British Journal of Anaesthesia **106** (4): 454–62 (2011)
Advance Access publication 26 February 2011 · doi:10.1093/bja/aer027

BJA

REVIEW ARTICLES

Efficacy of pregabalin in acute postoperative pain: a meta-analysis

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Editor's key points

- Meta-analysis of perioperative pregabalin and postoperative analgesia identified 11 studies.
- Pregabalin produced a dose-related reduction in postoperative opioid use.
- Pregabalin reduced postoperative nausea and vomiting, but the incidence of visual disturbance was increased.
- The diverse nature of the surgery and anaesthetic techniques included suggest that large randomized, controlled trials are still needed.

Multimodal treatment of postoperative pain using adjuncts such as gabapentin is becoming more common. Pregabalin has anti-hyperalgesic properties similar to gabapentin. In this systematic review, we evaluated randomized, controlled trials (RCTs) for the analgesic efficacy and opioid-sparing effect of pregabalin in acute postoperative pain. A systematic search of Medline (1966–2010), the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar was performed. We identified 11 valid RCTs that used pregabalin for acute postoperative pain. Postoperative pain intensity was not reduced by pregabalin. Cumulative opioid consumption at 24 h was significantly decreased with pregabalin. At pregabalin doses of $<$300 mg, there was a reduction of 8.8 mg [weighted mean difference (WMD)]. At pregabalin doses $\geq$300 mg, cumulative opioid consumption was even lower (WMD, −13.4 mg). Pregabalin reduced opioid-related adverse effects such as vomiting [risk ratio (RR) 0.73; 95% confidence interval (CI) 0.56–0.95]. However, the risk of visual disturbance was greater (RR 3.29; 95% CI 1.95–5.57). Perioperative pregabalin administration reduced opioid consumption and opioid-related adverse effects after surgery.

Keywords: analgesics; non-opioid; pain; postoperative; pregabalin

Pregabalin is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid, but it is not functionally related to it.[1] Like its predecessor, gabapentin, it binds to the α-2-δ subunit of voltage-gated calcium channels, reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization.[2 3] Pregabalin has anticonvulsant, anti-hyperalgesic, and anxiolytic properties similar to gabapentin, but it has a more favourable pharmacokinetic profile, including dose-independent absorption.[4 5] It is also several times more potent than gabapentin while producing fewer adverse effects.[1]

In recent years, pregabalin has been introduced as an adjunct in the multimodal management of postoperative analgesia.[6] Numerous studies have evaluated the efficacy and adverse effects of pregabalin in reducing acute postoperative pain. However, these studies have yielded conflicting results possibly due to differences in dosage, dosing regimen, and nature of surgery. The aim of this systematic review was to evaluate the available literature on the efficacy of perioperative pregabalin in the management of acute postoperative pain.

Methods

This review was performed according to the QUOROM guidelines for reporting meta-analyses.[7] We conducted a literature search of Medline (1966–2010), the Cochrane Central Register of Controlled Trials (CENTRAL 2010), and Google Scholar databases using the following words: 'pregabalin', 'Lyrica', 'gabapentinoids', 'adjuvants', 'postoperative pain', or 'surgical-related pain'. Searches were limited to clinical trials and randomized, controlled trials (RCTs) in humans, without language restriction. The last electronic search was performed in April 2010. We also searched the archives of relevant journals by hand to identify additional studies that could meet our inclusion criteria. Additional studies from the bibliographies of reviews or reports were also identified. Authors of original reports were contacted for original data if needed.

All randomized, placebo- or active-controlled clinical trials in humans who reported on relevant pain outcomes with intervention or treatment with perioperative pregabalin were included. Abstracts and unpublished observations were not considered. All studies included had a minimum of 10 patients in each study group as recommended by L'Abbe and colleagues.[8] Validity of the studies was evaluated using the Modified Oxford Scale (Table 1).[9 10] Two reviewers scored the studies independently. In the case of discrepancy, a third reviewer was consulted and consensus was reached by discussion. Each study could receive a maximum score of 7. Studies with scores of $<$3 were considered poor

quality and would be excluded from the analysis. Studies with scores of 3–5 were considered fair quality and those with scores of 6 or 7 were considered good-quality studies.

The following data were collected on the data extraction form: (i) publication details; (ii) quality score of studies; (iii) number of patients; (iv) pregabalin dosage and regimen; (v) study design and duration; (vi) analgesic outcome measures; (vii) adverse effects; and (viii) type of surgery and anaesthesia.

The three main outcome measures investigated in this review were pain intensity, total analgesic consumption in the first 24 h after surgery, and adverse effects. Quantitative analysis was performed for 24 h analgesic consumption and pain intensity reported on a visual analogue scale (VAS). Pain intensity was reported at different time points in different studies. However, most studies provided pain scores at 2 and 24 h after operation. To facilitate pooling of data, pain scores at these two time points were analysed as early and late postoperative period. All pain scores on a VAS or Numeric Rating Scale (NRS) were converted to a scale from 0 to 100. Morphine consumption was used as the standard for postoperative opioid consumption. All other opioids used in the studies were converted to equi-analgesic morphine equivalent doses based on the following conversion scale: 100:1 for fentanyl, 1:10 for tramadol, and 1:1.5 for oxycodone. When data were presented graphically, the originals were obtained from the authors or extracted from the graphs if no response was obtained from the authors. Adverse effects including nausea, vomiting, sedation, visual disturbances, dizziness, and headache were noted for analyses.

Meta-analysis

In studies where the study duration was at least 24 h, pain scores and 24 h opioid consumption were quantitatively analysed as weighted mean differences (WMDs) with 95% confidence intervals (CIs). Dichotomous data on adverse effects were summarized using risk ratio (RR) with 95% CI. The random effects model was chosen because of a high clinical heterogeneity among the studies. The significance level was set at 0.05. All analyses were performed using Review Manager Software [Review Manager (RevMan) (Computer program). Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008]. Number-needed-to-treat (NNT) or number-needed-to-harm (NNH) was calculated using pooled raw data to estimate the clinical impact of the beneficial or harmful effect of the intervention.

Table 1 Modified Oxford Scale

Score	0	1	2
Randomization	None	Mentioned	Described and adequate
Concealment of allocation	None	Yes	
Double blinding	None	Mentioned	Described and adequate
Flow of patients	None	Described but incomplete	Described and adequate

Results

The search identified 45 papers on perioperative pregabalin and postoperative pain between 2000 and 2010, but only 17 were relevant (Fig. 1). All reports were published in English. Three were reviews:[11–13] one was an animal study related to gabapentinoids,[14] one was not placebo-controlled,[15] and one reported on postoperative chronic pain.[16] None of the eligible studies was excluded due to poor quality. Therefore, 11 valid randomized, controlled clinical trials with 16 treatment arms were considered for review. The quality of seven of the studies was rated fair[17–22] and of five was rated good[23–27] (Table 2). As two treatment arms in two separate studies had used dexamethasone combined with pregabalin,[24 25] the data from these two arms were not included. Therefore, 14 treatment arms were included in the final analysis. A total of 899 patients were studied, of whom 521 patients received pregabalin.

The types of surgery were of great heterogeneity. Most patients in the studies received general anaesthesia, except in two studies where spinal anaesthesia and local anaesthesia were administered.[18 24] Pregabalin was administered as a single preoperative dose in seven studies,[19–21 23–25 27] as a single postoperative dose in one study,[18] and as two separate preoperative and postoperative doses in three studies.[17 22 26] The dose of pregabalin ranged from 50 to 600 mg. To facilitate quantitative analysis, a dose of 300 mg day^{-1} was used as a cut-off to divide the treatment groups into two groups: (i) group receiving $<$300 mg of pregabalin per day and (ii) group receiving $\geq$300 mg of pregabalin per day. Pain intensity and 24 h postoperative analgesic consumption were analysed separately in each group (Fig. 2). Data on adverse effects were pooled and analysed together because of the small number of clinical trials in each subgroup.

Pregabalin <300 mg day^{-1}

Five trials with six treatment arms used a perioperative pregabalin dose of $<$300 mg day^{-1}. Pregabalin was administered before operation as one dose in four of these trials,[19 20 23 27] whereas the remaining trial used pregabalin after operation.[18]

One study did not report pain intensity with VAS scores.[18] Postoperative pain intensity was presented as median or median with inter-quartile ranges or percentile ranges in the other four studies and was not suitable for meta-analysis.[19 20 23 27]

Three studies reported on mean opioid consumption 24 h after operation.[20 23 27] Combined data showed a statistically significant opioid-sparing effect of pregabalin (WMD, −8.80 mg; 95% CI −16.65 to −0.94) (Fig. 3).

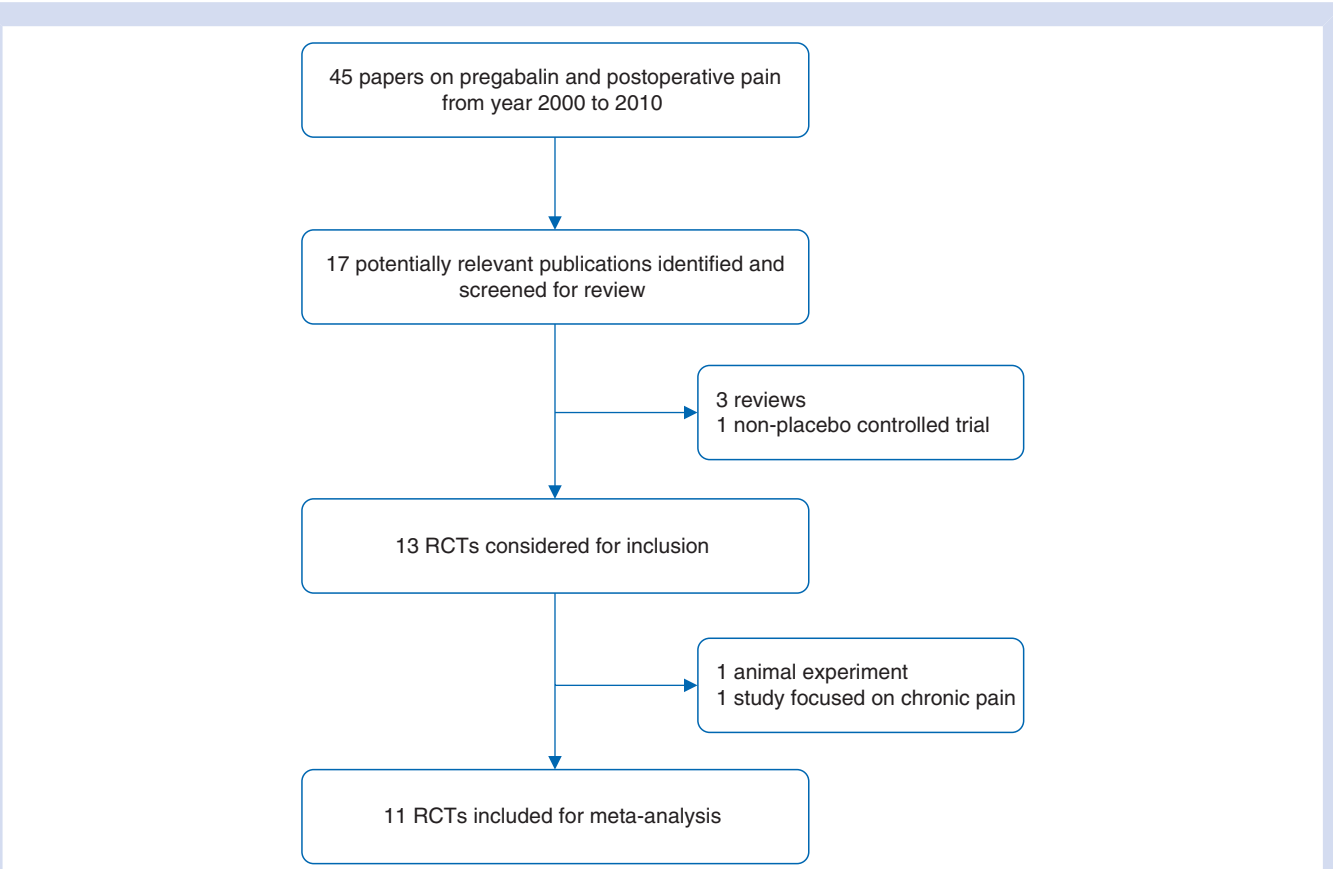

Fig 1 Flow diagram of screened, excluded, and analysed publications. RCTs, randomized, controlled trials.

Only one study with two treatment arms reported time to first dose of rescue analgesic and no significant difference was found between the pregabalin and control groups.[20]

Pregabalin ≥300 mg day^{-1}

Seven studies with eight treatment arms used a perioperative pregabalin dose of 300 or 600 mg.[17 18 21 22 24–26] Pregabalin was administered as a single dose (1 h before operation or after operation) in four trials[18 21 24 25] and in two separate doses (1 h before operation and 12 h after the first dose) in three trials.[17 22 26]

One study reported postoperative VAS pain intensity as median with inter-quartile ranges;[22] one study did not report VAS pain intensity.[18] Five studies reporting mean postoperative VAS pain intensity were analysed. Combined data from four studies[17 24–26] showed no significant difference in pain intensity at rest in the early postoperative period at 2 h (WMD, −2.40 mm; 95% CI −4.93 to 0.13). Combined data from five studies[17 21 24–26] also showed no significant difference in pain intensity at rest in the late postoperative period at 24 h (WMD, −2.57 mm; 95% CI −5.78 to 0.65) (Fig. 4). Two studies conducted by the same investigators reported on postoperative pain intensity on movement. Combined data showed no significant difference in pain intensity on movement at 2 h (WMD, −3.28 mm; 95% CI −7.62 to 1.05) and 24 h (WMD, 0.01 mm; 95% CI −6.24 to 6.27) after operation (Fig. 5).

One study did not report on postoperative analgesic consumption.[18] One study used ketorolac as a postoperative analgesic and showed no difference between pregabalin and placebo.[17] The study using oxycodone found that pregabalin 600 mg decreased postoperative analgesic consumption significantly compared with placebo.[26] One study reported that fewer patients in the pregabalin group needed additional analgesics after operation.[22] Combined data from three studies[21 24 25] showed that perioperative pregabalin reduced postoperative opioid consumption (WMD, −13.40 mg; 95% CI −22.78 to −4.02). Heterogeneity among the studies was significant (df = 2, $P = 0.007$) (Fig. 6).

Only one study with two treatment arms presented time to first dose of rescue analgesic and detected no difference between pregabalin and placebo.[26]

Adverse effects

The adverse effects analysed were nausea, vomiting, sedation, dizziness and headache, and visual disturbance occurring in the first 24 h after surgery. Six studies provided data on nausea (516 patients),[17 20 24–27] seven on vomiting (596 patients),[17 20 23–27]

Table 2 Randomized, placebo-controlled trials of perioperative pregabalin for acute postoperative pain management. P, pregabalin group; C, control group; NS, no significant difference between groups; preop, before operation; postop, after operation; PCA, patient controlled analgesia; PONV, postoperative nausea and vomiting; GA, general anaesthesia; RA, regional anaesthesia; LA, local anaesthesia; MOS, Modified Oxford Scale

Clinical trial	MOS score	Number of patients (P/C)	Dose of pregabalin (mg)	Time of pregabalin administration	Pain intensity at rest	Postoperative analgesia	Total analgesic consumption	Time to first analgesics	Adverse effects	Type of surgery and anaesthesia
Hill and colleagues[18]	3	99 (two P treatment arms)/50	50 and 300	Postop	$P<0.05$ in 300 mg group	Study discontinued if rescue analgesics given	—	—	More side-effects in 300 mg P group	Molar extraction, LA
Paech and colleagues[19]	5	41/45	100	1 h preop	NS	I.V. fentanyl	NS	—	More light headedness, visual disturbance, and walking difficulty in P group	Minor gynaecological surgery, GA
Agarwal and colleagues[27]	6	27/29	150	1 h preop	$P<0.05$	I.V. PCA fentanyl	$P<0.05$	—	NS	Laparoscopic cholecystectomy, GA
Jokela and colleagues[20]	6	56 (two P treatment arms)/29	300 and 600	1 h preop and 12 h after first dose	NS	I.V. PCA oxycodone	$P<0.05$	NS	More blurred vision in both P groups; more dizziness in 600 mg P group	Laparoscopic hysterectomy, GA
Jokela and colleagues[26]	5	56 (two P treatment arms)/28	75 and 150	1 h preop	$P<0.05$ in 150 mg group	I.V. fentanyl	NS	NS	NS	Day-case gynaecological laparoscopic surgery, GA
Mathiesen and colleagues[24]	7	82 (one of the treatment arm using dexamethasone)/38	300	1 h preop	NS	I.V. PCA morphine	$P<0.05$	—	More sedation in P group	Total hip arthroplasty, RA
Mathiesen and colleagues[25]	6	76 (one of the treatment arm using dexamethasone)/40	300	1 h preop	NS	I.V. PCA morphine	NS	—	Less vomit in P group	Abdominal hysterectomy, GA
Chang and colleagues[17]	3	39/38	300	1 h preop and 12 h after first dose	NS	I.V. ketorolac	NS	—	More sedation in P group	Laparoscopic cholecystectomy, GA
Cabrera Schulmeyer and colleagues[23]	6	39/41	150	2 h preop	$P<0.05$	I.V. morphine	$P<0.05$	—	Less PONV in P group	Laparoscopic sleeve gastrectomy, GA
Ittichaikulthol and colleagues[21]	3	38/40	300	1 h preop	$P<0.01$	I.V. PCA morphine	$P<0.01$	—	NS	Abdominal hysterectomy, GA
Kim and colleagues[22]	5	47/47	300	1 h preop and 12 h after first dose	$P<0.05$	I.V. ketorolac and p.o. ibuprofen	—	—	More sedation and dizziness in P group	Endoscopic thyroidectomy, GA

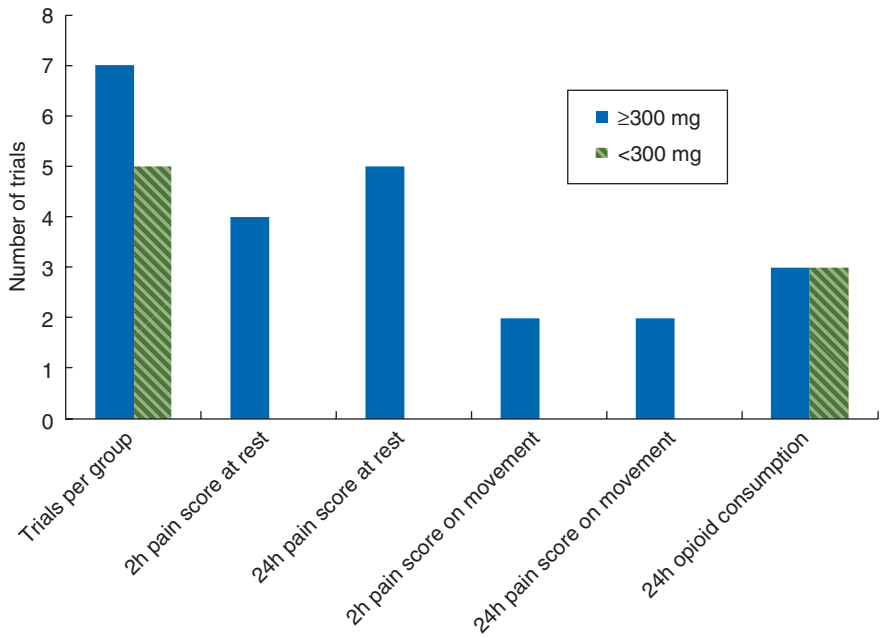

Fig 2 Number of RCTs analysed for each outcome in the two subgroups.

Study or subgroup	Pregabalin Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference I.V., random. 95% CI
Agarwal and colleagues[27] 150 mg	55.52	12.48	27	75.75	9.93	29	24.1	–20.23 (–26.16, –14.30)
Jokela and colleagues[26] 150 mg	17.3	10.2	26	18.6	10.7	28	24.5	–1.30 (–6.87, 4.27)
Jokela and colleagues[26] 75 mg	16.3	7.7	30	18.6	10.7	28	25.3	–2.30 (–7.13, 2.53)
Cabrera Schulmeyer and colleagues[23] 150 mg	11.51	7.93	39	23.07	9.57	41	26.2	–11.56 (–15.40, –7.72)
Total (95% CI)			**122**			**126**	**100.0%**	**–8.80 (–16.65, –0.94)**

Heterogeneity: τ^2=57.51; χ^2=30.15, df=3 (P<0.00001); I^2=90%
Test for overall effect: Z=2.20 (P=0.03)

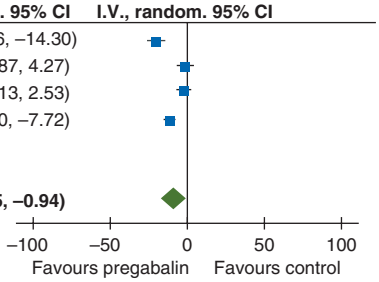

Fig 3 Forest plot of meta-analysis: 24 h morphine consumption (mg) in patients receiving pregabalin <300 mg day^{-1}. CI, confidence interval.

five on sedation (384 patients),[17 22 24 25 27] seven on dizziness and headache (618 patients),[17 19 20 22 25–27] and five on visual disturbance (483 patients).[17 19 20 22 26]

Combined data showed that patients who received pregabalin were at a lower risk of vomiting (RR 0.73; 95% CI 0.56–0.95), but at a higher risk of visual disturbance (RR 3.29; 95% CI 1.95–5.57) (Fig. 7). NNT and NNH were 18 and 6, respectively. There were no differences between the pregabalin and control groups for the other adverse effects.

Discussion

Our systematic review showed that perioperative pregabalin administration did not reduce pain intensity for the first 24 h after surgery, although significant differences were found in individual studies when compared with placebo. However, opioid consumption during the first 24 h after surgery was significantly reduced by pregabalin. Another clinically relevant outcome measure—time to first analgesic request—was only reported in two studies conducted by the same investigators, and no significant difference was detected.[20 26] Pregabalin reduced the incidence of postoperative vomiting, but was associated with a higher incidence of visual disturbance after surgery.

Pain after surgery is normally perceived as nociceptive pain. However, surgical trauma has been known to induce hyperalgesia, which can contribute to persistent postoperative pain after surgery.[14] In contrast to traditional analgesics

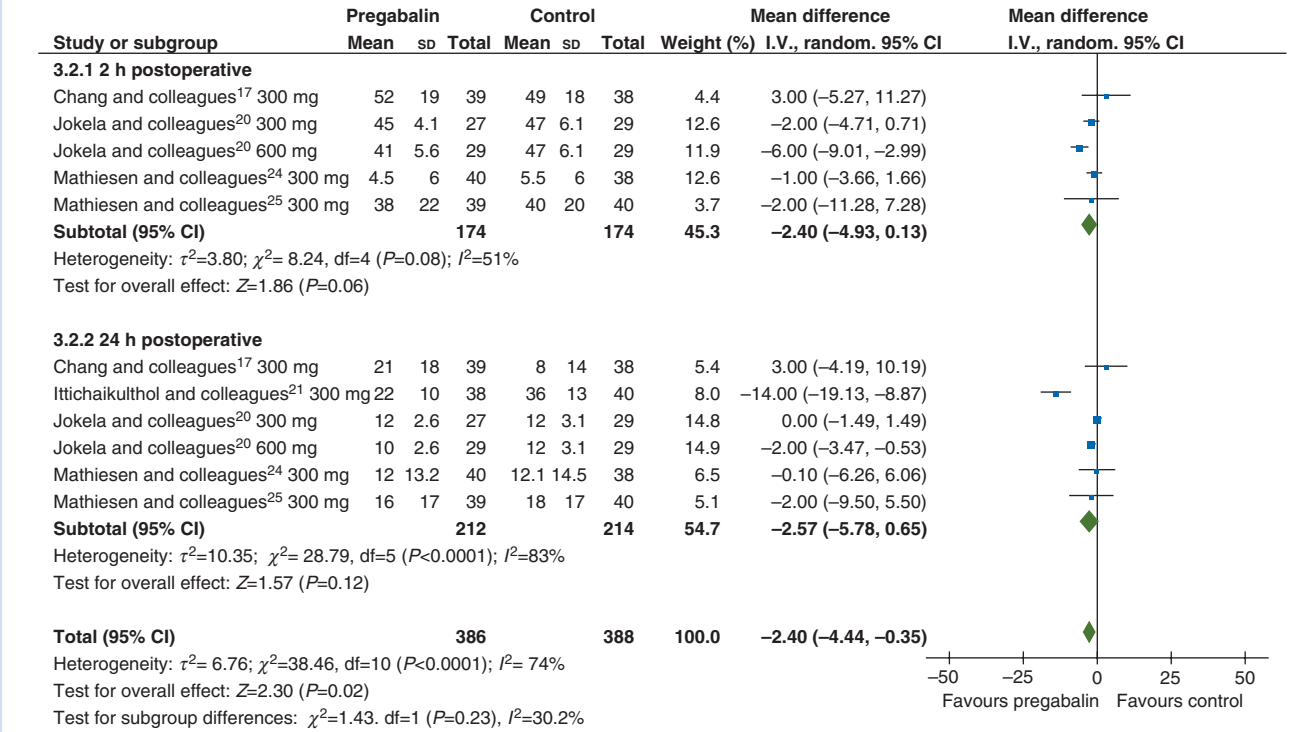

Fig 4 Forest plot of meta-analysis: VAS of postoperative pain intensity (0–100 mm) at rest in patients receiving pregabalin ≥300 mg day^{-1}. CI, confidence interval.

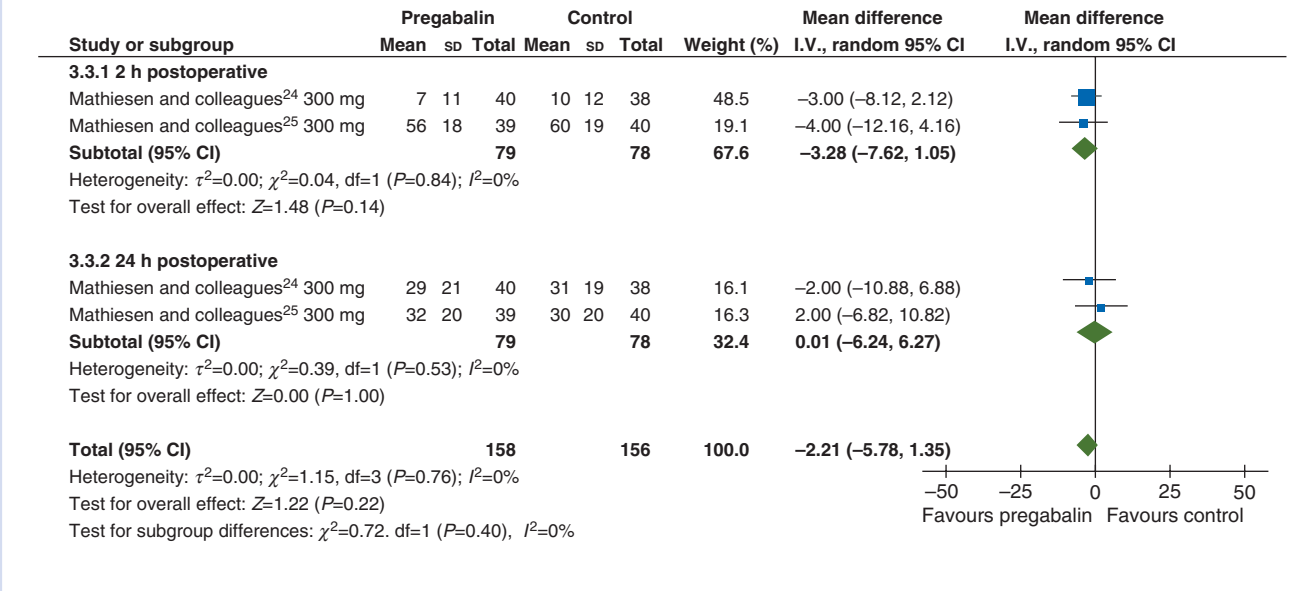

Fig 5 Forest plot of meta-analysis: VAS of postoperative pain intensity (0–100 mm) on movement in patients receiving pregabalin ≥300 mg day^{-1}. CI, confidence interval.

that are anti-nociceptive, gabapentinoids such as gabapentin and pregabalin reduce the hyperexcitability of dorsal horn neurones induced by tissue damage rather than reduce the afferent input from the site of tissue injury. Gabapentinoids have been recommended for perioperative administration to improve acute pain after surgery.[6]

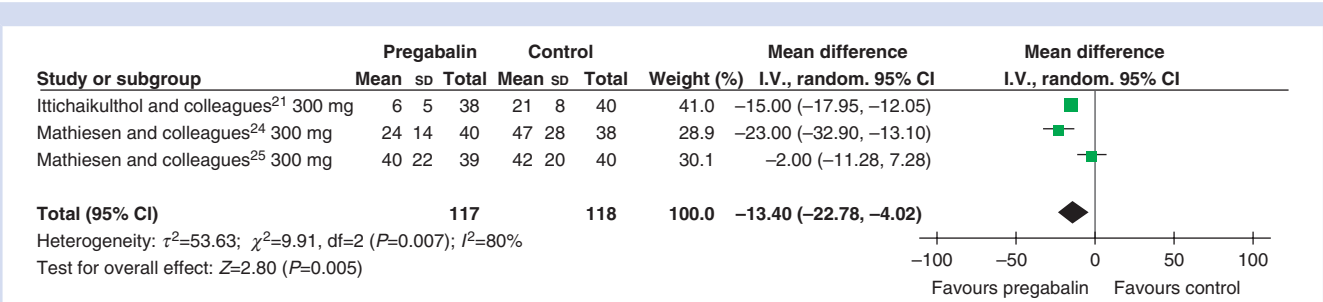

Fig 6 Forest plot of meta-analysis: 24 h morphine consumption (mg) in patients receiving pregabalin ≥300 mg day^{-1}. CI, confidence interval.

Systematic reviews have shown that gabapentin is effective in reducing pain intensity, opioid consumption, and opioid-related adverse effects after surgery.[10 13] Animal studies demonstrated that pregabalin was three- to 10-fold more potent than gabapentin as an antiepileptic[28] and two- to four-fold more potent as an analgesic in the treatment of chronic neuropathic pain.[29]

In our meta-analysis, pain intensity in the first 24 h after surgery was not reduced by perioperative pregabalin administration. This differed from the results of meta-analyses on perioperative gabapentin administration. Most of the studies in this review involved minimally invasive surgery such as laparoscopic surgery or day-case gynaecological surgery. Such surgery is generally not very painful. One study on hip arthroplasty[24] used spinal anaesthesia during surgery and another study on abdominal hysterectomy[25] had administered paracetamol before surgery.

However, our review demonstrated a statistically significant decrease in opioid consumption during the first 24 h after surgery in patients who received pregabalin. This suggested that pregabalin had an opioid-sparing effect that was similar to gabapentin. As patients had access to postoperative opioids, opioid consumption would be an appropriate surrogate indicator of the intensity of postoperative pain. The consumption of analgesics for measuring the efficacy of treatment is considered only valid when the test and control groups have achieved similar pain scores.[30] Some of the studies had different pain scores, but the pooled data showed no difference in postoperative pain scores. Therefore, opioid consumption can be viewed as a good indicator for assessing the efficacy of pregabalin in reducing postoperative pain.

The incidence of postoperative vomiting was significantly lower with the use of pregabalin. This might be related to the decreased use of opioids after surgery and the consequent decrease in opioid-related adverse effects. The incidence of visual disturbance, however, was significantly higher in the pregabalin group. There were also more patients with sedation, dizziness, and headache in the pregabalin group, although no statistically significant differences were observed. These side-effects are well known and have been reported in various chronic pain trials. Therefore, pregabalin should be used with caution in ambulatory surgery. Side-effects may also influence the use of opioids. It is possible that over the more sedated patients in the pregabalin group will use less opioid.

There are some limitations to this meta-analysis. First, there was a wide variability among the studies included with regard to the nature of surgery, pregabalin dose and dosing regimen, anaesthetic technique, and the use of other anaesthetic agents during surgery. Secondly, pregabalin was not the only analgesic adjuvant used for acute postoperative pain management. Thirdly, data presented in some studies were not suitable for pooling for meta-analyses *and some data were also documented as outcome measures to be available for analysis*. Finally, the number of trials that measured 'time to first analgesics' was small and the absence of a difference between the pregabalin and placebo groups cannot be conclusive and may need to be explored in larger trials.

Postoperative pain management is an important issue that deserves much attention. Gabapentin has been demonstrated to be an effective adjuvant for acute pain after surgery.[10 13] Pregabalin is a new gabapentinoid with greater potency and a more favourable pharmacological profile than gabapentin. Therefore, it could be a better choice for postoperative analgesia. Further studies should investigate the analgesic efficacy of pregabalin in painful surgery and its effect in reducing the incidence of chronic post-surgical pain. Our search only identified one study that focused on chronic pain after total knee arthroplasty.[16] It showed that perioperative pregabalin reduced the incidence of chronic neuropathic pain.[16] Therefore, pregabalin may have a promising role in the prevention of chronic pain development.

In conclusion, the perioperative administration of pregabalin has a significant opioid-sparing effect in the first 24 h after surgery. Postoperative vomiting was reduced, whereas visual disturbance was more common with pregabalin administration. The efficacy of perioperative pregabalin in more painful procedures and on the prevention of chronic pain should be investigated in future studies.

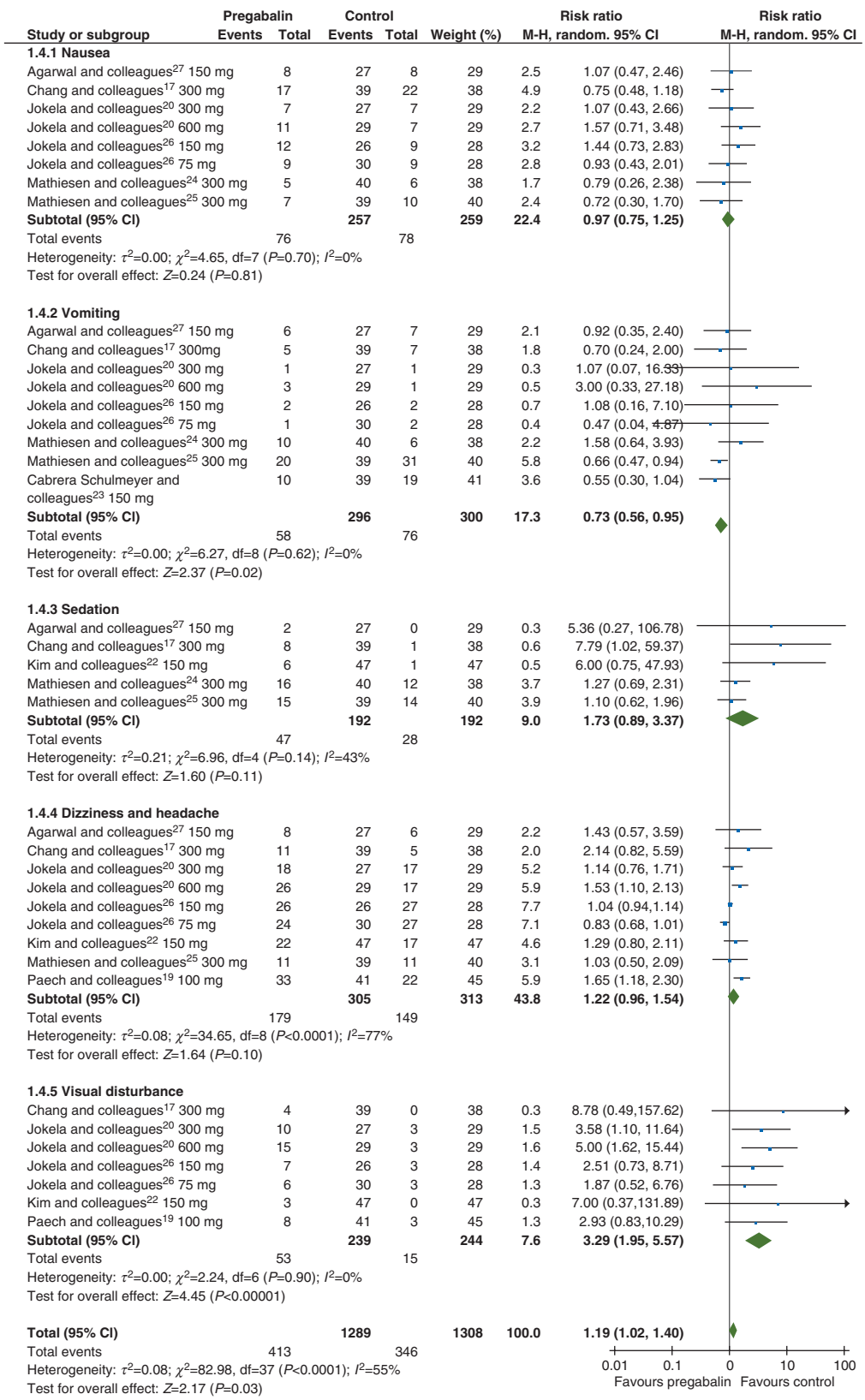

Fig 7 Forest plot of meta-analysis: adverse effects (nausea, vomiting, sedation, dizziness and headache, and visual disturbance). CI, confidence interval.

Conflict of interest

None declared.

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Secondly, we completely agree with Dr Ziemann-Gimmel that our results are not to be interpreted that untreated or unrecognized OSA is not associated with increased risk of complications. Our manuscript explicitly states this point. Our results are only applicable to those obese patients evaluated before bariatric surgery by polysomnography and their obesity-related sleeping disorder managed accordingly in the postoperative period.

Conflict of interest

None declared.

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doi:10.1093/bja/aer208

Efficacy of pregabalin in acute postoperative pain: a meta-analysis

Editor—We read with interest the meta-analysis on the efficacy of pregabalin in acute postoperative pain.[1] However, we would like to highlight some of our concerns about the study.

Although the authors have mentioned about the limitations in their study, it would have been perhaps better if they had performed a subgroup analysis on morphine consumption, depending on the different types of surgery in which pregabalin has been used, because not all operations have the same opioid requirement after operation. In the studies where intraoperative opioids have been given,[2–7] the authors did not provide a subgroup analysis of whether there was a reduced requirement for intraoperative opioid in the group of patients having had preoperative pregabalin. We found it surprising that the authors chose to analyse opioid consumption where pregabalin had been administered both 1 h before operation and 12 h after operation[6] along with studies[2–5 7] in which pregabalin was only administered 1 h before operation. Certainly, these cohorts of patients would have had varying postoperative requirement for opioids.

We noted that studies have been included where intraoperative opioids,[3–5 7] acetaminophen,[8] and non-steroidal drugs[2 4] have been given either before operation or as an infusion after operation[4] and yet a subgroup analysis has not been undertaken to elicit an influence of these analgesics on the efficacy of pregabalin.

The authors did not take into consideration the use of ondansetron, droperidol, and dexamethasone,[2 6] while considering the effect on postoperative nausea and vomiting of pregabalin, when all three drugs are known to reduce postoperative nausea and vomiting.[9]

The number of patients in the control group in Figures 3 (24 h morphine consumption), 4 (VAS postoperative pain intensity), and 7 (nausea, vomiting, dizziness and headache, and visual disturbance) have been duplicated thereby creating a unit-of-analysis error. This could have been avoided by either splitting the shared group resulting in a smaller sample size and including two or more comparisons, by combining groups to create pair-wise comparisons, or by undertaking a multiple treatment analysis.[10]

Conflict of interest

None declared.

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doi:10.1093/bja/aer207