I^2=88%)] and during movement [MD (95% CI)=−0.58 (−0.94, −0.21, I^2=82%)] in pregabalin-treated patients. There was no evidence of publication bias for pain scores at rest or movement (*P*=0.07 and 0.71, respectively). For pain scores at rest, 9% of the total variance was explained by the dose of pregabalin used, 11% by the type of surgery, and 1% by the type of anaesthesia. For pain scores on movement, 16% of the total variance was explained by the dose of pregabalin, 10% by type of surgery, and none was explained by type of anaesthesia.

In subgroup analysis, pain scores at rest were reduced with all doses of pregabalin (Fig. 2). Pain scores with movement were only reduced with the 300 mg dose. There were no significant differences between the three dose groups for pain at rest (*P*=0.95) or with movement (*P*=0.29). Sensitivity analysis according to type of surgery showed a reduction in pain scores at rest for all types of surgery except minor surgery and cardiac surgery (Table 3). Pain scores on movement were only reduced in open abdominal and head and neck surgeries. Pain scores at rest and on movement were reduced in studies using general anaesthesia but not regional anaesthesia.

The meta-regression found type of surgery (*P*=0.02), but not pregabalin dose (*P*=0.74) or type of anaesthesia (0.16) to be a significant predictor of 2 h pain scores at rest. The type of anaesthesia was a significant predictor of pain scores on movement at 2 h (*P*=0.046), but not type of surgery (*P*=0.10) or pregabalin dose (0.81).

Pain scores at 24 h Pain scores at rest at 24 h (Fig. 3) were investigated in 40 studies[7 9–11 13–15 23 26–28 31 32 34–38 40–57 59 62 64 66] and during movement in 18 studies.[7 9–11 13 14 23 29 31 36 37 40–42 46 51 57 59] Pooled results showed a statistically significant reduction in pain scores at rest [MD (95% CI)=−0.38 (−0.57, −0.20, I^2=77%)] and during movement [MD (95% CI)=−0.47 (−0.76, −0.18, I^2=70%)] with the perioperative administration of pregabalin. There was no evidence of publication bias (*P*=0.94 and 0.65 for pain scores

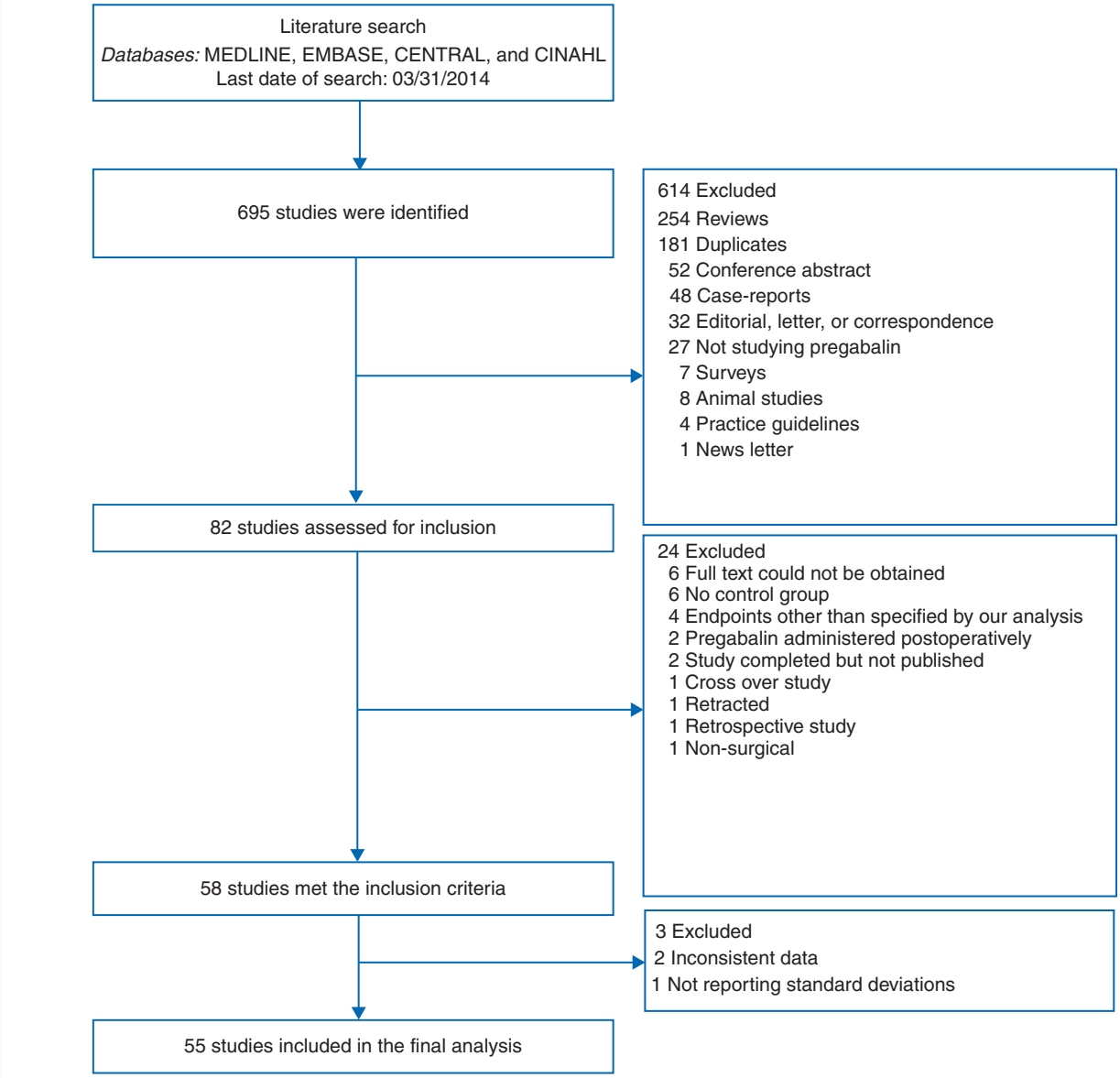

Fig 1 PRISMA flow chart detailing retrieved, excluded, assessed, and included trials.

at rest and on movement, respectively). For pain scores at rest, 1% of the total variance was explained by the dose of pregabalin used, 32% by the type of surgery, 0.28% by the frequency of pregabalin administration, and none was explained by the type of anaesthesia. For pain scores on movement, type of surgery explained 26% of the total variance and type of anaesthesia 0.22%. The dose of pregabalin and frequency of administration did not explain any of the total variance.

In subgroup analysis, pain scores at rest were reduced with pregabalin doses $\geq$100 mg, but not $\leq$75 mg (Fig. 3), with no significant differences between dose levels (P=0.87). When accounting for dosing frequency (Table 4), pain scores at rest were not reduced by any of the doses of pregabalin compared with placebo when given in single doses, but were reduced with multiple dosing of pregabalin $\leq$75 mg (P=0.03) and 100–150 mg (P=0.0001). There were no significant differences between single and multiple dosing at the $\leq$75 mg (P=0.17), 100–150 mg (P=0.86), or 300 mg (P=0.27) dose levels. Pain scores at rest were only reduced in open abdominal and head and neck surgeries (Table 3). Sensitivity analysis according to type of anaesthesia showed a reduction in pain scores at rest with general but not regional anaesthesia. The meta-regression found type of surgery (P=0.008), but not type of anaesthesia (P=0.21), pregabalin dose (P=0.67), or pregabalin frequency (P=0.61) to be a significant predictor of 24 h pain scores at rest.

Pain scores on movement were reduced only with doses of 300 mg compared with placebo, but there were no significant differences between the three dose levels of pregabalin (P=0.42). When accounting for dosing frequency (Table 3),

Table 1 Characteristics of included studies. *n*, number of patients in the group; PGB, pregabalin; GA, general anaesthesia; POD, postoperative day; Dex, dexamethasone; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; VAS, verbal analogue scale; NSAID, non-steroidal anti-inflammatory drug; PACU, post-anaesthesia care unit; ICU, intensive care unit; CSE, combined spinal–epidural. *Group not included in the analysis

Participant characteristics				Interventions		Comparison	Outcomes	
Reference	**Surgery type**	**Anaesthesia**	**Postoperative analgesia**	**Experimental groups (*n*)**	**PGB administration time**	**Control group (*n*)**	**Primary outcome**	**Study follow-up**
Acin and colleagues[12]	Mesh hernia repair	GA	Non-steroidal anti-inflammatory drugs	PGB 75 mg (70)	Multiple dosing: 75 mg at night for 3 days before operation and 75 mg at night till POD 12	Placebo (70)	Persistent pain	12 months
Agarwal and colleagues[23]	Laparoscopic cholecystectomy	GA	PCA fentanyl	PGB 150 mg (27)	Single dosing: 1 h before surgery	Placebo (29)	Pain scores and opioid consumption	24 h
Alimian and colleagues[52]	Dacrocystorhinos-tomy	GA	PRN opioid	PGB 300 (40)	Single dosing: 1 h before surgery	Placebo (40)	Pain scores	24 h
Balaban and colleagues[24]	Laparoscopic cholecystectomy	GA	I.V. fentanyl 25 μg as needed	PGB 150 mg (30); PGB 300 mg (30)	Single dosing: 1 h before surgery	Placebo (30)	Pain scores and opioid consumption	24 h
Bekawi and colleagues[53]	Laparoscopic cholecystectomy	GA	I.M. meperidine and diclofenac PRN	PGB 150 mg (30)	Multiple dosing: 2 h before surgery and then every 12 h for 2 days	Placebo (30); gabapentin 1200 mg* (30)	Pain scores and opioid consumption	24 h
Bornemann-Cimenti and colleagues[25]	Transperitoneal nephrectomy	GA	PCA piritramide	PGB 300 mg (13)	Single dosing: 1 h before surgery	Placebo (13)	Opioid consumption	48 h
Burke and Shorten[7]	Lumbar discectomy	GA	PACU: i.v. morphine; ward: regular oral codeine phosphate, paracetamol, and diclofenac+i.m. opioids (dihydrocodeine, tramadol, and morphine) for breakthrough pain	PGB 300 mg (18)	Multiple dosing: 300 mg 90 min before operation and 150 mg at 12 and 24 h after operation	Placebo (20)	Pain score up to 3 months after operation	3 months
Buvanendran and colleagues[6]	Total knee arthroplasty	GA	PCEA followed by oral opioids as needed to keep pain score <4	PGB 300 mg (120)	Multiple dosing: 300 mg 1–2 h before surgery, 150 mg twice daily for 10 days, 75 mg twice daily on days 11 and 12, and 50 mg twice daily on days 13 and 14	Placebo (120)	Neuropathic pain at 6 months	6 months

Buvanendran and colleagues[26]	Total knee replacement	Spinal	Patient-controlled intrathecal analgesia	PGB 150 mg multi-dose (16); PGB 150 mg single dose (16)	1 h before surgery (single and multiple dosing groups)+150 mg at 12 and 24 h in multi-dose group	Placebo (16)	Level of spinal neurotransmitters	32 h
Cabrera Schulmeyer and colleagues[27]	Laparoscopic sleeve gastrectomy	GA	Infusion of ketoprofen 300 mg 24 h^{-1}+i.v. morphine as rescue therapy	PGB 150 mg (39)	Single dosing: 2 h before surgery	Placebo (40)	Opioid consumption	24 h
Chang and colleagues[28]	Laparoscopic cholecystectomy	GA	I.V. ketorolac 30 mg as needed	PGB 300 mg (39)	Multiple dosing: 1 h before induction of anaesthesia and 12 h after the initial dose	Placebo (38)	Shoulder pain and abdominal pain	48 h
Clendenen and colleagues[32]	Arthroscopic rotator cuff repair	GA	Oral celecoxib, oxycodone, and paracetamol 325 mg every 4–6 h as needed	PGB 150 mg (23)	Multiple dosing: 150 mg before sedation then every 12 h for a total of 4 doses	Placebo (24)	Opioid consumption	48 h
Chaparro and colleagues[29]	Liposuction ± augmentation mammoplasty/ abdominoplasty	GA	PACU: i.v. morphine; then: oral paracetamol and codeine or tramadol or hydrocodone+ibuprofen or diclofenac for rescue	PGB 75 mg (50)	Multiple dosing: 75 mg the night before surgery and 1 h before surgery, then every 12 h through POD 4	Placebo (49)	Pain score during movement	96 h
Choi and colleagues[31]	Lumbar spinal surgery	GA	Continuous infusion of i.v. fentanyl until 48 h+i.v. ketorolac 30 mg for VAS pain ≥5	PGB 150 mg+placebo (36); PGB 150 mg+Dex* (36)	Multiple dosing: 1 h before surgery and every 12 h after initial dose until POD 3	Placebo (36)	Pain scores and need for rescue analgesia	6 months
Demirhan and colleagues[55]	Rhinoplasty	GA	Tramadol PCA	PGB 300 mg+placebo (20); PGB 300 mg+Dex* (20)	Single dosing: 1 h before surgery	Placebo (20)	Opioid consumption and pain scores	24 h
El Rahmawy and colleagues[65]	Elective general surgeries below the umbilicus (inguinal hernia, varicocele, varicose veins)	Spinal	I.M. diclofenac every 12 h	PGB 150 (43)	Single dosing: 2 h before surgery	Placebo (43)	Incidence of post-dural puncture headache	24 h
Eskandar and Ebeid[56]	Shoulder arthroscopy	GA	PRN nalbuphine	PGB 300 mg (40)	Multiple dosing: 12 and 1 h before surgery	Placebo (40)	Postoperative pain scores	24 h

Continued

Table 1 *Continued*

Participant characteristics				Interventions		Comparison	Outcomes	
Reference	**Surgery type**	**Anaesthesia**	**Postoperative analgesia**	**Experimental groups (*n*)**	**PGB administration time**	**Control group (*n*)**	**Primary outcome**	**Study follow-up**
Fassoulaki and colleagues[13]	Abdominal hysterectomy or myomectomy	GA	First 2 days: PCA morphine, then oral codeine with paracetamol as needed	PGB 150 mg (39)	Multiple dosing: 8 hourly administration starting on the day before surgery and continued to POD 5	Placebo (41)	Opioid consumption	3 months
George and colleagues[57]	Abdominal hysterectomy	GA	PCA morphine, scheduled oral NSAID	PGB 75 mg (31); PGB 150 mg (28)	Multiple dosing: 2 h before surgery and 12 h after initial dose	Placebo (30)	Opioid consumption	24 h
Ghai and colleagues[33]	Abdominal hysterectomy	GA	I.M. diclofenac sodium; i.v. tramadol if pain not controlled	PGB 300 mg (30)	Single dosing: 1–2 h before surgery	Placebo (30); gabapentin 900 mg* (30)	Opioid consumption	24 h
Ghoneim Hegazy[58]	Cystectomy with urinary diversion	GA	Morphine PCA and i.v. paracetamol	PGB 75 mg (30)	Multiple dosing: 75 mg every 12 h for 10 days before surgery	Placebo (30)	Opioid consumption	48 h
Gianesello and colleagues[14]	Major spinal surgery	GA	Continuous infusion of morphine+ketorolac until 48 h after surgery, VAS $\geq$3: i.v. morphine	PGB 300 mg (30)	Multiple dosing: 300 mg 1 h before surgery then 150 mg twice daily for 48 h	Placebo (30)	Opioid consumption	48 h
Gonano and colleagues[34]	Minor orthopaedic surgery	GA	PACU: i.v. piritramide; after PACU: oral mefenamic acid	PGB 300 mg (20)	Single dosing: at least 1 h before surgery	Placebo (20)	VAS anxiety immediately before anaesthesia induction	24 h
Ittichaikulthol and colleagues[35]	Abdominal hysterectomy	GA	PACU: i.v. morphine; ward: PCA morphine	PGB 300 mg (38)	Single dosing: 1 h before surgery	Placebo (40)	Pain scores	24 h
Jain and colleagues[59]	Unilateral total knee arthroplasty	Epidural	Bupivacaine/morphine PCEA, oral diclofenac rescue	PGB 75 (20)	Multiple dosing: 75 mg twice daily starting preop and continued through POD2	Placebo (20)	PCEA morphine use	48 h
Jo and colleagues[11]	Abdominal hysterectomy	GA	PACU: i.v. fentanyl; after PACU: PCA fentanyl	Remifentanil–PGB 150 mg (20)	Single dosing: 1 h before surgery	Remifentanil (20); placebo* (20)	PACU opioid consumption	48 h
Jokela and colleagues[36]	Day-case gynaecological laparoscopic surgery	GA	I.V. fentanyl (in PACU) or oral paracetamol and codeine (after PACU) as needed	PGB 75 mg (30); PGB 150 mg (26)	Single dosing: 1 h before surgery	Placebo (28)	Pain scores and opioid consumption	24 h

Jokela and colleagues[37]	Laparoscopic hysterectomy	GA	I.V. oxycodone then PCA oxycodone until next morning, then oral ibuprofen and paracetamol/codeine for breakthrough pain	PGB 150 mg (27); PGB 300 mg (29)	Multiple dosing: 1 h before surgery and 12 h after the initial dose	Placebo (29)	Pain scores and opioid consumption	5 days
Joshi and Jagadeesh[9]	Off-pump coronary artery bypass grafting	GA	I.V. paracetamol every 6 h, breakthrough pain treated with tramadol first, then i.v. diclofenac	PGB 150 mg (20)	Multiple dosing: 150 mg before operation, then 75 mg every 12 h for 2 postoperative days	Placebo (20)	Pain scores	3 months
Khurana and colleagues[60]	Lumbar discectomy	GA	I.V. tramadol for breakthrough pain	PGB 75 mg (30)	Multiple dosing: 75 mg before operation, then 75 mg every 8 h for 7 postoperative days	Placebo (30); gabapentin 300 mg* (30)	Pain scores	3 months
Kim and colleagues[15]	Robot-assisted endoscopic thyroidectomy	GA	PACU: i.v. fentanyl; ward: i.m. tramadol	PGB 150 mg (47)	Multiple dosing: 1 h before surgery and 12 h after the initial dose	Placebo (47)	Pain scores	48 h
Kim and colleagues[10]	Mastectomy	GA	PACU: i.v. fentanyl; ward: i.m. tramadol	PGB 75 mg (42)	Multiple dosing: 1 h before surgery and 12 h after the initial dose	Placebo (42)	Pain scores on movement	48 h
Kim and colleagues[38]	Lumbar spinal fusion surgery	GA	PCA fentanyl+ketorolac	PGB 75 mg (28); PGB 150 mg (28)	Multiple dosing: 1 h before surgery and 12 h after surgery	Placebo (28)	Analgesic consumption, pain scores, and need for rescue analgesics	48 h
Kohli and colleagues[39]	Hysterectomy	Spinal	Not reported	PGB 150 mg (50); PGB 300 mg (50)	Single dosing: 1 h before surgery	Placebo (50)	VAS anxiety scores	24 h
Koyuncu and colleagues[54]	Modified radical mastectomy	GA	PCA morphine	PGB 150 (30)	Multiple dosing: 150 mg preop and 75 mg 12 h postop	Placebo (30)	Pain scores and opioid consumption	12 h
Kumar and colleagues[61]	Lumbar discectomy	GA	I.V. fentanyl, i.v. diclofenac, or both for breakthrough pain	PGB 150 (25); tramadol 100 (25)*	Single dosing: 1 h before operation	Placebo (25)	Pain scores	6 h
Lee and colleagues[62]	Laparoscopic urologic surgery	GA	PCA with solution containing morphine, ketorolac, and 5-HT_3 antagonist	PGB 300+high dose (0.3 $\mu g\ kg^{-1}\ min^{-1}$) remifentanil (31)	Single dosing: 1 h before operation	High-dose remifentanil (0.3 $\mu g\ kg^{-1}\ min^{-1}$) (29); low-dose remifentanil (0.05 $\mu g\ kg^{-1}\ min^{-1}$)* (30)	Pain scores, PCA use, and hyperalgesia	24 h
Martinez and colleagues[63]	Total hip arthroplasty	GA	Morphine PCA	PGB 150 mg (35); PGB 150 mg+intraoperative ketamine (35)*; Intraoperative ketamine (34)*	Single dosing: 1 h before operation	Placebo (38)	Pain scores	48 h

Continued

Table 1 *Continued*

Participant characteristics				Interventions		Comparison	Outcomes	
Reference	**Surgery type**	**Anaesthesia**	**Postoperative analgesia**	**Experimental groups (*n*)**	**PGB administration time**	**Control group (*n*)**	**Primary outcome**	**Study follow-up**
Mathiesen and colleagues[41]	Tonsillectomy	GA	Paracetamol+i.v. morphine and oral ketobemidone upon patient request	Paracetamol+PGB 300 mg+placebo (45); paracetamol+PGB 300 mg+Dex* (43)	Single dosing: 1 h before surgery	Paracetamol+placebo +placebo (43)	Pain during swallowing at 2 h	24 h
Mathiesen and colleagues[42]	Abdominal hysterectomy	GA	PACU: i.v. morphine; after PACU: regular paracetamol+PCA morphine	Paracetamol+PGB 300 mg+placebo (43); Paracetamol+PGB 300 mg+Dex* (42)	Single dosing: 1 h before surgery	Paracetamol+placebo +placebo (43)	Opioid consumption	24 h
Mathiesen and colleagues[40]	Hip arthroplasty	Spinal	Regular oral paracetamol+PCA morphine	PGB 300 mg+placebo (40); PGB 300 mg+Dex* (38)	Single dosing: 1 h before surgery	Placebo+placebo (42)	Opioid consumption	24 h
Nutthachote and colleagues[64]	Laparoscopic gynaecologic surgery	GA	Scheduled oral NSAID, oral paracetamol, and i.v. meperidine for breakthrough pain	PGB 75 mg (27)	Multiple dosing: 2 h before surgery and every 12 h for total of three doses	Placebo (27)	Pain scores (shoulder)	48 h
Ozgencil and colleagues[43]	Lumbar laminectomy and discectomy	GA	PCA morphine	PGB 150 mg (30)	Multiple dosing: 2 h before surgery and every 12 h from initial dose for 2 days	Placebo (30); gabapentin 600 mg* (30)	Opioid consumption	24 h
Paech and colleagues[68]	Minor gynaecological surgery	GA	PACU: i.v. fentanyl then i.v. tramadol followed by oral diclofenac if target pain score not achieved. After discharge: paracetamol as needed	PGB 100 mg (45)	Single dosing: 1 h before surgery	Placebo (45)	Pain scores	24 h
Peng and colleagues[44]	Laparoscopic cholecystectomy	GA	PACU: i.v. fentanyl as needed; after PACU: paracetamol/ codeine orally upon request	PGB 50 mg (48); PGB 75 mg (48)	Multiple dosing: 1 h before surgery and every 12 h after initial dose for a total of 3 doses	Placebo (46)	Pain scores	7 days
Pesonen and colleagues[8]	Cardiac surgery	GA	ICU: i.v. oxycodone; ward: oral or i.m. oxycodone; after discharge: oral paracetamol	PGB 150 mg (32)	Multiple dosing: 150 mg 1 h before surgery then 75 mg every 12 h from POD 1 to POD 5	Placebo (32)	Opioid consumption	3 months
Sagit and colleagues[66]	Septoplasty	GA	I.M. diclofenac	PGB 75 mg (50); PGB 150 mg (46)	Single dosing: 1 h before surgery	Placebo (47)	Pain scores	24 h

Sahu and colleagues[45]	Infra-umbilical surgeries	Spinal	Not reported	PGB 150 mg (35)	Multiple dosing: 12 and 1 h before surgery	Placebo (35)	Pain scores	24 h
Sarakatsianou and colleagues[67]	Laparoscopic cholecystectomy	GA	PCA morphine	PGB 300 (20)	Multiple dosing: the night before surgery and immediately before operation	Placebo (20)	Pain scores	24 h
Spreng and colleagues[46]	Lumbar discectomy	GA	PCA morphine	PGB 150 mg (22)	Single dosing: 1 h before surgery	Placebo (24)	Pain scores	24 h
Sundar and colleagues[47]	Off-pump coronary artery bypass grafting	GA	I.V. fentanyl	PGB 150 mg (30)	Single dosing: 1 h before surgery	Placebo (30)	Haemodynamic response to intubation and opioid consumption	24 h
Wang and colleagues[48]	Bunionectomy	Regional	PCA hydromorphone then oral hydrocodone/ paracetamol	PGB 300 mg (32)	Multiple dosing: 300 mg 1 h before surgery then 150 mg every 8 h up to 40 h	Placebo (28); naproxen sodium* (29)	Opioid consumption and time to first PCA use	48 h
White and colleagues[49]	Elective ambulatory and short stay surgical procedures	GA	I.V. fentanyl	PGB 75 mg (27); PGB 150 mg (27); PGB 300 mg (27)	Single dosing: 60–90 min before surgery	Placebo (27)	VAS anxiety	7 days
Yadeau and colleagues[50]	Foot or ankle surgery	Popliteal nerve block+CSE	PCA hydromorphone then oral oxycodone or hydrocodone or hydromorphone and paracetamol	PGB 100 mg (30)	Multiple dosing: 100 mg 1 h before surgery and 50 mg every 12 h for 3 days	Placebo (30)	Number of hours of moderate to severe pain	48 h
Yucel and colleagues[51]	Abdominal hysterectomy	GA	PCA morphine	PGB 150 mg (30); PGB 300 mg (30)	Multiple dosing: 4 h before surgery and at 12 h after operation	Placebo (30)	Opioid consumption	24 h

Table 2 Risk of bias table. Low, low risk of bias; high, high risk of bias; unclear, unclear risk of bias

Reference	Randomization sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Acin and colleagues[12]	Unclear	High	High	High	Low	Low
Agarwal and colleagues[23]	Low	Low	Low	Low	Low	Low
Alimian and colleagues[52]	Unclear	Low	Low	Low	Low	Low
Balaban and colleagues[24]	Low	Low	Low	Low	Low	Low
Bekawi and colleagues[53]	Low	Low	Low	Low	Unclear	Low
Bornemann-Cimenti and colleagues[25]	Low	Low	Low	Low	Low	Low
Burke and Shorten[7]	Unclear	Low	Unclear	Unclear	Low	Low
Buvanendran and colleagues[6]	Low	Low	Low	Low	Low	Low
Buvanendran and colleagues[26]	Low	Low	Low	Low	Low	Low
Cabrera Schulmeyer and colleagues[27]	Low	Unclear	Low	Low	Low	Low
Chang and colleagues[28]	Unclear	Low	Low	Low	Low	Low
Clendenen and colleagues[32]	Low	Low	Low	Unclear	Low	Low
Chaparro and colleagues[29]	Low	Low	Low	Low	Low	Low
Choi and colleagues[31]	Low	Low	Low	Low	Low	Low
Demirhan and colleagues[55]	Low	Low	Low	Low	Low	Low
El Rahmawy and colleagues[65]	Low	Low	Low	Low	Unclear	Low
Eskandar and Ebeid[56]	Low	Low	Low	Unclear	Low	Low
Fassoulaki and colleagues[13]	Low	Low	Low	Unclear	Low	Low
George and colleagues[57]	Low	Low	Low	Low	Low	Low
Ghai and colleagues[33]	Low	Low	Low	Low	Low	Low
Ghoneim and Hegazy[58]	Low	Low	Low	Low	Low	Low
Gianesello and colleagues[14]	Low	Low	Low	Low	Low	Low
Gonano and colleagues[34]	Low	Unclear	Low	Low	Low	Low
Ittichaikulthol and colleagues[35]	Unclear	Unclear	Low	Low	Low	Low
Jain and colleagues[59]	Low	Low	Low	Low	Low	Low
Jo and colleagues[11]	Low	Unclear	Low	Low	Low	Low
Jokela and colleagues[36]	Low	Low	Low	Low	Low	Low
Jokela and colleagues[37]	Low	Low	Low	Low	Low	Low
Joshi and Jagadeesh[9]	Low	Low	Low	Low	Low	Low
Khurana and colleagues[60]	Low	Low	Low	Low	Unclear	Unclear
Kim and colleagues[15]	Unclear	Low	Low	Low	Low	Low
Kim and colleagues[10]	Low	Low	Low	Low	Low	Low
Kim and colleagues[38]	Low	Low	Low	Low	Low	Low
Kohli and colleagues[39]	Low	Low	Unclear	Unclear	Low	Low
Koyuncu and colleagues[54]	Low	Low	Unclear	Unclear	Unclear	Unclear
Kumar and colleagues[61]	Low	Low	Low	Low	Low	Low
Lee and colleagues[62]	Unclear	Unclear	Unclear	Unclear	Low	Low
Martinez and colleagues[63]	Low	Low	Low	Low	Low	Low
Mathiesen and colleagues[41]	Low	Low	Low	Low	Low	Low
Mathiesen and colleagues[42]	Low	Low	Low	Low	Low	Low
Mathiesen and colleagues[40]	Low	Low	Low	Low	Low	Low
Nutthachote and colleagues[64]	Low	Low	Low	Low	Low	Low
Ozgencil and colleagues[43]	Low	Unclear	Low	Unclear	Low	Low
Paech and colleagues[68]	Low	Low	Low	Low	Low	Low
Peng and colleagues[44]	Low	Low	Low	Low	Low	Low

Continued

Table 2 *Continued*

Reference	Randomization sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Pesonen and colleagues[8]	Low	Low	Low	Low	Low	Low
Sagit and colleagues[66]	Low	Unclear	Low	Low	Low	Low
Sahu and colleagues[45]	Low	Unclear	Unclear	Low	Low	Low
Sarakatsianou and colleagues[67]	Low	Low	Low	Low	Low	Low
Spreng and colleagues[46]	Low	Low	Low	Low	Low	Low
Sundar and colleagues[47]	Low	Unclear	Low	Low	Low	Low
Wang and colleagues[48]	Low	Low	Low	Low	Low	Low
White and colleagues[49]	Low	Low	Low	Low	Low	Low
Yadeau and colleagues[50]	Low	Low	Low	Low	Low	Low
Yucel and colleagues[51]	Low	Low	Low	Low	Low	Low

pain on movement was not reduced by any of the doses of pregabalin compared with placebo when given in single doses, but were reduced by multiple doses at the ≤75 mg (P=0.02) and 300 mg dose levels (P=0.04). Multiple dosing was significantly more effective than single dosing at the ≤75 mg level (P=0.02), but not at the 100–150 mg (P=0.39) or the 300 mg (P=0.89) doses. Pain scores on movement were reduced in open abdominal, orthopaedic, and cardiac surgery (Table 3). Sensitivity analysis according to type of anaesthesia showed a reduction in pain scores with movement with general but not regional anaesthesia. None of the covariates was a significant predictor in the meta-regression model [type of surgery (P=0.08), pregabalin dose (P=0.14), pregabalin frequency (P=0.27), and type of anaesthesia (P=0.77)].

Opioid consumption

Opioid consumption at 2 h Opioid consumption at 2 h (Fig. 4) was investigated in 23 studies.[7 11 13 14 24 28 29 34–36 38 40–44 46 49 51 55–57 68] Pooled results showed a statistically significant reduction in opioid consumption [MD (95% CI)=−2.09 mg ME (−2.87, −1.30, I^2=94%)] with the administration of pregabalin. There was no evidence of publication bias (P=0.83). Twenty per cent of the total variance was explained by the dose of pregabalin. Type of anaesthesia or surgery did not explain any of the total variance.

In subgroup analysis, opioid consumption was reduced by the 100–150 and 300 mg doses compared with placebo, but not the ≤75 mg dose (Fig. 4). This reduction was significantly different among the three groups (P=0.005) with pairwise comparisons showing significantly lower opioid sparing in the ≤75 mg group compared with the 100–150 mg (P=0.001) and the 300 mg (P=0.0007) groups, and no difference between the 100–150 and 300 mg groups. Sensitivity analysis according to type of surgery showed a reduction in opioid consumption at 2 h in orthopaedic, open abdominal, and minor surgical procedures. Two hours opioid sparing was seen with general anaesthesia but not regional anaesthesia (Table 3). In the meta-regression model, pregabalin dose was a significant predictor of 2 h opioid consumption (P=0.02), but not type of surgery (P=0.34) or type of anaesthesia (0.34).

Opioid consumption at 24 h Opioid consumption at 24 h (Fig. 5) was investigated in 29 studies.[8 11 13 14 23 25 27–29 33 35–38 40–44 46–48 50 51 54–58] Pooled results showed a statistically significant reduction in opioid consumption with the administration of pregabalin [MD (95% CI)=−8.27 mg ME (−10.08, −6.47, I^2=95%)]. There was no evidence of publication bias (P=0.21). Fourteen per cent of the total variance was explained by the dose of pregabalin, 3% by the type of anaesthesia, whereas type of surgery and frequency of pregabalin administration did not explain any of the variance.

In subgroup analysis, all doses of pregabalin reduced 24 h opioid consumption compared with placebo when given as a single preoperative dose or as multiple doses (Table 3). There were no statistically significant differences between administration of a single preoperative dose and administration of multiple doses for the ≤75 mg (P=0.87), 100–150 mg (P=0.44), and the 300 mg (P=0.66) dose levels. There were also no significant differences between the three dose levels of pregabalin when all studies were combined (P=0.25, Fig. 5). Opioid consumption at 24 h was reduced in all types of surgery except minor surgical procedures and head and neck surgery. Pooled results of both general anaesthesia and regional anaesthesia studies showed a reduction in 24 h opioid consumption (Table 3).

The type of anaesthesia was a significant predictor of 24 h opioid consumption (P=0.0496) in the meta-regression model, but not type of surgery (P=0.11), pregabalin dose (P=0.92), or frequency of pregabalin administration (P=0.26).

Sensitivity analysis according to study risk of bias assessment

Our sensitivity analysis showed no difference in primary outcomes when papers with unclear risk of bias[7 11–13 15 27 28 32 34 35 39 43 45–47 52–54 56 60 62 65 66] in any of the risk of bias assessments were removed from the analysis.

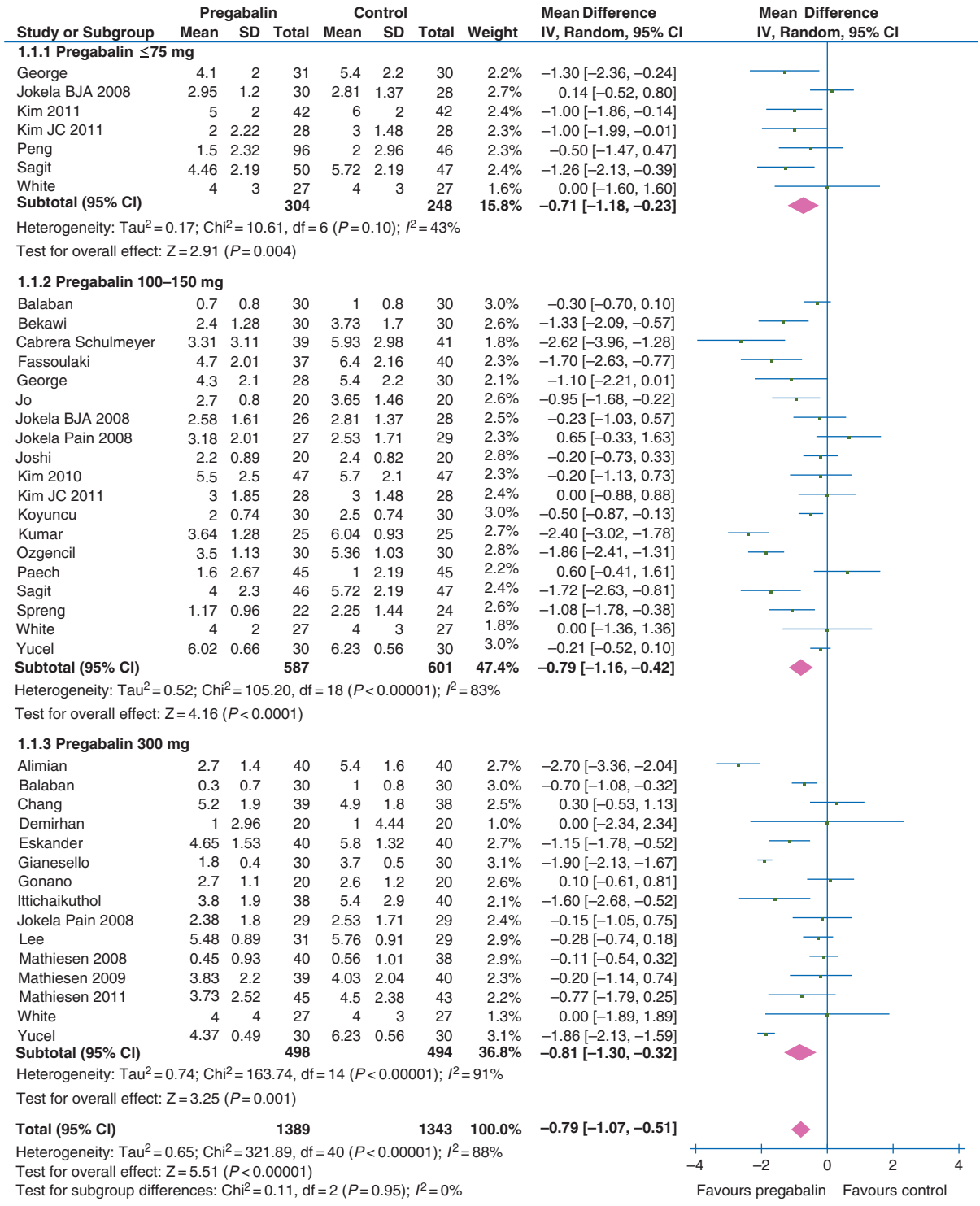

Fig 2 Forest plot for pain scores at rest at 2 h. SD, standard deviation; CI, confidence interval; IV, inverse variance.

Comparing random effects and fixed effect models for primary outcomes

The fixed effect model yielded very comparable results with the random effects model for the primary outcomes of our review.

Secondary outcomes

Duration of PACU and hospital stay

The duration of PACU stay was reported in four studies[28 34 46 49] and duration of hospital stay or time to achieve hospital discharge criteria in five studies.[6 8 14 32 49] There was no difference

Table 3 Sensitivity analysis according to type of surgery and type of anaesthesia. Data are MD (95% CI) (number of studies included in the analysis). ME, morphine equivalents; NA, not applicable; NE, not estimable

Type of surgery or anaesthesia	Pain scores at rest at 2 h	Pain scores during movement at 2 h	Opioid consumption at 2 h (mg ME)	Pain scores at rest at 24 h	Pain scores during movement at 24 h	Opioid consumption at 24 h (mg ME)
Orthopaedic surgery	−1.13 (−1.77, −0.48, I^2=92%) (8)[14 34 38 40 43 46 56 61]	−1.07 (−2.73, 0.58, I^2=95%) (2)[14 40]	−1.99 (−3.48, −0.49, I^2=94%) (8)[7 14 34 38 40 43 46 56]	−0.25 (−0.52, 0.03, I^2=53%) (14)[7 14 26 31 32 34 38 40 43 46 48 50 56 59]	−0.65 (−1.27, −0.02, I^2=69%) (6)[7 14 40 46 59 31]	−11.70 (−15.41, −7.99, I^2=84%) (8)[14 38 40 43 46 48 50 56]
Open abdominal surgery	−1.05 (−1.34, −0.76, I^2=16%) (6)[11 13 35 42 51 57]	−0.58 (−0.85, −0.32, I^2=0%) (5)[11 13 42 51 57]	−3.13 (−4.54, −1.72, I^2=80%) (6)[11 13 35 42 51 57]	−0.67 (−1.12, −0.21, I^2=73%) (7)[11 13 35 42 51 45 57]	−0.31 (−0.60, −0.02, I^2=0%) (5)[11 13 42 51 57]	−12.70 (−17.41, −7.99, I^2=94%) (9)[11 13 33 35 42 51 25 57 58]
Laparoscopic abdominal surgery	−0.47 (−0.90, −0.03, I^2=70%) (8)[24 27 28 36 37 44 53 62]	−0.00 (−0.49, 0.49, I^2=0%) (3)[36 37 44]	−2.17 (−4.98, 0.64, I^2=97%) (4)[24 28 36 44]	−0.39 (−0.84, 0.07, I^2=83%) (9)[23 27 28 37 44 36 53 62 64]	−0.05 (−0.83, 0.73, I^2=73%) (3)[23 36 37]	−6.59 (−11.65, −1.52, I^2=90%) (6)[23 27 28 36 37 44]
Minor surgical procedures	0.38 (−0.42, 1.18, I^2=0%) (2)[49 68]	NA	−0.99 (−1.78, −0.19, I^2=0%) (2)[49 68]	1.33 (0.42, 2.24, I^2=NE) (1)[49]	NA	−1.78 (−6.98, 3.42, I^2=83%) (2)[29 36]
Head and neck surgery	−1.18 (−2.23, −0.13, I^2=83%) (5)[15 41 52 55 66]	−1.71 (−2.79, −0.63, I^2=NE) (1)[41]	−0.74 (−2.11, 0.63, I^2=83%) (2)[41 55]	−0.94 (−1.25, −0.64, I^2=18%) (5)[15 41 52 66 55]	−0.80 (−1.80, 0.20, I^2=NE) (1)[41]	−2.29 (−3.52, −1.06, I^2=0%) (2)[41 55]
Cardiac surgery	−0.20 (−0.73, 0.33, I^2=NE) (1)[9]	−0.20 (−0.52, 0.12, I^2=NE) (1)[9]	NA	−0.36 (−1.22, 0.49, I^2=91) (2)[9 47]	−1.30 (−1.88, −0.72, I^2=NE) (1)[9]	−3.87 (−5.27, −2.47, I^2=0%) (2)[8 47]
Breast and plastic surgery	−0.60 (−0.98, −0.21, I^2=9%) (2)[10 54]	−0.76 (−3.21, 1.69, I^2=94%) (2)[10 29]	0.00 (−0.58, 0.58, I^2=NE%) (1)[10 29]	−0.49 (−1.47, 0.49, I^2=77%) (2)[10 54]	−1.08 (−2.94, 0.78, I^2=89%) (2)[10 29]	0.48 (−0.43, 1.40, I^2=0%) (2)[29 54]
General anaesthesia	−0.88 (−1.17, −0.58, I^2=86%) (32)[9–11 13–15 24 27 28 34–38 41–44 46 49 51–57 61–63 66 68]	−0.69 (−1.15, −0.23, I^2=85%) (13)[9–11 13 14 29 36 37 41 42 44 51 57]	−2.05 (−2.89, −1.21, I^2=94%) (22)[7 11 13 14 24 28 29 34–36 38 41–44 46 49 51 55–57 68]	−0.40 (−0.60, −0.20, I^2=75%) (34)[7 9–11 13–15 23 27 28 31 32 34–38 41–44 46 47 49 51–57 62 64 66]	−0.54 (−0.90, −0.18, I^2=73%) (16)[7 9 11 13 14 23 29 31 36–38 41 42 46 51 57]	−8.04 (−10.03, −6.05, I^2=95%) (26)[8 11 13 14 23 25 27–29 33 35–38 41–44 46 47 51 54–58]
Regional anaesthesia	−0.11 (−0.54, 0.32, I^2=NE%) (1)[40]	−0.21 (−0.80, 0.38, I^2=NE%) (1)[40]	−0.70 (−1.48, 0.08, I^2=NE) (1)[40]	−0.71 (−1.42, 0.00, I^2=77%) (6)[26 40 45 48 50 59]	−0.77 (−1.89, 0.34, I^2=74%) (2)[40 59]	−19.24 (−26.49, −11.98, I^2=38%) (3)[40 48 50]

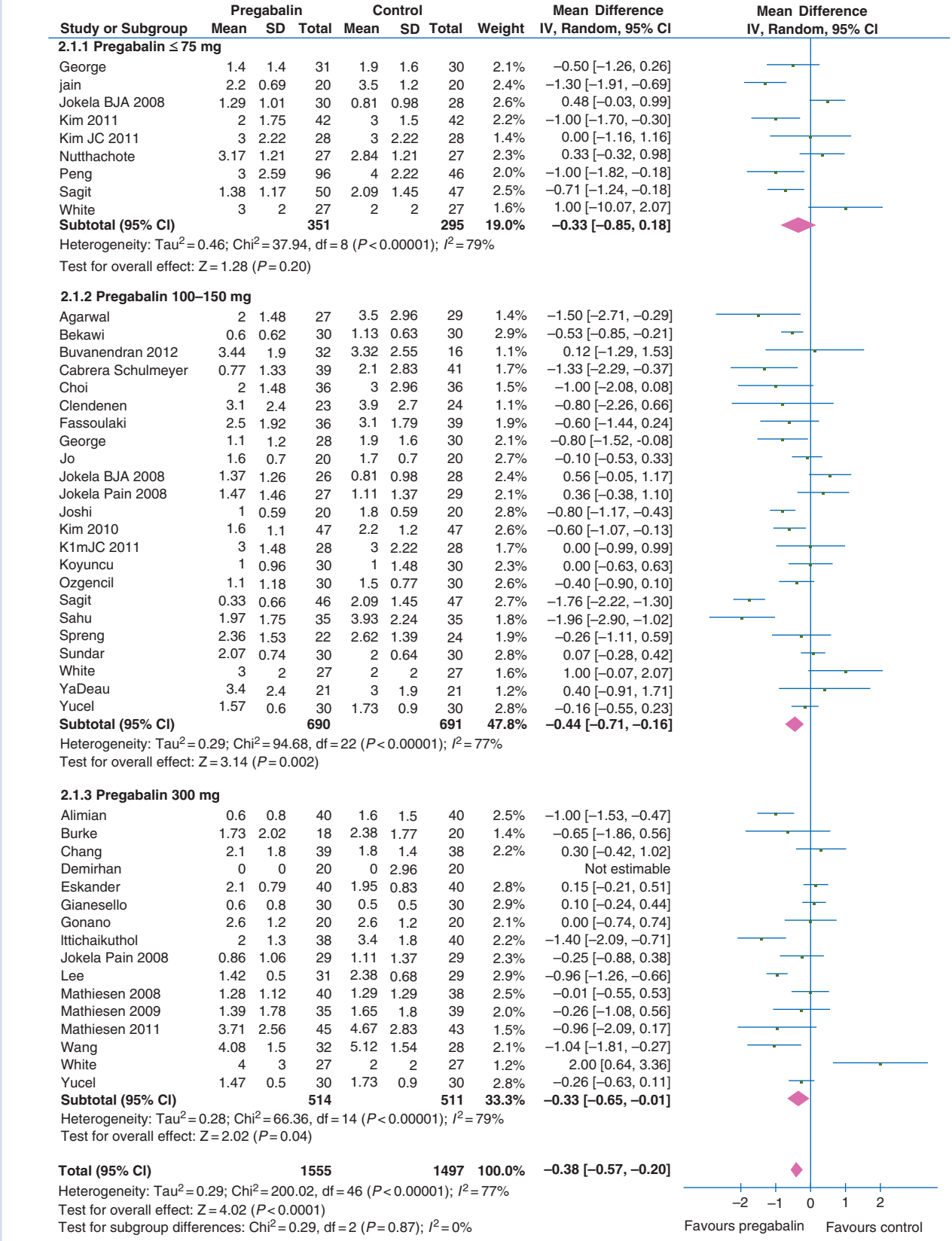

Fig 3 Forest plot for pain scores at rest at 24 h. SD, standard deviation; CI, confidence interval; IV, inverse variance.

Table 4 Impact of single and multiple dosing regimens of different doses of pregabalin on 24 h outcomes. Data are MD or RR (95% CI) (number of studies included in the analysis); NA, not applicable; NE, not estimable

Outcome	Pregabalin ≤75 mg		Pregabalin 100–150 mg		Pregabalin 300 mg	
	Single dose	Multiple dosing	Single dose	Multiple dosing	Single dose	Multiple dosing
Pain scores at rest, 0–10 scale	0.19 (−0.79, 1.18), I^2=85%, (3)[36 49 66]	−0.61 (−1.16, −0.05), I^2=69% (6)[10 38 44 57 59 64]	−0.40 (−1.07, 0.27), I^2=89% (8)[11 23 27 36 46 47 49 66]	−0.47 (−0.70, −0.23) I^2=50% (15)[9 13 15 26 31 32 37 38 43 45 50 51 53 54 57]	−0.45 (−0.96, 0.05), I^2=80% (9)[34 35 40–42 49 52 55 62]	−0.13 (−0.40, 0.15), I^2=49% (7)[7 14 28 37 48 51 56]
Pain scores with movement, 0–10 scale	0.23 (−0.48, 0.94), I^2=NE%, (1)[36]	−1.08 (−1.89, −0.27), I^2=72%, (4)[10 29 57 59]	−0.23 (−0.91, 0.45), I^2=59%, (4)[11 23 36 46]	−0.67 (−1.41, 0.07), I^2=82%, (6)[9 13 31 37 51 57]	−0.22 (−0.82, 0.39), I^2=14%, (3)[40–42]	−0.27 (−0.51, −0.02), I^2=0%, (4)[7 14 37 51]
Opioid consumption, mg morphine equivalents	−4.75 (−9.20, −0.30), I^2=NE%, (1)[36]	−5.28 (−9.98, −0.57), I^2=96%, (5)[29 38 44 57 58]	−10.01 (−15.58, −4.45), I^2=75%, (6)[11 23 27 36 46 47]	−7.51 (−10.56, −4.45), I^2=77%, (9)[8 13 37 38 43 50 51 54 57]	−10.02 (−14.91, −5.14), I^2=97%, (7)[25 33 35 40–42 55]	−8.66 (−12.18, −5.14), I^2=90%, (6)[14 28 37 48 51 56]
Sedation	NA	1.00 (0.83, 1.21), I^2=22%, (3)[44 57 60]	1.41 (0.85, 2.34), I^2=19%, (5)[11 23 24 27 39]	1.25 (0.55, 2.87), I^2=66%, (4)[32 43 50 57]	1.73 (1.02, 2.94), I^2=94%, (9)[24 33 34 39–42 52 67]	3.36 (1.25, 9.07), I^2=0%, (2)[6 7]
Severe sedation	NA	0.50 (0.03, 7.41), I^2=NE%, (2)[38 57]	2.72 (1.05, 7.02), I^2=0%, (5)[11 23 26 27 39]	2.50 (0.35, 17.97), I^2=NE%, (3)[26 38 57]	2.03 (0.85, 4.87), I^2=61%, (4)[39–42]	7.79 (1.02, 59.37), I^2=NE%, (2)[28 67]

between the groups in the duration of PACU stay [MD (95% CI)=−2.05 min (−9.76, 5.66, I^2=66%)]. On the other hand, pregabalin-treated patients had a shorter hospital stay or achieved hospital discharge criteria 13.75 h earlier than those receiving placebo (95% CI=−23.26, −4.24, I^2=97%).

Persistent pain

Four studies[9 10 13 15] reported VAS pain scores at 1 month with no difference in pooled results between the groups [MD (95% CI)=0.04 (−0.34, 0.26, I^2=70%)]. VAS pain scores at 3 months at rest were investigated in three studies[7 9 13] and during movement in two studies[7 9] with no statistically significant differences between the groups. The incidence of persistent pain at 1, 3, 6, and 12 months were reported in four,[8 11–13] six,[6 8 11 13–15] two,[6 12] and two[12 14] studies, respectively. Two studies specified that the pain was neuropathic,[6 12] while the other five studies[8 10 11 13 14] reported the presence of persistent pain without specifying the type. Both studies specifying that the pain was neuropathic reported a significant reduction in the incidence of neuropathic pain with pregabalin at 3,[6] 6,[6 12] and 12[12] months. Pooled results showed a statistically significant reduction in the incidence of pain at 6 (4 *vs* 15%) and 12 months (9 *vs* 20%) with pregabalin administration [RR (95% CI)=0.31 (0.10, 0.92, I^2=15%) and 0.47 (0.23, 0.97, I^2=0%), respectively], while at 1 and 3 months, no conclusion can be made due to the wide CIs of the pooled results [RR (95% CI)=0.65 (0.27, 1.56, I^2=81%) and 0.73 (0.40, 1.33, I^2=41%), respectively]. Excluding studies with a higher baseline risk of persistent pain[13 14] did not change the overall results. For the 3 month assessment, excluding the one study reporting neuropathic pain[6] abolished the heterogeneity but did not change the overall pooled results [RR (95% CI)=0.88 (0.60, 1.30, I^2=0%)]. Excluding one study with a high risk of bias[12] leaves only one study for the 6 and 12 month assessments. For the 6 month assessment, the study by Buvanendran and colleagues[6] reported a statistically significant reduction in the incidence of neuropathic pain with pregabalin (P=0.014), while at 12 months, the study by Gianesello and colleagues[14] did not report a reduction in the incidence of pain in pregabalin-treated patients.

Side-effects

Side-effects are presented in Table 5. Sedation, severe sedation, and dizziness at 24 h, and visual disturbance up to 24 h were significantly more common in pregabalin-treated patients. At 0–2 h, no conclusion could be reached about those outcomes due to the wide CIs of the pooled results. On the other hand, the administration of pregabalin was associated with a lower incidence of postoperative nausea and vomiting (PONV) and pruritus at 24 h when compared with control. Sedation scores at 2 and 24 h were reported using a VAS scale in seven[8 24 43 47 49 56 58] and seven[8 23 43 47 48 51 56] studies, respectively, with pregabalin being associated with significantly more sedation at 2 h, but not at 24 h [MD (95% CI)=0.62 (0.19, 1.05, I^2=85%) and −0.06 (−0.29, 0.18, I^2=82%), respectively]. The risk of sedation and severe

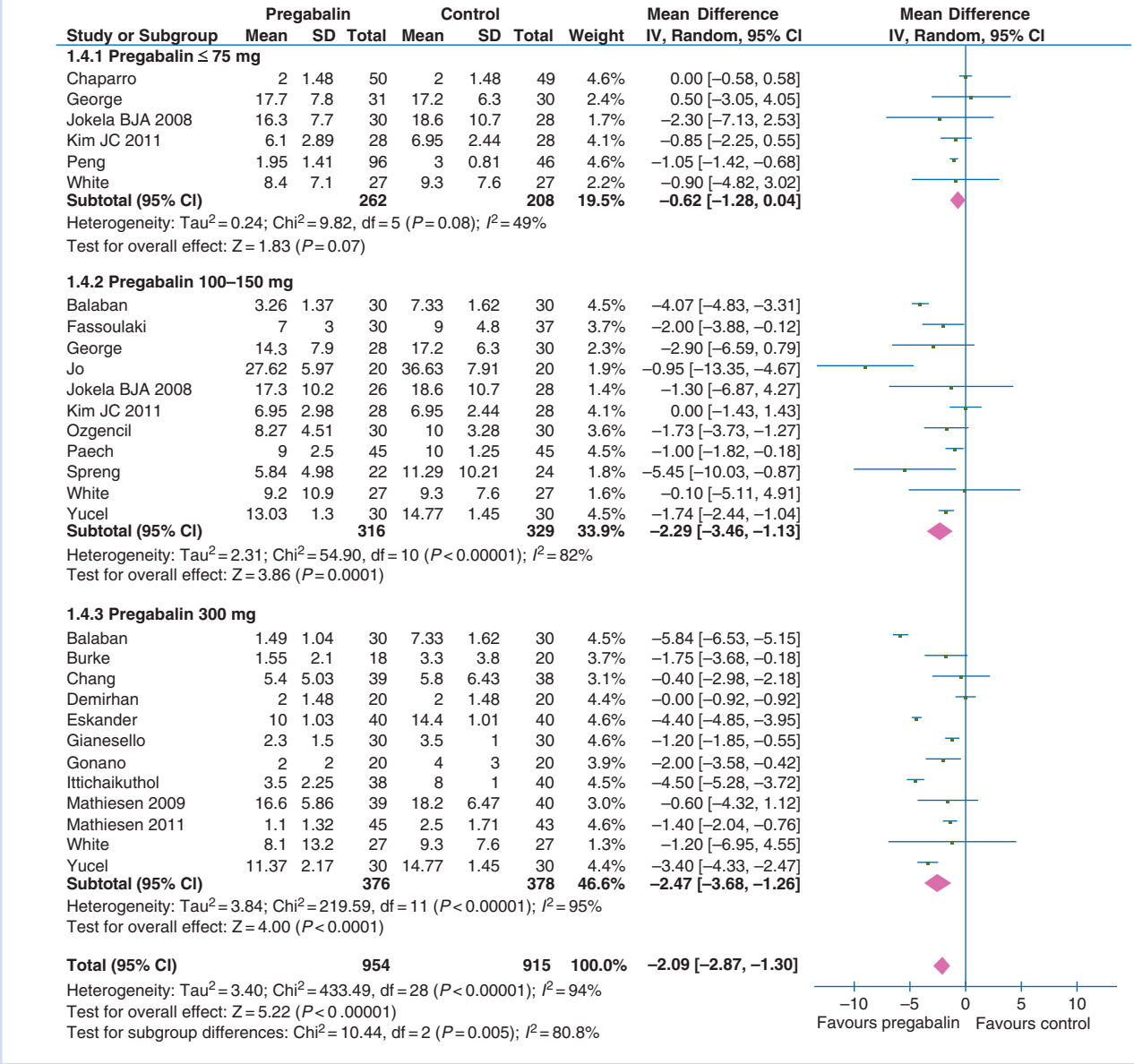

Fig 4 Forest plot for opioid consumption at 2 h. SD, standard deviation; CI, confidence interval; IV, inverse variance.

sedation according to pregabalin dosing regimens is presented in Table 3. There was a statistically significant increase in the risk of sedation with single and multiple dosing of pregabalin 300 mg and the risk of severe sedation with multiple doses of 300 mg. The CIs with other pregabalin regimens were wide, suggesting that the data are insufficient to draw conclusions with the lower two doses of pregabalin.

Preoperative anxiety scores

Preoperative anxiety scores after pregabalin administration were investigated in 10 studies (general anaesthesia in nine[7 13 34 36 37 43 46 49 61] and spinal anaesthesia in one).[39] Seven studies[13 34 36 37 39 46 49] used VAS scale, one[43] used a seven-point scale (1, relaxed; 2, apprehension; 3, mild anxiety; 4, moderate anxiety; 5, manifest anxiety; 6, severe anxiety; 7, very severe anxiety), one used a five-point scale (0, calm and comfortable; 1, uneasy; 2, worried and anxious; 3, very upset and worried; 4, frightened/terrified),[61] and one[7] used hospital anxiety and depression scale. Pooled results from the seven studies[13 34 36 37 39 46 49] that used the VAS scale had wide CIs, and therefore, no conclusion could be reached about this outcome [MD (95% CI)= −0.68 (−1.58, 0.22, I^2=82%)]. Significantly lower preoperative anxiety scores with pregabalin administration were reported in the three studies[7 43 61] that used scales other than the VAS scale.

Discussion

In this systematic review and meta-analysis, we found that the perioperative administration of pregabalin was associated

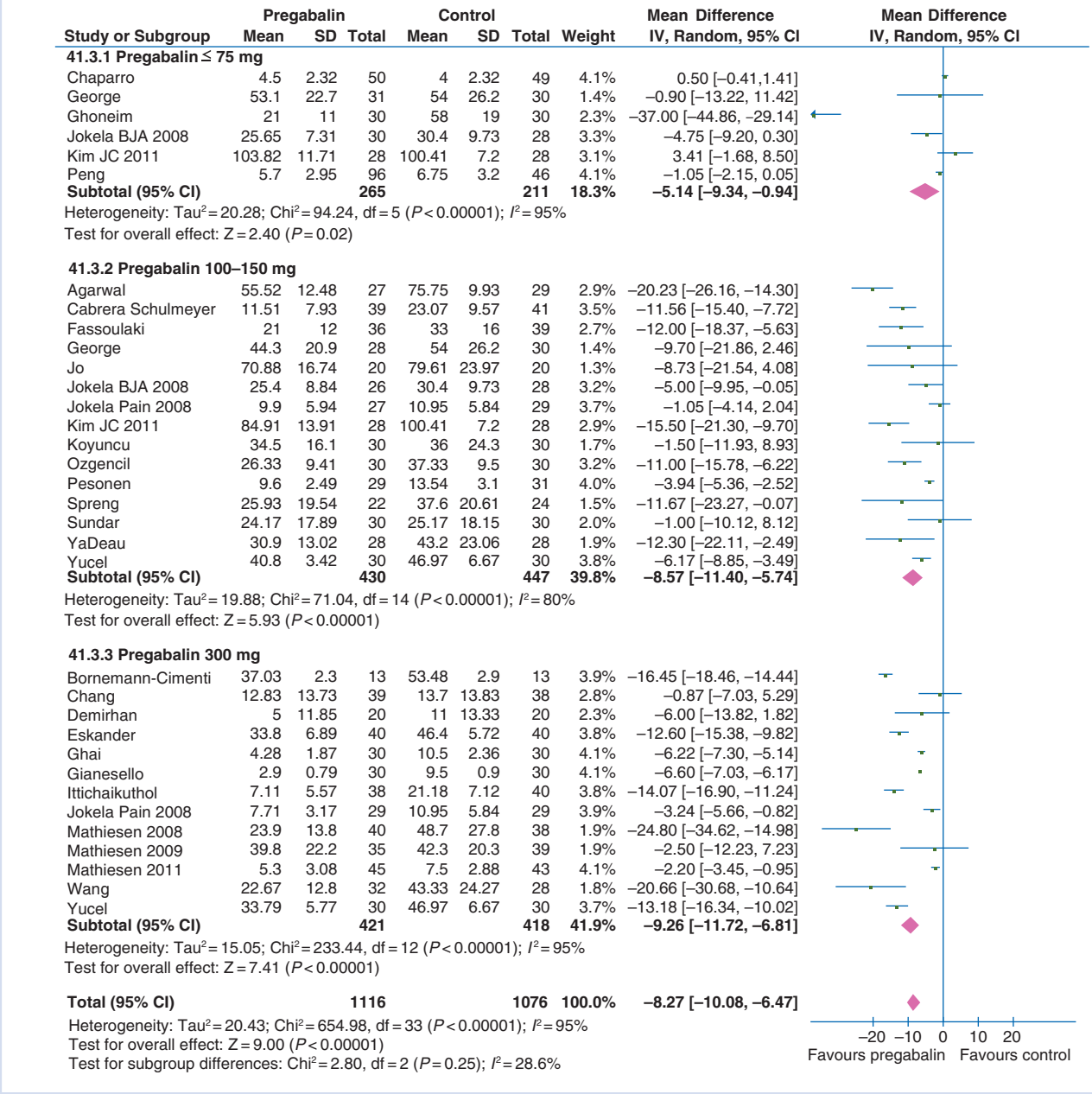

Fig 5 Forest plot for opioid consumption at 24 h. SD, standard deviation; CI, confidence interval; IV, inverse variance.

with a statistically significant reduction in pain scores at rest (MD of 0.81 at 2 h and 0.38 at 24 h), pain scores during movement (MD of 0.58 at 2 h, and 0.47 at 24 h), and opioid consumption (MD of 2.09 mg ME at 2 h, and 8.27 mg ME at 24 h) after surgery compared with placebo. The incidence of opioid-related side-effects (PONV and pruritus) was significantly reduced with pregabalin administration by 38% and 51%, respectively, relative to placebo at 24 h after surgery. The administration of pregabalin was associated with a significantly higher incidence of sedation (46% increase), dizziness (33% increase), and visual disturbance (3.5 times more likely) relative to placebo. Of note, pregabalin-treated patients achieved hospital discharge criteria 14 h earlier than controls. Although we were not able to reach a definitive conclusion regarding preoperative anxiety due to the wide CIs of the non-statistically significant pooled results, six of the 10 studies investigating preoperative anxiety reported significantly lower anxiety with pregabalin. Similarly for persistent pain, we were not able to reach a conclusion regarding the incidence at 3 months, while at 6 and 12 months, there was limited information suggesting a possible benefit. The only two studies investigating neuropathic pain reported a benefit from pregabalin administration.

The optimal dose or frequency of administration of pregabalin is unclear.[69] In the included studies, the individual dose of pregabalin administered before surgery ranged from 50 to 300 mg. Our analyses suggested that the opioid-sparing

Table 5 Side-effects after pregabalin administration. Data are presented as RR (95% CI) (number of studies included in the analysis); PONV, postoperative nausea and vomiting; NA, not applicable; NE, not estimable

	0–2 h	0–24 h
Sedation	1.11 (0.88, 1.40, I^2=91%) (8)[11 27 34 35 40–42 57]	1.46 (1.08, 1.98, I^2=81%) (21)[6 7 11 23 24 27 32–34 39–44 50 52 57 60 63 67]
Severe sedation	1.52 (1.02, 2.26, I^2=0%) (10)[11 27 28 35 38 40–42 49 57]	2.11 (1.14, 3.90, I^2=40%) (12)[11 23 26–28 38–42 57 67]
Dizziness	1.44 (0.97, 2.14, I^2=49%) (9)[13 27 32 34 38 41 42 49 68]	1.33 (1.07, 1.64, I^2=53%) (31)[6 7 13 27 32–41 43 44 46 47 51–53 55 56 60 62–68]
Confusion	NA	3.44 (0.57, 20.77, I^2=31%) (2)[6 44]
Visual disturbance	3.55 (1.21, 10.40, I^2=0%) (2)[13 68]	3.52 (2.05, 6.04, I^2=0%) (16)[6 7 13 34 36–38 43 52 55 56 62 64 65 67 68]
Dry mouth	NA	0.84 (0.64, 1.12, I^2=13%) (5)[6 34 44 62 66]
Headache	0.40 (0.08, 1.96, I^2=NE) (2)[38 68]	0.91 (0.64, 1.29, I^2=39%) (15)[6 23 26 36–38 43 44 46 50 52 55 56 67 68]
Lack of concentration	NA	1.04 (0.85, 1.26, I^2=0%) (5)[36 37 44 66 67]
Difficulty passing urine	NA	0.89 (0.56, 1.43, I^2=17%) (6)[24 43 44 46 56 63]
Fatigue	NA	0.72 (0.49, 1.05, I^2=NE) (1)[44]
Opioid-related side-effects		
Nausea	0.62 (0.39, 1.01, I^2=0%) (8)[32 34 38 40–42 46 61]	0.83 (0.71, 0.96, I^2=1%) (20)[6 8 24 26 32 38–44 46 50 52 55 56 60 63 68]
Vomiting	0.33 (0.04, 2.99, I^2=0%) (5)[34 36–38 61]	0.86 (0.69, 1.06, I^2=5%) (22)[6 8 24 26 36–44 46 47 50 52 55 56 60 63 68]
PONV	0.76 (0.32, 1.84, I^2=4%) (5)[34 36–38 61]	0.62 (0.48, 0.80, I^2=46%) (20)[7 23 27 31 33 35–38 46 51–53 55 60 62–66]
Rescue antiemetic	NA	0.84 (0.72, 0.99, I^2=7%) (11)[8 23 27 40–42 50 55 59 67 68]
Pruritus	NA	0.49 (0.34, 0.70, I^2=13%) (13)[6 24 26 36 37 43 44 46 50 51 56 63 67]
Constipation	NA	0.88 (0.59, 1.31, I^2=0) (2)[44 66]

effect of pregabalin seemed to be limited to doses 100–150 and 300 mg but not ≤75 mg at 2 h after surgery, whereas at 24 h, no statistically significant differences were detected between the three dose levels. These doses are lower than the lowest effective daily dose of 225 mg suggested in an earlier meta-analysis.[4]

Pregabalin has an elimination half-life estimated to range from 5.5 to 6.7 h which is independent of the dose and frequency of administration.[69] With nearly half the included trials studying single dosing while the other half using multiple dosing, we investigated whether the frequency of administration impacts the analgesic efficacy of pregabalin. While the opioid-sparing effect was statistically significant with both single and multiple dosing of pregabalin ≤75–300 mg, the reduction in pain scores seemed to be limited in general to multiple dosing. The further reduction in pain scores with multiple dosing over single dosing however was modest and likely not clinically relevant. In fact, there were no statistically significant differences between single and multiple dosing with regard to opioid consumption and pain scores, except for pain scores on movement with the ≤75 mg dose. These results might suggest that for acute pain outcomes, there is no significant benefit of repeated dosing of pregabalin compared with a single preoperative dose. This agrees with the results of the only study that prospectively compared single dose of pregabalin 150 mg *vs* three perioperative doses and reported no difference in acute pain outcomes between the groups.[26]

In a previous meta-analysis, Clarke and colleagues[3] investigated the incidence of persistent pain at 3–6 months after surgery and, pooling results from two studies, reported an odds ratio (95% CI) of 0.09 (0.02–0.52) with pregabalin compared with control. More recently, Chaparro and colleagues[70] investigated the incidence of persistent pain at 3 months after surgery and found a reduction in this incidence with pregabalin after pooling the results of four studies [RR (95% CI)=0.70 (0.51, 0.95)]. However, the authors stated that these positive results in favour of pregabalin were mainly due to one positive study, while the other three studies showed no benefit. This positive overall result is likely due to the use of the fixed effect model in that review. We however used a random effects model, which we deemed more appropriate, given the clinical heterogeneity of the studies, and including six studies, we found the data insufficient to reach a conclusion about pain at 3 months due to the wide CIs of the pooled results. While we found a statistically significant reduction in the incidence of persistent pain at 6 months [RR (95% CI)=0.31 (0.10, 0.92) and 12 months [0.47 (0.23, 0.97)], each of these two analyses included only two studies, with one of them[12] having a high risk of bias. Only two studies investigated neuropathic pain,[6 12] with both studies reporting a benefit from pregabalin administration; however, one of those studies[12] had a high risk of bias. The optimum pregabalin regimen needed for affecting chronic pain is not clear. Most of the studies studying the impact of pregabalin on chronic pain used multiple doses starting before operation and extending to several days after operation.[6–8 10 12–15] Studies comparing the impact of single *vs* multiple dosing of pregabalin on the incidence of chronic post-surgical pain are lacking.

Overall, pregabalin produced a clinically relevant opioid sparing of 25% at 24 h. The impact on pain scores was less pronounced with 19% and 16% reduction in the mean pain scores at rest and on movement at 24 h, and therefore might not be clinically relevant. Pregabalin-induced opioid sparing was however associated with a reduction in opioid-related side-effects such as PONV and pruritus. However, these benefits were at the expense of increased risk of sedation and dizziness. The available

data allowed only limited assessment of the impact of sedation on patients' recovery. For instance, only four studies reported on the duration of PACU stay, and this did not seem to be impacted by pregabalin. Furthermore, interestingly, the duration of hospital stay was reduced with pregabalin administration, but this was only reported in five of the included studies.

Since type of surgery and type of anaesthesia can influence postoperative analgesic outcomes, we included both in addition to pregabalin dosing in the meta-regression models. In fact, both were significant predictors of some of the outcomes in our analysis. For instance, type of surgery was a significant predictor of pain scores at rest at 2 and 24 h. This agrees with previous studies showing that type of surgery is a significant predictor of postoperative analgesic outcomes.[71] The type of anaesthesia also predicted 2 h pain scores on movement and 24 h opioid consumption, likely due to the analgesic effect of regional anaesthesia in the early postoperative period.

There are several limitations to this review:

- Heterogeneity: We combined different types of surgery, different pregabalin doses, different anaesthetic types, and different regimens (single and multiple dosing) in our main analysis, which created heterogeneity within that analysis. It has been suggested that this is expected and inevitable in a meta-analysis, and that any amount of heterogeneity is acceptable, provided that the predefined eligibility criteria for the meta-analysis are sound and the data are correct.[72] In order to investigate the efficacy of different dosing regimens of pregabalin and the efficacy of pregabalin in different types of surgery and with different anaesthetic techniques, we performed a number of sensitivity and subgroup analyses and meta-regressions. However, results from these analyses should be regarded as observational in nature, may be biased and limited by the small number of studies included in some of the subgroups, and should therefore be interpreted with caution.[17] While included trials might have allocated treatment randomly, their inclusion in this review is not random. Furthermore, while we used a random effects meta-analysis due to the clinical heterogeneity, this method weighs the studies more equally than a fixed effect meta-analysis. To exclude a small study effect on the results of our analysis, we compared the results of the fixed and random effects model on our primary outcomes and those yielded comparable results further strengthening the internal validity of our findings.
- Risk of bias in individual studies: Limiting the review to RCTs limits the potential for bias. Our risk of bias assessment indicated that most included studies had a low risk of bias. Furthermore, our sensitivity analysis excluding the few studies with unclear or high risk of bias did not affect our conclusions. Another limitation was the inconsistency of reporting outcomes among the studies, and the lack of response from some authors with regard to data that we requested. However, the results of our review were consistent in the various sensitivity analyses. Some important clinically relevant outcomes such as the duration of PACU stay and of hospital stay were only rarely reported.

Multiple areas for future research have been identified. Large studies with adequate power are needed to compare the efficacy and side-effect profile of different doses of pregabalin. Studies are also needed to assess the efficacy and side-effects of single *vs* multiple dosing of pregabalin. In addition, further investigation is needed to assess the ideal pregabalin regimen for the reduction in persistent pain in surgical patients. Those studies should focus on surgeries associated with a high risk of chronic post-surgical pain. Studies also need to specifically address neuropathic pain and make a distinction between different types of persistent pain.

In conclusion, this systematic review and meta-analysis confirms previous meta-analyses suggesting that the perioperative administration of pregabalin is associated with a significant reduction in opioid consumption after surgery. In this review, we also found a significant reduction in pain scores with pregabalin administration. The impact on opioid consumption seemed to be more pronounced, while the reduction in pain scores was only modest. Other new findings from our review are the fact that the analgesic effect of pregabalin seemed to be associated with much lower doses than previously reported.[4] Furthermore, our review suggested that overall there was no difference in acute pain outcomes between single and multiple dosing of pregabalin. Neuropathic pain might be reduced with pregabalin, but available data are sparse. Consistent with previous meta-analyses, sedation, dizziness, and visual disturbance occurred more commonly in pregabalin-treated patients.

Authors' contributions

B.M.M. was involved in conducting the study, extracting data, data analysis, and manuscript preparation. N.H.W. was involved in conducting the study, extracting data, data analysis, and manuscript preparation. A.S.H. was responsible for the concept and design of the study, conduct of study, extracting data, data analysis, and manuscript preparation.

Declaration of interest

None declared.

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