British Journal of Anaesthesia **105** (2): 155–61 (2010)
Advance Access publication 25 June 2010 · doi:10.1093/bja/aeq116

BJA

Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy

P. W. H. Peng[1]*, C. Li[2], E. Farcas[1], A. Haley[1], W. Wong[3], J. Bender[3] and F. Chung[1]

[1] Department of Anesthesia, Toronto Western Hospital, University of Toronto, McL 2-405, 399 Bathurst Street, Toronto, ON, Canada M5T 2S8
[2] Pain Management Clinic, Hong Kong Sanatorium Hospital, Hong Kong
[3] Department of Anesthesia, St Joseph Health Centre, Toronto, Ontario, Canada

* Corresponding author. E-mail: philip.peng@uhn.on.ca

Key points

- Pregabalin 50 or 75 mg provided limited analgesic benefit compared with placebo in patients undergoing day-case cholecystectomy.
- Median postoperative pain scores at rest and on movement were ≤5/10 in all groups up to 7 days after surgery.
- Minor adverse effects were common in all groups after operation.
- These data confirm the results of a meta-analysis of published studies.

Background. The objective of this study was to examine the effects of low-dose pregabalin on the analgesic efficacy, side-effects, and recovery profile in patients undergoing laparoscopic cholecystectomy.

Methods. One hundred and sixty-two patients aged 18–65 yr, of ASA physical status I–III, undergoing elective outpatient laparoscopic cholecystectomy were recruited and randomized in this prospective, placebo-controlled, double-blind study to receive one of the following study medications orally: pregabalin 50 mg, pregabalin 75 mg, or placebo, 1 h before surgery and then every 12 h after operation for a total of three doses. Postoperative numeric pain scores, analgesic consumption, recovery score (QoR-40), and side-effects (opioid-related symptom distress scale) were assessed in the early postoperative period (every 15 min during the first hour, at 90, 120 min, 6, and 12 h) and at days 1, 2, and 7. Data were analysed using an intention-to-treat method.

Results. Compared with the placebo group, the pain scores were lower in the pregabalin 75 mg group in the first 90 min after surgery ($P<0.05$). Pregabalin 50 mg resulted in pain reduction at 30 and 45 min ($P<0.05$) relative to placebo. The analgesic consumption, side-effects, and recovery scores were similar among the three groups.

Conclusions. Perioperative administration of pregabalin 75 mg provided limited analgesic benefit in the postoperative period. An updated meta-analysis confirms this finding (see Supplementary material).

Keywords: anaesthesia; cholecystectomy; general surgery; pain, postoperative; pregabalin; premedication

Accepted for publication: 9 April 2010

Gabapentinoids are anti-convulsants with membrane stabilizing and anti-nociceptive effects. These drugs bind to the presynaptic α2–δ subunit voltage-dependent calcium channel.[1 2] The anti-nociceptive effect is believed to be related to the reduction of the Ca^{2+} influx at presynaptic terminals in *hyperexcited* neurones, which may lead to the reduction of the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide.[3 4] Thus, gabapentinoids appear to reduce the hyperexcitability of dorsal horn neurones that is induced by tissue damage.

The analgesic effect of gabapentin has been well established in various surgical populations and was described in multiple systematic reviews.[5–9] Compared with gabapentin, pregabalin has a more favourable pharmacokinetic profile with better, faster, and more predictable absorption. It is rapidly and extensively absorbed after oral dosing, with maximal plasma concentration at 1 h after single or multiple doses. The oral bioavailability is 90% and is independent of dose.[1 3] These properties offer some advantages over gabapentin as a perioperative medication. Pregabalin has recently been investigated for perioperative use, but the results are inconsistent.[10–18] Four out of nine perioperative trials were negative[10 13 14 16] and only two trials showed a reduction in both analgesic consumption and pain scores.[17 18] Two other trials demonstrated a reduction in the analgesic consumption at the expense of an increase in pregabalin-related side-effects.[12 15] The doses of pregabalin used in the aforementioned studies ranged from 75 to 300 mg.

The hypothesis of this study was that multiple low doses of pregabalin would provide superior analgesic effects with minimal pregabalin-related side-effects in the first 24 h after day surgery. The objective of the study was to examine the effects of pregabalin in low doses, 50 and 75 mg, on the

analgesic efficacy, side-effects, and recovery profile in patients undergoing outpatient laparoscopic cholecystectomy.

Methods

This double-blind, randomized, controlled study was designed to recruit patients aged between 18 and 65, of ASA physical status I–III, undergoing laparoscopic cholecystectomy. After Institutional Ethic Review Board approval and written consent, patients were randomized to receive one of the study medications orally: pregabalin 50 mg, pregabalin 75 mg, or placebo, 1 h before surgery and then every 12 h after operation for a total of three doses. This study was registered with www.controlled-trial.com (ISRCTN01000893).

Patients were excluded from recruitment if they required urgent or emergent cholecystectomy, or analgesics in 24 h before surgery (except the premedication as per protocol); had a body mass index more than 40, a clinical diagnosis of acute pancreatitis or a history of allergy or contraindication to gabapentin or pregabalin, non-steroidal anti-inflammatory agents, codeine or acetaminophen, or serious organ disease or dysfunction, severe psychiatric disease, or drug addiction; or were pregnant or could not communicate in English.

The study medications were prepared in capsules of identical colour and appearance and were packaged by the hospital pharmacy according to a computer-generated randomization list. On the day of surgery, patients received standard premedications as per our institution protocol: naprosyn® 500 mg and acetaminophen 1000 mg 1 h before surgery in the preadmission unit. The study medication was given to the patient together with the premedications. The anaesthetist responsible for the operating theatre list, the patient, the surgeon, nurses, and the research assistant were blinded to the randomization. Before surgery, patients were instructed to rate their pain using a numeric verbal rating score (NRS) on a scale of 10 (0, no pain; and 10, worst imaginable pain).

Patients received standardized general anaesthesia. Induction of general anaesthesia was achieved with i.v. propofol 1–2 mg kg^{-1} and fentanyl 2–5 $\mu g\ kg^{-1}$, followed by rocuronium 0.8–1 mg kg^{-1} to facilitate orotracheal intubation with a cuff tube. Balanced anaesthesia was maintained using nitrous oxide and desflurane at end-tidal concentration 3–6% in oxygen, and i.v. fentanyl. The amount of the induction agent and volatile agent were titrated by the attending anaesthetist and recorded. All patients were given a single i.v. dose of prophylactic antiemetic, granisetron 1 mg, at the end of operation. The surgeon administered local anaesthetic (bupivacaine 0.25% with epinephrine 1 in 200 000 to a volume of 30 ml) around the gall bladder bed and the laparascopy port sites (10 ml of the same solution). Neuromuscular block was antagonized with neostigmine 70 $\mu g\ kg^{-1}$ and glycopyrrolate 0.05 $\mu g\ kg^{-1}$ i.v.

On completion of surgery, patients were transferred to the post-anaesthesia care unit (PACU) where their pain scores (NRS) were measured on arrival and every 30 min until discharge from the PACU. Pain was assessed at rest and on active movement (or coughing). When patients requested analgesia, a fentanyl bolus at an increment of 25–50 μg was titrated according to patient's comfort with the standard protocol in the PACU every 5–10 min. Dimenhydrinate 25–50 mg i.v. was given as a rescue antiemetic if needed. Patients were discharged to the day surgery unit (DSU) when the Aldrete[19] score was $\geq$9. In the DSU, patients received combination tablets of acetaminophen 325 mg with codeine 30 mg when NRS was $>$3 or on request. Eligibility for discharge from DSU was based on the post-anaesthesia discharge score which was recorded every 15 min.[20]

Patients took their pregabalin medication or oral placebo 12 and 24 h after the first dose regardless of the level of pain they were experiencing. Patients who experienced insufficient pain relief were allowed to take supplementary combination tablets of acetaminophen 325 mg and codeine 30 mg 1–2 tablets orally every 4–6 h as needed (maximum of 12 tablets per day).

Patients were instructed to complete a diary to record the pain score, adverse events experienced, satisfaction, amount of analgesics taken, sleep quality, the opioid-related symptom distress scale (SDS), and the 40-item recovery score (QoR-40). They were followed up on the first, second, and seventh day after operation by telephone to determine the completion of the diary. The patients mailed the questionnaire package back after completion.

The opioid-related SDS is a validated instrument recording 12 opioid-related symptoms for the assessment of patient postoperative recovery functional status and side-effects.[21] This questionnaire measures the interference of pain (frequency, severity, and bothersomeness) with various daily activities by using a categorical scale (Appendix). Clinically meaningful events (CME) were defined based on the level of patient response to each symptom in the three measured dimensions: frequency, severity, and bothersomeness.[22] For each study symptom, a patient with a response of 'frequently' to 'almost constantly' for the frequency dimension, 'moderate' to 'very severe' for the severity dimension, or 'quite a bit' to 'very much bothered' for the bothersomeness dimension was considered to have a CME.

Postoperative quality of functional recovery was assessed by a well-validated QoR-40, which measured five dimensions of recovery: physical comfort (12 items), emotional state (nine items), physical independence (five items), psychological support (seven items), and pain (seven items).[23] Each item was rated on a five-point Likert scale. The QoR-40 has a possible score of 40 (extremely poor quality of recovery) to 200 (excellent quality of recovery). It was specifically designed to measure a patient's health status after surgery and anaesthesia and has been proposed as a measure of outcome in clinical trials.[24]

The patient's sleep quality was recorded with the Likert scale: a rating scale measuring sleep quality on a scale of 0–10, where 0, poor sleep, and 10, best sleep.

Pain scores are presented as a median and inter-quartile range. All other data are presented as mean and standard deviation. *P*-values of <0.05 were considered significant. Pain scores were analysed with the Kruskal–Wallis test. If there was a significant difference among the groups, individual groups were compared in a pairwise manner using a Mann–Whitney *U*-test. Patient data, analgesic consumption, side-effects, and recovery scores were analysed with analysis of variance. If there was a significant difference among the groups, *post hoc* analysis was performed with the Bonferroni test. Categorical data were analysed with a χ^2 test. Data were analysed using SPSS 16.0 for Windows (SPSS, Chicago, IL, USA). All analyses were performed on the intent-to-treat population, which included all patients who were randomized into the study and received at least one dose of study medication.

For intention-to-treat analysis, missing data were managed with the 'last observation carried forward' imputation method.[25 26] A sensitivity analysis was performed with the results of the pain score and analgesic consumption compared with those from 'per protocol' analysis, and also those assuming the best and worst outcome analysis. In 'per protocol' analysis, only data that were available were analysed. The other analysis was conducted by imputing the best or worst outcome (pain score or analgesic requirement) for the missing data.[26]

Sample size was calculated based on the null hypothesis of no difference across all groups following the methods described by Pandey and colleagues.[27] On the basis of Pandey and colleagues' gabapentin study in laparoscopic cholecystectomy patients, we estimated that a sample of 41 patients per treatment group would be sufficient to detect a power of 0.8 with a mean difference of 25 mm (out of 100 mm) NRS between any two groups with a power of 0.8 and a type 1 error of 0.05. Factoring in a drop-out rate of ~10%, we anticipated 45 patients required for each group.

Results

A total of 284 patients were assessed for eligibility and 165 of them were consented and randomized. The data from 142 patients were used for intention-to-treat analysis. The flow of the patients through the trial, including the reasons for exclusion, was summarized in Figure 1.

Patient data were similar among the three groups (Table 1). Similarly, there were no differences in the duration of anaesthesia and the intraoperative dose of fentanyl.

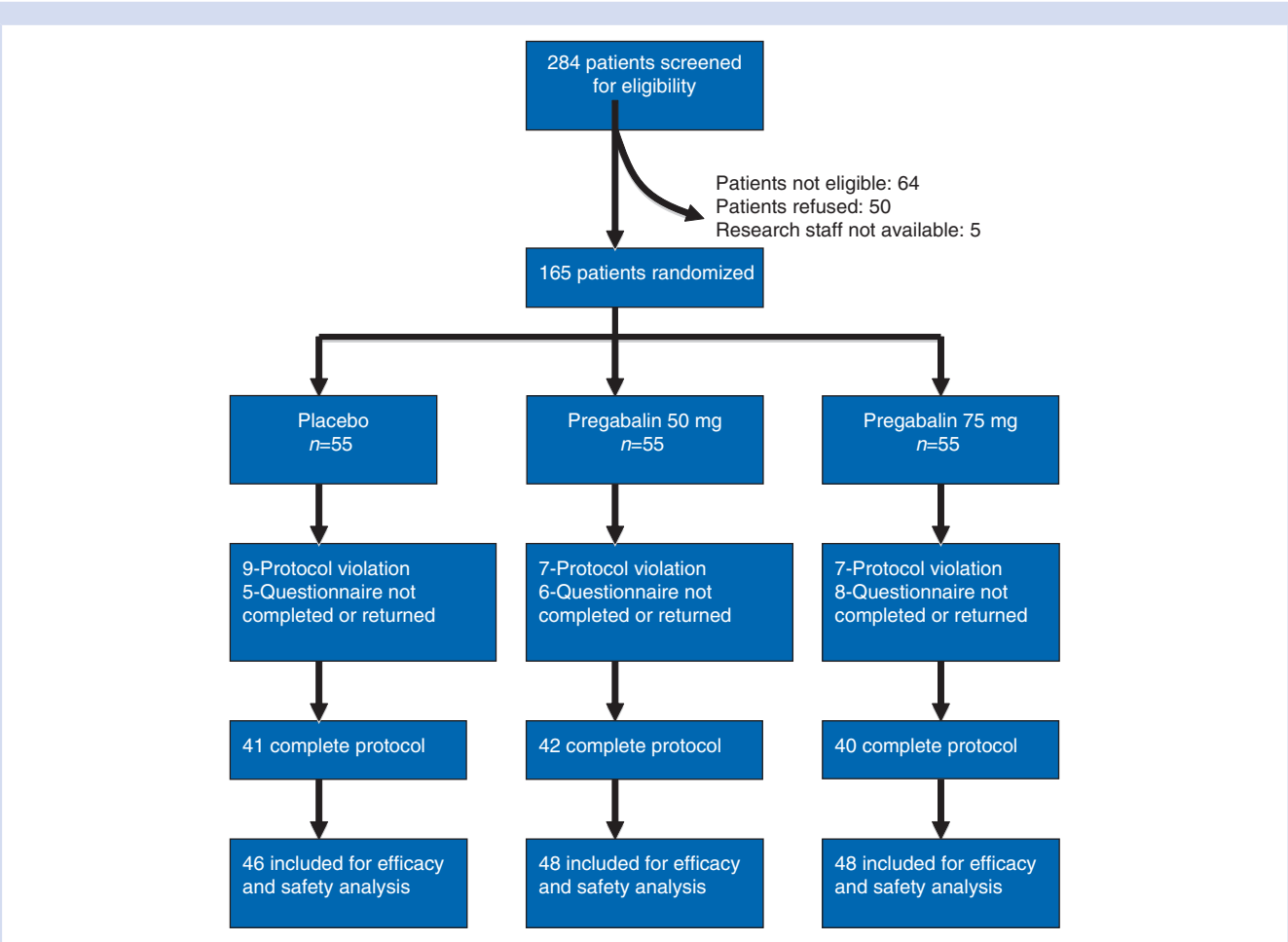

Fig 1 Flow diagram of the study.

Comparing with the placebo group, pain scores at rest were lower in the pregabalin 75 mg group in the first 90 min after surgery (15, 30, 45, and 90 min). The benefit from the pregabalin 50 mg group was more transient with lower pain scores at 30 and 45 min *vs* placebo (Table 2). Pain scores with movement were lower in the pregabalin 75 mg group in the first 45 min after surgery (Table 3). Analgesic consumption throughout the postoperative period was similar among the three groups (Table 4).

Table 1 Patient characteristics and intraoperative dose of fentanyl, presented as mean (SD) or number. Data are presented as mean (range) for age, or mean (SD) with the exception of gender in which ratios are presented. $P<0.05$ is defined as significant

Characteristic	Placebo	50 mg	75 mg
M/F	13/33	14/34	20/28
Age	47 (21–65)	46 (22–65)	43 (22–65)
Height (cm)	156 (24)	161 (24)	161 (23)
Body mass index (kg m^{-2})	29 (4)	27 (5)	29 (6)
Intraoperative fentanyl (μg)	185 (57)	187 (65)	195 (73)

Table 2 Pain scores at rest, presented as median (inter-quartile range). *$P<0.05$ when comparing with the placebo group; †$P<0.005$ when compared with placebo in the *post hoc* analysis

	Placebo	Pregabalin 50	Pregabalin 75
Baseline	0 (0)	0 (0)	0 (0)
15 min	2 (1–5)	2 (0–5)	0 (0–3)*
30 min	3 (1–6)	2 (0–5)*	2 (0–3)†
45 min	4 (2–6)	2 (1–4)*	2 (0–4)†
60 min	3 (2–5)	2 (1–4)	2 (0–4)
90 min	3 (1–5)	2 (1–4)	2 (0–3)*
120 min	2 (1–5)	2 (1–5)	1 (0–2)
6 h	4 (2–6)	4 (2–6)	3 (2–5)
12 h	4 (1–6)	3 (2–5)	4 (2–5)
Day 1	4 (2–5)	3 (2–5)	3 (2–6)
Day 2	3 (1–5)	3 (2–5)	3 (1–5)
Day 7	0 (0–1)	0 (0–1)	0 (0–1)

Table 3 Pain scores with movement, presented as median (inter-quartile range). *$P<0.05$ when comparing the pregabalin 75 mg group with placebo

	Placebo	Pregabalin 50	Pregabalin 75	*P*-value
15 min	3 (1–6)	2 (0–5)	0 (0–3)*	0.01
30 min	5 (1–7)	3 (1–5)	2 (0–3)*	0.002
45 min	4 (2–6)	3 (1–5)	2 (0–4)*	0.01
60 min	3 (2–6)	2 (1–5)	2 (0–4)	0.11
90 min	4 (1–5)	3 (1–5)	3 (1–4)	0.23
120 min	3 (1–5)	3 (1–5)	2 (1–4)	0.13

The composite score of all 12 opioid-related side-effects were similar among the three groups in days 1, 2, and 7. The incidence of all 12 clinical meaningful adverse effects on days 1, 2, and 7 were similar with two exceptions: the incidence of itchiness was lower in the pregabalin 50 mg group on day 1, and the incidence of fatigue was lower in the pregabalin 75 mg group on day 3 (Table 5). Recovery scores, both overall and individual domains, were similar among the three groups on days 1, 2, and 7. There was no difference in the ratings for satisfaction and sleep quality.

The analysis of pain scores from the 'per protocol' or 'assuming worst outcome' analysis did not differ from our initial analysis with the 'last observation carried forward' imputation method. With the 'assuming best outcome' imputation method, however, the pain score at rest was lower in the pregabalin 75 mg group at 6 h after surgery *vs* the placebo and pregabalin 50 mg group, with median pain score (IQR) as 2 (0–4), 3.5 (0–6), 4 (2–6), respectively ($P=0.009$ pregabalin 75 mg *vs* pregabalin 50 mg). The result of analgesic consumption did not change by imputing data with those three methods.

Discussion

With the use of multimodal analgesia, multiple doses of pregabalin 75 mg provided superior analgesia over the placebo group in the early postoperative period (first 90 min) without an increase in side-effects after day-case laparoscopic cholecystectomy. Compared with the 50 mg group, pregabalin 75 mg was more effective in the early postoperative period. Because the overall pain scores were low (pain score $\leq$4) among all three groups (Table 2), the reduction in the pain score was modest (1 to 2 out of a total score of 10). The aforementioned short-term analgesic benefit did not extend beyond the early postoperative period, nor result in any opioid-sparing effects, or improvement in recovery profile. Repeated dosing of low doses of pregabalin did not extend the analgesic effect beyond the early postoperative period.

The present study is the only one that investigates the use of low doses of 50 and 75 mg of pregabalin in the perioperative period. The common adverse effects of pregabalin are dose-dependent drowsiness and dizziness.[10 15] Therefore, the advantages of pregabalin may be mitigated by these troublesome side-effects, especially in the day surgical population. It is important to determine the lowest optimal dose of pregabalin for analgesic use without the adverse outcomes of downiness and dizziness. With this low dose, we were able to demonstrate superior analgesia with both 50 and 75 mg of pregabalin over placebo in the early postoperative period, even though patients were premedicated with acetaminophen and naprosyn®. One study in dental patients investigated the use of pregabalin 50 and 300 mg, but did not demonstrate any analgesic benefit with pregabalin 50 mg. However, there are several differences between this and our study, including the fact that pregabalin was given to patients with moderate pain only after the dental anaesthetic wore off after the dental procedure.[28]

Table 4 Analgesic consumption, presented as median (inter-quartile range). *ACP+codeine, combination tablet of acetaminophen 325 mg and codeine 30 mg and the dose of which are presented as number of tablets. D_0, day of the surgery; PACU, post-anaesthetia care unit. There were no significant differences between the groups

	Placebo	Pregabalin 50	Pregabalin 75
PACU fentanyl (μg)	30 (24–35)	23 (12–34)	16 (12–28)
In hospital ACP+codeine*	0.5 (0–3)	0.5 (0–2)	0.5 (0–2)
ACP+codeine* D_0	2.0 (1–5)	2.0 (1–5)	2.0 (0–4)
ACP+codeine* Day 1	2.5 (1–5)	2.0 (0–4)	3.0 (1–4)
ACP+codeine* Day 2	2.0 (0–4)	1.5 (0–4)	2.0 (1–4)
Total ACP+codeine*	8.0 (4–11)	7.0 (3–10)	8.0 (3–11)

Table 5 Incidences of opioid-related side-effects—CME on days 1, 2 and 7. P50, pregabalin 50 mg; P75, pregabalin 75 mg. *$P<0.05$ comparing the P75 group with the placebo and P50 groups. †$P<0.05$ comparing the P50 group with the placebo and P75 groups. ‡The incidence of experiencing any side-effects

	Day 1			Day 2			Day 3		
	Placebo (%)	P50 (%)	P75 (%)	Placebo (%)	P50 (%)	P75 (%)	Placebo (%)	P50 (%)	P75 (%)
Nausea	33	22	34	10	9	21	10	0	3
Vomiting	5	4	5	2	2	5	0	0	0
Constipation	43	29	47	43	44	45	14	11	5
Difficulty passing urine	12	18	18	10	9	11	2	0	0
Difficulty concentrating	17	11	18	5	4	11	0	2	5
Drowsiness	48	49	42	21	22	18	10	0	5
Feeling lightheaded or dizzy	36	38	40	14	16	18	10	0	8
Feeling confused	5	7	11	5	2	5	0	0	3
Fatigue	52	38	37	38	40	34	33	47	16*
Itchiness	17	2†	21	14	9	21	7	20	16
Dry mouth	62	51	53	17	38	29	7	4	8
Headache	29	36	21	12	18	13	17	16	16
Any‡	90	93	97	86	87	92	57	64	50

To date, the analgesic effects of pregabalin in the perioperative period have been mixed. In four studies, single or multiple doses of pregabalin ranging from 75 to 300 mg have been shown to be ineffective.[10 13 14 16] Although the pain score in one study was low (ranging from 0 to 16 on a scale of 0–100), the other studies comprised a large variety of surgeries with moderate pain intensity. Of the five positive studies on the analgesic effects of pregabalin, two[12 15] showed only opioid-sparing effects at the expense of an increase in pregabalin-related side-effects such as dizziness, blurred vision, or sedation. Pregabalin dose 300 mg was implicated for the increased side-effects in both studies.[12 15] Pregabalin 75 mg was chosen in two perioperative trials. In one trial, a single preoperative dose did not result in any analgesic benefit.[11] In another trial, pregabalin was administered in twice daily dosing for 7 consecutive days resulting in superior analgesia and lower analgesic consumption throughout the 7 days of study.[10] The discrepancy between these results can be due to the procedure-specific analgesic response[29] and difference in the study and quality of design. We subsequently performed a meta-analysis; the methodology and the details of which are available in the Supplementary material. From the pooled data of the seven eligible studies, the only significant difference in pain score in favour of pregabalin was in the immediate postoperative period (2 h).[10–16] The mean difference was very small, 4.1 out of the scale of 100 (95% CI 1.4–6.8; heterogeneity $I^2=66\%$), with minimal difference in analgesic consumption. Seven commonly reported adverse effects: nausea, vomiting, or both, sedation, dizziness, headache, blurred vision, pruritus, and lack of concentration were examined. The incidences of sedation and blurred vision were higher in the pregabalin group [odds ratio 3.48 (95% CI 1.79–6.75, $I^2=41\%$) and 5.37 (95% CI 2.31–12.47, $I^2=0\%$), respectively]. However, caution should be taken in the interpretation of the analgesia data and adverse effects as the number of studies and thus the sample size included in the pool data was limited. A meta-analysis including more studies in the future is therefore needed, but we note that the results of our study are very similar to that from the pooled data of the meta-analysis with an analgesic benefit limited to the immediate postoperative period despite the fact that three doses were prescribed.

In the present study, the adverse effects profile over the first 7 days was characterized by examining the CME based

on the opioid-related SDS over days 1, 2, and 7. We chose to report the 'clinical meaningful' side-effects because most of the studies that reported the incidence of side-effects did not characterize their frequency, severity, and bothersomeness.[30] The CME was similar among the three groups on days 1, 2, and 7. This can be explained by the absence of opioid-sparing effects of pregabalin in our study despite the analgesic benefit in the early postoperative period. The most frequent CME on day 1 were dry mouth, fatigue, dizziness, drowsiness, nausea, and constipation. By day 7, most of the side-effects largely improved except fatigue. Interestingly, the incidence of fatigue was the lowest in the pregabalin 75 mg group on day 7. The cause for the lower incidence of fatigue is unknown as the opioid consumption and the sleep quality were quite similar among the three groups. The lower incidence also did not translate to any improvement in the recovery score (QoR-40).

One of the major limitations of our study is the high incidence of drop-out. In our study, each patient had to complete a lengthy questionnaire for days 1, 2, and 7. Both the opioid-related SDS and QoR-40 contributed to 156 questions in each patient's questionnaire. This is likely to have affected patients' compliance. However, the missing data were imputed in an intention-to-treat principle, and our sensitivity analysis suggested that the missing data did not cause much alteration in the study results.

In conclusion, multiple doses of pregabalin resulted in superior analgesia only in the first 90 min over placebo. Pregabalin 75 mg offered better analgesia compared with pregabalin 50 mg. However, pregabalin did not result in a reduction in opioid consumption, clinical meaningful side-effects, or an improvement in quality of recovery.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgement

The authors would like to thank Dr Amir Abrishami for the assistance in the meta-analysis.

Conflict of interest

P.W.H.P., F.C. and C.L. have received an honorarium and travel grant from Pfizer Canada. P.W.H.P and F.C. have received research grants form Pfizer Inc.

Funding

This research was funded by the Pfizer Global Investigator Initiated Grant. The medications in this study were provided by Pfizer Inc.

Appendix 1. Opioid–related Symptom Distress Scale

Please circle the most appropriate one

Symptoms	Yes/No	If Yes, How Often 1 to 4 1 = Rarely 2 = Occasionally 3 = Frequently 4 = Almost constantly	If Yes, How Severe 1 to 4 1 = Slightly severe 2 = Moderately severe 3 = Severe 4 = Very severe	Bothersomeness Rating 1 to 5 1 = not at all 2 = a little bit 3 = somewhat 4 = quite a bit 5 = very much	Possible cause or Comments
1. Nausea	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
2. Vomiting	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
3. Constipation	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
4. Difficulty passing urine	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
5. Difficulty concentrating	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
6. Drowsiness/Difficulty staying awake	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
7. Feeling lightheaded or dizzy	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
8. Feeling confused	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
9. Fatigue	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
10. Itchiness	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
11. Dry mouth	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	
12. Headache	Y/N	1 2 3 4	1 2 3 4	1 2 3 4 5	

Were there any other symptoms that affected your recovery? (Please specify)

References

1 Kavoussi R. Pregabalin: from molecule to medicine. *Eur Neuropsychopharmacol* 2006; **16**: S128–S33

2 Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005; **39**: 2029–37

3 Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia* 2004; **45**: 13–8

4 Martin DJ, McClelland D, Herd MB *et al.* Gabapentin-mediated inhibition of voltage-activated Ca^{2+} channel currents in cultured sensory neurons is dependent on culture conditions and channel subunit expression. *Neuropharmacology* 2002; **42**: 353–66

5 Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. *Reg Anesth Pain Med* 2006; **31**: 237–47

6 Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta-analysis. *Can J Anaesth* 2006; **53**: 461–9

7 Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain—a systematic review of randomized controlled trials. *Pain* 2006; **126**: 91–101

8 Peng PWH, Wijeysundera DN, Li CCF. Use of gabapentin for perioperative pain control—a meta-analysis. *Pain Res Manag* 2007; **12**: 85–92

9 Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104**: 1545–56

10 White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. *Anesth Analg* 2009; **108**: 1140–5

11 Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth* 2008; **100**: 834–40

12 Mathiesen O, Jacobsen LS, Holm HE *et al.* Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. *Br J Anaesth* 2008; **101**: 535–41

13 Mathiesen O, Rasmussen ML, Dierkiing G *et al.* Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. *Acta Anaesthesiol Scand* 2009; **53**: 227–35

14 Chang SH, Lee HW, Kim HK, Kim SH, Kim DK. An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. *Anesth Analg* 2009; **109**: 1284–6

15 Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. *Pain* 2008; **134**: 106–12

16 Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. *Anesth Analg* 2007; **105**: 1449–53

17 Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. *Br J Anaesth* 2008; **101**: 700–4

18 Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. *Aesthet Surg J* 2008; **28**: 421–4

19 Aldrete JA. Modifications to the postanesthesia score for the use in ambulatory surgery. *J Perianesth Nurs* 1998; **13**: 148–57

20 Chung F, Chan V, Ong D. A postanesthesia discharging score system for home readiness after ambulatory surgery. *J Clin Anesth* 1995; **7**: 500–6

21 Apfelbaum JL, Gan TJ, Zhao S, Hanna DB, Chen C. Reliability and validity of the perioperative opioid-related symptom distress scale. *Anesth Analg* 2004; **99**: 699–709

22 Zhao SZ, Chung F, Hanna DB, Raymundo AL, Cheung RY, Chen C. Dose–response relationship between opioid use and adverse effects after ambulatory surgery. *J Pain Symptom Manage* 2004; **28**: 35–46

23 Myles PS, Hunt JO, Nightingale CE *et al.* Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults. *Anesth Analg* 1999; **88**: 83–90

24 Myles PS, Weitkamp B, Jones K, Merlick J, Hesen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth* 2000; **4**: 11–5

25 Montori VM, Guyatt GH. Intention-to-treat principle. *Can Med Assoc J* 2001; **165**: 1339–41

26 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Br Med J* 1999; **319**: 670–47

27 Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. *Can J Anaesth* 2004; **51**: 358–63

28 Hill M, Balkenohl M, Thomas DW, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. *Eur J Pain* 2001; **5**: 119–24

29 Kehlet H. Procedure-specific postoperative pain management. *Anesthesiol Clin N Am* 2005; **23**: 203–10

30 Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *J Pain Symptom Manage* 1999; **18**: 427–37