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**ORIGINAL ARTICLE**

# Perioperative gabapentin for the prevention of persistent pain after thoracotomy: a randomized controlled trial

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## Abstract

**OBJECTIVES**: To evaluate the effect of perioperative gabapentin treatment for the prevention of persistent post-thoracotomy pain and to establish whether gabapentin has a significant therapeutic impact on acute postoperative pain.

**METHODS**: Consecutive patients with pulmonary malignancies scheduled for anterior thoracotomy were enrolled in this randomized, double-blinded, placebo-controlled trial. Patients were given 1200 mg gabapentin or placebo 2 h before surgery followed by increasing doses during 5 postoperative days: 600 mg for day 1; 900 mg for day 2; and 1200 mg for days 3–5. Effective pain relief was provided with perioperative multimodal analgesia with epidural infusion of bupivacaine and morphine for 72 h, and oral acetaminophen, ibuprofen and morphine. The main outcome was persistent post-thoracotomy pain at 6 months. Secondary outcomes included measures of early postoperative post-thoracotomy pain, morphine requirements, recovery and analgesia-related adverse effects over the first 3 weeks as well as persistent post-thoracotomy pain at 3 months.

**RESULTS**: A total of 104 patients were randomly assigned to the intervention or control group; 86 (83%) patients were available for the 14-day analysis, 76 (73%) for the 3-month analysis and 67 (64%) for the 6-month follow-up. At 6 months postoperatively, 47% of patients treated with gabapentin reported persistent post-thoracotomy pain compared with 49% in the placebo group ($P = 0.9$). No overall clinically or statistically significant differences were observed between groups receiving placebo and gabapentin, respectively, for the secondary outcome measures and treatment-related adverse events.

**CONCLUSIONS**: We found no evidence for the superiority of gabapentin over placebo for the treatment of acute pain following thoracotomy or for the prevention of persistent post-thoracotomy pain.

**Keywords:** Gabapentin • Thoracotomy • Pain • Postoperative • Chronic pain • Analgesics • Randomized controlled trial

## INTRODUCTION

Most patients recover spontaneously from thoracotomy within weeks to a few months; however, in 25–60% of patients, the postoperative pain may persist for several months to years [1]. The mechanisms behind the transition from acute postoperative pain to persistent pain are not fully understood [2]. Concerning the pathophysiology of post-thoracotomy pain, it has been shown that thoracotomy may reduce superficial abdominal reflexes and impair intercostal nerve performance [3, 4]. Thus, intraoperative damage to the neurovascular bundle has been proposed as the most important pathogenic factor for post-thoracotomy pain [1, 4]. To further support this assumption, post-thoracotomy pain has been associated with signs and symptoms of neuropathic pain [1, 2, 5]. It has been advocated that a multimodal approach that combines different classes of analgesics, antihyperalgesics and local anaesthetics is effective as it provides additive and/or synergistic analgesic effects. At the same time, it may reduce opioid-related side effects and peripheral and central sensitization, and potentially prevent pain persistence [2, 6, 7]. The anticonvulsant drug gabapentin presumably acts on central sensitization by binding to the alpha-2-delta subunit of voltage-dependent calcium channels in the dorsal root ganglia and spinal cord, thus causing a decrease in neuronal excitability and synaptic transmission [8]. Gabapentin has shown analgesic and opioid-sparing effects in early postoperative pain treatment [9, 10], in addition to its established efficacy in treating several neuropathic pain conditions [11]. This includes refractory and persistent pain following thoracic surgery [12, 13]. The use of gabapentin in the prevention

The research was carried out at Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark.

of post-thoracotomy pain has been scarcely investigated. Two previous studies have shown that gabapentin had no apparent effect on early post-thoracotomy pain, shoulder-specific pain and opioid consumption during the first 24–48 h following thoracotomy [14, 15], and frequency of post-thoracotomy pain persistence at 3 months [15].

The primary objective of the present trial was to investigate whether a multimodal analgesia regimen would benefit from longer-term gabapentin administration (i.e. a single preoperative dose followed by 5-day postoperative treatment) in the prevention of persistent postoperative pain development in patients undergoing thoracotomy for resectable pulmonary malignancies. A secondary objective of the trial was to establish whether gabapentin has a significant therapeutic impact on pain, recovery and analgesia-related side effects in the early postoperative phase.

## PATIENTS AND METHODS

### Trial design

This investigator-initiated, single-centre, parallel group trial used a randomized, double-blind, placebo-controlled design. The Danish Health and Medicines Agency (2007-002769-11), the Central Denmark Region Committee on Biomedical Research Ethics (M-20090226) and the Danish Data Protection Agency (2009-41-4149) approved the trial. The trial was registered in the Clinicaltrials.gov database (NCT01116583) and reporting was guided by the principles outlined in the CONSORT 2010 Statement [16].

### Trial overview

From April 2011 to November 2012, we enrolled consecutive patients scheduled for thoracotomy for pulmonary malignancies at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, in Denmark. Clinical visits were done the day before scheduled surgery and between 14 and 21 days postoperatively. Mail correspondence between the site and the trial patient was scheduled at 3 and 6 months postoperatively. Surgical patients received information on the purpose of the trial along with the appointment for surgery. Upon arrival at the department, a research nurse restated the trial purpose verbally to eligible patients and explained the trial protocol. No compensation was offered at any time during the trial. All patients gave their written informed consent before enrolment.

### Patients

The trial enrolled adults aged 18–80 years with pulmonary malignancies scheduled for anterior thoracotomy, including lobectomy, bilobectomy, pneumonectomy, resection of the tracheobronchial bifurcation, wedge resection, sleeve resection and combinations hereof. Exclusion criteria were: inability to fill in detailed health- and pain-related questionnaires; psychiatric disease; serum creatinine concentrations ≥120 μmol/l; allergy to gabapentin, morphine, bupivacaine and/or ibuprofen; average pain during the last week ≥4 on a numerical rating scale (NRS) from 0 to 10, with 0 indicating 'no pain' and 10 indicating 'the worst pain imaginable'; standardized treatment with opioids, anticonvulsants and/or tricyclic antidepressants; use of antacids 24 h before intake of trial medication; issues precluding thoracic epidural catheter placement; previous ipsilateral thoracotomy; acute pancreatitis; a history of past or present alcohol and/or illegal substance abuse; a history of gastric or duodenal ulcer; gastrointestinal obstruction; pregnancy; and/or participation in another intervention trial. Randomized patients were a priori excluded from the primary analysis in case ineligible patients were mistakenly included, if patients never received trial medication, epidural analgesia, underwent thoracotomy, if patients were assessed inoperable during surgery, or in the event of any intentional or unintentional breaking of the blinding procedure.

### Treatment

Patients were randomly assigned to one of two treatment groups: gabapentin or placebo. The gabapentin group received an initial single oral dose of 1200 mg gabapentin 2 h before scheduled surgery followed by an increasing oral dose of gabapentin over 5 consecutive days in a step-up multi-dose manner: postoperative day 1: 300 mg twice a day; postoperative day 2: 300 mg three times a day; and postoperative days 3–5: 300 mg four times a day, equivalent to a total dose of 6300 mg. Capsules matching the original light yellow gabapentin 300 mg capsule were administered to patients in the placebo group in a similar manner. Trial medication was prepared in accordance with Good Manufacturing Practice, Good Distribution Practice and Good Clinical Practice Guidelines. Nursing staff administered trial medication and ensured its intake.

### Outcomes

Outcome measures were chosen in concordance with Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) Guidelines [17], and thus included measures of pain intensity, interference with function and mood. A research nurse assessed all outcome measures at baseline and clinical follow-up visits in addition to the forwarding of trial questionnaires via mail at 3 and 6 months postoperatively. Trial nurses assessed outcome measures during hospitalization as part of daily standard clinical care. To ensure equal assessment methods, all assessors were instructed carefully by the primary investigator (Kasper Grosen) before the trial and at regular intervals hereafter.

***Primary outcome.*** The primary outcome measure was the effect of gabapentin on the incidence of persistent post-thoracotomy pain, and the potentially protective role of gabapentin. Persistent post-thoracotomy pain was assessed according to responses to the short forms of the Brief Pain Inventory (BPI) [18] and the McGill Pain Questionnaire (MPQ) [19] at 3 and 6 months postoperatively. Clinically relevant persistent post-thoracotomy pain was defined as BPI average pain during the past week equal to or higher than 4/10 on the NRS. Average pain was chosen as the main pain intensity criterion, as this item has been considered a measure of the patient's subjective average experience of pain [20] and the cut-off corresponds to at least moderate pain with a potential impact on physical or emotional functioning [21].

***Secondary analgesia-related outcomes.*** Acute postoperative pain intensity was scored on a NRS. Postoperative pain was assessed at rest and during cough every 3 h for 12 h in the

post-anaesthesia care unit and every 6 h for 120 h upon arrival at the surgical ward. Shoulder-specific pain was assessed on the operated side at rest and after arm abduction of the shoulder every 6 h for 120 h in the surgical ward. Consumption of morphine equivalents was assessed according to medical records [22]. Based on inspection of individual daily morphine consumption, missing data on morphine consumption on postoperative days 4–5 were acceptably imputed using the daily morphine dose as prescribed at discharge. The use of epidural analgesia was assessed according to recordings from the epidural infusion syringe pump history (Graseby™ 3500 Syringe Pump, Smiths Medical, Ashford, UK) and constituted supplementary information.

***Postoperative recovery.*** Convalescence of gastrointestinal function was assessed according to time elapsed from surgery to first passage of stool. Convalescence of pulmonary capacity was assessed according to daily recordings on a portable computerized spirometer (Spirodoc, MIR Medical International Research Srl, Rome, Italy) on forced vital capacity, forced expiratory volume exhaled in 1 s and peak expiratory flow. Daily sleep quality was scored on a scale from 0 to 10, with 0 indicating 'extremely poor sleep' and 10 indicating 'extremely good sleep'. Functional exercise capacity was assessed according to a six-minute walk test on postoperative day 3 and between postoperative days 14 and 21 [23]. Hospital length of stay was recorded as an overall measure of the quality of postoperative recovery.

***Analgesia-related adverse effects.*** To determine safety and tolerability measures, trial staff conducted active surveillance of predefined analgesia-related side effects. The following adverse effects were assessed every 6 h for 120 h in the surgical ward: confusion (absent/present) and/or hallucinations (absent/present) in response to an evaluation of the patient's orientation in time, place and personal data; intensity of nausea (on a NRS from 0 to 10, with 0 indicating 'no nausea' and 10 indicating 'worst nausea imaginable'); number of vomit events; use of antiemetic drugs assessed according to recordings in medical records; urinary retention (absent/present); severity of sedation (on a four-point scale, with 0 indicating 'fully awake', 1 indicating 'asleep some of the time, awaken by direct address', 2 indicating 'asleep all the time, awaken by physical stimulation' and 3 indicating 'not responding to any stimulation'); severity of itching, dizziness and fatigue (on a four-point Likert scale, with the categories: none, mild, moderate and severe); and respiratory status (on a four-point scale, with 0 indicating sufficient and regular respiration with clear airways, '10–20 breathing cycles/min'; 1 indicating regular respiration with partly clear airways, '10–20 breathings/min'; 2 indicating affected respiration with reduced 'less than 10 breathings/min' or accelerated with 'more than 20 breathings/min' respiration; and 3 indicating insufficient respiration, '0–8 breathings/minute'), with a respiratory status score ≥2 defining respiratory depression.

***Additional adverse events and surgical complications.*** Passive surveillance of adverse events was based on medical record audit conducted by the independent external GCP trial monitor. The time frame of surveillance of harms was set at 35 h after administration of the last trial medication dose (i.e. five times the half-life of gabapentin). Predefined categories for determining the intensity and the relationship to trial medication were used. The expert clinical judgement from the sponsor investigator (Hans Kristian Pilegaard) was used to determine the intensity and causal relationship of adverse events and serious adverse events.

A number of surgery-related parameters were assessed separately as exploratory endpoints, including: reoperation, time until chest tube removal, wound infection, pneumonia, additional need of intensive care and 30-day readmission. In contrast, it was decided in advance that a number of frequent adverse events in the course of surgery were not to be recorded, including: weight gain, reduced pulmonary capacity, low serum haemoglobin concentrations, fever, changes in serum C-reactive protein and/or leucocyte concentrations, and reduced gastrointestinal motility.

## Sample size

A sample size of 45 patients per group was required to complete the double-blind treatment period to provide 80% power with a two-sided significance level of 0.05 to detect a reduction in the incidence of persistent post-thoracotomy pain from 50 to 20%. It was anticipated that 15% of the included patients would not complete the trial and, consequently, the final sample size was set at a total of 104 patients, corresponding to 52 patients in each treatment group.

## Randomization and blinding

An external trial pharmacist from the Hospital Pharmacy at Aarhus University Hospital, Denmark, prepared a computer-generated concealed treatment allocation schedule randomizing the two treatments in blocks of eight at a 1 : 1 ratio to a consecutive series of patient numbers (001–104). The Hospital Pharmacy kept the allocation sequence concealed during the entire study period. Each participant's allocation was concealed in sequentially numbered, opaque and sealed envelopes and kept in the medical records. The identical gabapentin or placebo capsules were then prepacked in numbered containers according to the randomization schedule to obtain double blinding. As patients entered the trial, they were assigned in turn to the next consecutive number and subsequently received the capsules in the corresponding prepacked container.

## Anaesthesia and epidural analgesia

Patients in both treatment groups were offered premedication 2 h before scheduled surgery with oral diazepam (2.5–5 mg) and acetaminophen (2000 mg). Preoperative anxiety was scored before and 2 h after premedication on a NRS, with 0 indicating 'no anxiety' and 10 indicating 'the worst anxiety imaginable'. Additionally, all patients had an epidural catheter placed at the T4–6 level prior to induction of general anaesthesia. The epidural blockade was activated and verified with an injection of 0.5% bupivacaine with simultaneous intravenous infusion of a 6% hydroxyethyl starch. General anaesthesia was initiated with an intravenous injection of fentanyl (0.05–0.1 mg), propofol (1.5–2.5 mg $kg^{-1}$) and cisatracurium (0.1–0.15 mg $kg^{-1}$). The epidural blockade was reactivated during surgery at the discretion of the attending anaesthesiologist and subsequently provided continuously for an additional 72 h postoperatively. Epidural analgesia was provided with continuous infusion of 0.25% bupivacaine + morphine, 50 μg $ml^{-1}$, with a maximum infusion rate of 10 ml $h^{-1}$. The patient was extubated at the end of surgery and subsequently transferred to the post-anaesthesia care unit for overnight observation before being transferred to the surgical ward.

## Surgery

All lung resections were performed through an anterior thoracotomy incision completely anterior to the latissimus dorsi muscle. A curved incision was made below the nipple in males and in the submammary groove in females. The latissimus dorsi muscle was thus totally spared and the musculus serratus anterior divided in the direction of the fibres. The thoracic cavity was accessed between the fourth and fifth ribs. The intercostal muscles were detached from the rib with the periosteum. The closing was done with single sutures around the lower rib and the periosteum raphe.

## Postoperative management

All patients received a standardized perioperative multimodal analgesia regimen with the purpose of preserving effective respiratory function and physical activity. Non-opioid analgesic treatments with acetaminophen (4 g $day^{-1}$) and ibuprofen (800 mg $day^{-1}$) and constipation prophylaxis with bisocodyl (10 mg $day^{-1}$) were initiated from the day of surgery in all patients. Postoperative nausea and vomiting was treated as needed with ondensatrone (1–4 mg) or metoclopramide (10–20 mg). Pain relief was tailored with epidural analgesia and/or systemic opioids on the basis of patient report, nurse evaluation and vital signs. In brief, intermittent epidural bolus injections were given if the patient was uncomfortable due to pain (2–4 ml bolus; lockout of 15–20 min). If the patient required additional boluses within the hour, the continuous basal infusion was either increased or the epidural catheter was retracted (as appropriate) to optimize the spread of injected solutions and thus avoid fluctuations in the level of analgesia. Following discontinuation of epidural analgesia, pain was managed with controlled-release morphine, dose-adjusted every 24 h on the basis of the preceding morphine requirements. Additionally, bolus intravenous injections of 2 mg of morphine followed by an upward titration in 1–2 mg increments were available as rescue analgesia throughout hospitalization. Of note, morphine was acceptably exchanged for oxycodone in cases of intolerance and/or untreatable adverse effects related to morphine analgesia (urinary retention, respiratory depression, nausea and vomiting, and/or itching).

## Statistical methods

Stata/IC 12.1 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. Two-tailed *P*-values of <0.05 were considered statistically significant unless stated otherwise. Analyses were performed according to the intention-to-treat principle including all patients who took at least one dose of trial medication and had at least one post-randomization efficacy assessment. Relative effects (risk ratios) and absolute effects (risk differences) were calculated with 95% confidence intervals (95% CIs) for the primary outcome. Logistic regression models were applied to examine the influence of gabapentin on moderate to severe postoperative pain by treating each patient as a cluster in order to take account of the repeated measurements on each patient (intracluster correlation). Maximum pain of daily pain reports was calculated and the patients subsequently dichotomized into those reporting clinically relevant pain (NRS ≥4) and those reporting only mild pain (NRS <4). Adjusted odds ratios (ORs) and 95% CIs were calculated (adjusted for days since surgery). A similar logistic regression model was applied to assess daily sleep quality reports dichotomizing into patients reporting poor sleep (NRS ≤5) and patients reporting good sleep (NRS >5). Daily consumption of morphine equivalents was analysed using a repeated-measures mixed model with group and time since surgery (and the interaction between them) as factors. Secondary analgesia-related outcomes, and measures of preoperative anxiety and postoperative recovery, were analysed depending on distribution using an unpaired *t*-test or a Wilcoxon rank-sum (Mann–Whitney) test. Analgesia-related adverse effects were dichotomized (absent/present) over the 5-day treatment period, and the proportion of patients with at least one event per day was calculated with exact binomial 95% CIs.

# RESULTS

Eligible patients were recruited from April 2011 to November 2012, and recruitment was terminated according to plan after the randomization of 104 patients. A flow chart of the progress through the phases of the trial is depicted in Fig. 1. Patients were aged 20–79 years. There were no clinically important differences between the treatment groups in baseline demographic and clinical characteristics, perioperative data and surgical outcomes (Table 1). A total of 10 patients discontinued treatment. Additionally, 6 patients withdrew consent, 1 became terminally ill, 5 died and 15 did not respond to the mailed follow-up questionnaires. Accordingly, 86 patients (83%) were available for the 14-day analysis, 76 (73%) for the 3-month analysis and 67 (64%) for the 6-month follow-up analysis.

## Incidence of persistent post-thoracotomy pain

The overall risk of persistent post-thoracotomy pain decreased from 59% (95% CI 47–70%) at 3 months postoperatively to 48% (95% CI 45–60%) at 6 months postoperatively (Table 2). At 6 months postoperatively, the risk of persistent postoperative pain was 47% in patients treated with gabapentin compared with 49% in the placebo-treated patients, with a corresponding insignificant risk difference of 2% (95% CI −26–22%), and a risk ratio of 0.96 (95% CI 0.58–1.59), $P = 0.9$. Similarly, there was no benefit of gabapentin when only patients categorized with moderate to severe post-thoracotomy pain (NRS ≥4 for average pain) were considered at 3 ($n = 10$, $P = 1.0$) and 6 months postoperatively ($n = 8$, $P = 0.2$). Correspondingly, there were no differences between the treatment groups in terms of intensity, interference and quality of persistent post-thoracotomy pain (Table 3).

## Secondary analgesia-related outcomes

There were no differences between groups in terms of daily risk of moderate to severe postoperative pain for pain at rest, pain upon cough, shoulder pain at rest and shoulder pain upon abduction (Fig. 2) or in postoperative consumption of morphine equivalents (Fig. 3). Along this line, comparison of total local anaesthetic (bupivacaine) use for placebo (829 ± 362 mg) and gabapentin-treated patients (714 ± 336 mg) revealed no differences between the groups; 116 mg (95% CI −26 to 257 mg); $P = 0.1$. However, significantly more epidural morphine was used in the placebo group (14.1 ± 8.4 mg) than in the gabapentin group (10.0 ± 6.4 mg),

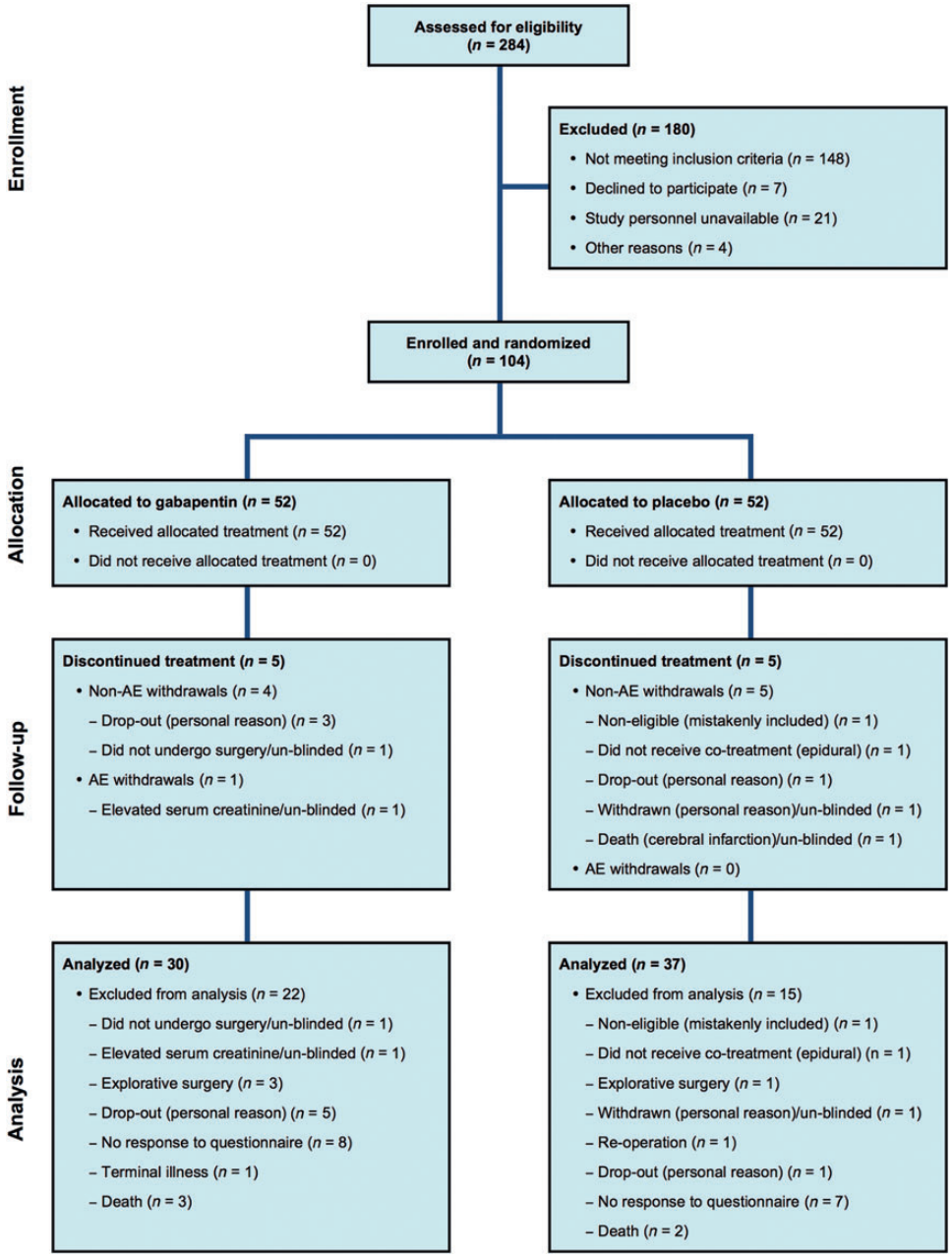


**Figure 1:** CONSORT flowchart. Numbers of patients screened for eligibility, randomly assigned, receiving intended treatment and analysed for primary outcome.

equal to a mean difference of 4.1 mg (95% CI 1.0–6.1 mg), $P = 0.01$.

## Postoperative recovery

Gabapentin had no effect on postoperative lung and exercise capacities (Table 4). First passage of stools was noted at a median of 2 days (1–5 days) in both treatment groups ($P = 0.5$). The proportion of patients reporting good sleep quality did not differ by treatment group over the 5-day treatment period; OR: 1.27 (95% CI 0.71–2.29), $P = 0.4$. Consequently, the duration of hospitalization was a median of 5 days in both groups ($P = 0.8$). Notably, postoperative pain remained prevalent in a comparable proportion of patients at 14–21 days postoperatively, i.e. 79% in the placebo group versus 80% in the gabapentin group ($P = 0.9$).

## Analgesia-related adverse effects

No clinically meaningful differences between the treatment groups were observed in the frequencies of predefined analgesia-related adverse effects over the 5-day treatment period (Table 5). Furthermore, the use of ondansetrone and metoclopramide, and risk of postoperative urinary retention, were comparable between groups (all $P$-values >0.1).

**Table 1:** Patient characteristics at baseline, perioperative data and surgical complications by treatment group

| | Placebo ($n$ = 52) | Gabapentin ($n$ = 52[a]) |
|---|---|---|
| Number of patients | 52 (50%) | 52 (50%) |
| Sex | | |
| Male | 29 (56%) | 23 (44%) |
| Female | 23 (44%) | 29 (56%) |
| Age (year) | 62 [56 to 69] | 67 [58 to 72] |
| Height (cm) | 173 ± 9 | 172 ± 10 |
| Weight (kg) | 74 ± 15 | 78 ± 18 |
| BMI (kg/m$^2$) | 25 ± 4 | 26 ± 5 |
| Exercise and lung capacities | | |
| 6MWT (m) | 419 ± 112 | 384 ± 109 |
| FVC (l) | 3.2 ± 0.9 | 3.0 ± 0.9 |
| FVC (%) | 85 ± 19 | 87 ± 20 |
| FEV-1 (l) | 2.5 ± 0.8 | 2.2 ± 0.7 |
| FEV-1 (%) | 80 ± 19 | 77 ± 21 |
| PEF (l s$^{-1}$) | 5.0 ± 2.2 | 4.3 ± 1.8 |
| PEF (%) | 67 ± 24 | 62 ± 23 |
| Premedication anxiety (NRS 0–10) | 4 [2 to 6] | 5 [2 to 7] |
| Post-medication anxiety (NRS 0–10) | 2 [2 to 4] | 2 [0 to 5] |
| Duration of anaesthesia (min) | 227 ± 70 | 229 ± 67 |
| Duration of surgery (min) | 120 ± 58 | 113 ± 43 |
| Surgical procedure | | |
| Lobectomy | 29 (56%) | 35 (67%) |
| Wedge | 7 (14%) | 5 (10%) |
| Sleeve | 2 (14%) | 1 (2%) |
| Bilobectomy | 2 (4%) | 3 (6%) |
| Pneumonectomy | 2 (4%) | 3 (6%) |
| Explorative | 1 (2%) | 3 (6%) |
| Other | 6 (12%) | 2 (4%) |
| Right-sided surgery | 31 (60%) | 22 (43%) |
| Length of skin incision (cm) | 19 ± 3 | 19 ± 3 |
| Length of chest wall incision (cm) | 25 ± 4 | 25 ± 3 |
| Duration of rib retraction (min) | 79 ± 48 | 76 ± 45 |
| Width of rib retraction (cm) | 9 [8 to 10] | 9 [8 to 10] |
| No. of inserted chest tubes (1/2) | 50 (98%)/1 (2%) | 48 (98%)/1 (2%) |
| Impression of cortex | 3 (6%) | 5 (11%) |
| Rib fracture | 9 (18%) | 12 (27%) |
| Dislocation of the costochondral junction | 12 (25%) | 11 (25%) |
| Complications related to surgery | | |
| Reoperation | 4 (8%) | 3 (6%) |
| Wound infection | 1 (2%) | 2 (4%) |
| Pneumonia | 3 (6%) | 3 (6%) |
| Extended need of intermediate care | 5 (10%) | 5 (10%) |
| Persistent air leak (>7 days) | 4 (8%) | 5 (10%) |
| Arterial fibrillation | 7 (13%) | 4 (8%) |
| Subcutaneous emphysema | 3 (6%) | 4 (8%) |
| 30-day readmission | 5 (10%) | 0 (0%) |

Values are presented as numbers (%), means ± SD or medians [interquartile range], as appropriate. Percentages may not sum up to 100 because of rounding. There were no clinically meaningful differences between the treatment groups.
6MWT: six-minute walk test; FVC: forced vital capacity; FEV-1: forced expiratory volume exhaled in 1 s; PEF: peak expiratory flow; (%): percent of predicted values; NRS 0–10: numerical rating scale, with 0 indicating 'no anxiety' and 10 indicating 'the worst anxiety imaginable'.
[a]Perioperative data and surgical complications in the gabapentin group are based on $n$ = 51.

## Additional adverse events and surgical complications

A total of 79 adverse events were reported in medical case records over the 5-day treatment period: 34 adverse events were reported among 25 patients in the placebo group, compared with 45 among 28 patients in the gabapentin group. The proportion of patients reporting treatment-related adverse events was 14% (7 patients, 5 adverse events) in the placebo group compared with 20% (10 patients, 5 adverse events) in the gabapentin group ($P$ = 0.4). Importantly, all treatment-related adverse events were transient. There were no treatment-related serious adverse events (Table 1).

# DISCUSSION

## Main findings

The results of this trial indicate that patients undergoing thoracotomy for the treatment of pulmonary malignancies gained no specific therapeutic benefit from a single preoperative gabapentin dose followed by a 5-day postoperative treatment, in addition to perioperative multimodal analgesia with epidural analgesia. No overall clinically or statistically significant differences were observed between placebo and gabapentin for the primary outcome measure (i.e. incidence of persistent post-thoracotomy pain at 6 months postoperatively), the BPI, the MPQ, measures of thoracotomy and shoulder pain, consumption of morphine equivalents, convalescence or analgesia-related side effects in the early postoperative phase.

## Comparison with other studies

Surgical trauma to nerves and tissues is associated with neuroplastic changes in the peripheral and central nervous system in response to nociceptive input, and sensitization is a potentially important factor for the transition from acute to chronic pain. Gabapentin has been a mainstay in the treatment of chronic neuropathic pain and there is some clinical evidence suggesting a beneficial therapeutic benefit in the treatment of established persistent post-thoracotomy pain [12, 13]. Although the efficacy and effectiveness of gabapentin in acute postoperative pain treatment have been investigated in several trials over the last decade, only a limited number of studies have assessed the efficacy of gabapentin in the prevention of persistent postoperative pain [15, 24, 25]. In theory, reduced neurotransmission and suppressed neuronal excitability affected by gabapentin may not only improve postoperative analgesia following surgical trauma to nerves and tissues, but may also prevent the development of persistent post-thoracotomy pain. Our findings add to the growing body of evidence indicating that a single preoperative dose of gabapentin (600–1200 mg) has no impact on postoperative pain persistence [15, 24]. Furthermore, our findings replicate and extend the observations of previous studies that perioperative gabapentin treatment had no effect on longer-term postoperative pain in patients undergoing mastectomy or lumpectomy for breast cancer, lower

**Table 2:** Incidence of persistent post-thoracotomy pain at 3 and 6 months postoperatively by treatment group

| | Placebo | Gabapentin | Relative difference (95% CI) | Relative risk (95% CI) | *P*-value |
|---|---|---|---|---|---|
| Pain at 3 months | *n* = 37 | *n* = 39 | | | |
| Any pain | 22 (59%) | 23 (59%) | 0.5% (−22 to 23%) | 1.01 (0.69 to 1.46) | 0.96 |
| NRS ≥4 | 5 (23%) | 5 (23%) | 0.0% (−25 to 25%) | 1.00 (0.34 to 2.97) | 1.00 |
| Pain at 6 months | *n* = 37 | *n* = 30 | | | |
| Any pain | 18 (49%) | 14 (47%) | −2% (−26 to 22%) | 0.96 (0.58 to 1.59) | 0.87 |
| NRS ≥4 | 3 (17%) | 5 (36%) | 19% (−0.11 to 0.50%) | 2.14 (0.61 to 7.47) | 0.22 |

Values are presented as numbers (%) unless stated otherwise.
*n:* number of patients available at that time point; Any pain: pain of any intensity related to surgery (yes/no); NRS ≥4: moderate to severe pain (i.e. clinically relevant pain): average pain related to surgery during the past week equal to or greater than 4/10 on a NRS.

**Table 3:** Intensity, interference and quality of persistent post-thoracotomy pain at 3 and 6 months postoperatively by treatment group

| | 3 months | | | 6 months | | |
|---|---|---|---|---|---|---|
| | Placebo (*n* = 22) | Gabapentin (*n* = 23) | *P*-value | Placebo (*n* = 18) | Gabapentin (*n* = 14) | *P*-value |
| BPI (NRS 0–10) | | | | | | |
| Worst | 3.3 ± 2.0 | 3.6 ± 2.4 | 0.69 | 3.2 ± 2.2 | 3.6 ± 1.6 | 0.55 |
| Least | 1.1 ± 1.3 | 1.8 ± 1.6 | 0.14 | 1.7 ± 1.6 | 2.1 ± 1.5 | 0.48 |
| Average | 2.2 ± 1.4 | 2.6 ± 1.7 | 0.38 | 2.3 ± 1.8 | 3.0 ± 1.5 | 0.23 |
| Current | 1.8 ± 1.8 | 2.0 ± 2.0 | 0.76 | 1.9 ± 2.4 | 2.3 ± 1.5 | 0.65 |
| Mean pain severity | 2.1 ± 1.4 | 2.4 ± 1.7 | 0.52 | 2.3 ± 1.8 | 2.7 ± 1.3 | 0.53 |
| Pain interference | 2.1 ± 1.8 | 3.0 ± 2.8 | 0.14 | 2.5 ± 2.0 | 1.8 ± 1.5 | 0.28 |
| MPQ | | | | | | |
| Sensory-PRI (0–12) | 5.3 ± 5.7 | 5.9 ± 4.7 | 0.70 | 4.9 ± 5.3 | 7.6 ± 5.2 | 0.21 |
| Affective-PRI (0–33) | 1.4 ± 1.9 | 2.3 ± 2.8 | 0.26 | 1.3 ± 2.3 | 1.8 ± 1.8 | 0.54 |
| Total-PRI (0–45) | 6.7 ± 7.3 | 8.4 ± 6.5 | 0.46 | 6.3 ± 7.4 | 9.5 ± 6.6 | 0.26 |
| Present pain (VAS 0–10) | 2.3 ± 2.3 | 2.5 ± 2.0 | 0.72 | 1.9 ± 2.0 | 3.0 ± 2.2 | 0.17 |
| Present pain evaluation | | | | | | |
| No pain | 8 (35%) | 4 (20%) | 0.23 | 4 (25%) | 2 (17%) | 0.62 |
| Mild pain | 13 (57%) | 10 (50%) | | 6 (38%) | 8 (67%) | |
| Discomforting pain | 1 (4%) | 5 (25%) | | 3 (19%) | 2 (17%) | |
| Distressing pain | 1 (4%) | 1 (5%) | | 2 (13%) | 0 (0%) | |
| Horrible pain | 0 (0%) | 0 (0%) | | 1 (6%) | 0 (0%) | |

Measures of persistent post-thoracotomy pain at 3 and 6 months postoperatively according to responses to the BPI and MPQ by treatment group (lower is better for all measurements). Values are presented as means ± SD or numbers (%) unless stated otherwise. Percentages may not sum up to 100 because of rounding.
*n*: number of patients available at that specific time point; NRS 0–10: numerical rating scale, with 0 indicating 'no pain' and 10 indicating 'the worst pain imaginable'; Mean pain severity: a composite score of the four BPI pain items: worst, least, average and current pain; Pain interference: the mean of the seven BPI interference items: general activity, walking, work, mood, enjoyment of life, relations with others and sleep; Sensory-PRI: sensory pain rating index; Affective-PRI: affective pain rating index; Total-PRI: total pain rating index; VAS: visual analogue scale, with 0 indicating 'no pain' and 10 indicating 'the worst pain imaginable'.

limb amputation for peripheral vascular disease and sternotomy for coronary artery bypass grafting (i.e. pain at 3 and 6 months after surgery) [24]. The potential reduction in sensitization has been suggested as the underlying mechanism of the beneficial long-term effects of preventive analgesia. However, at present, central sensitization is not easily investigated in patients, postoperative pain persistence remains unpredictable and preventive analgesia strategies are obviously not effective in all patients. Moreover, it should be emphasized that if the relationship between perioperative pain and persistent pain is non-causal, and both are caused by one or more interrelated factors, the pharmacological blockade of nociceptive activity (regardless of type, amount or duration) will not prevent the development of persistent postoperative pain [6].

## Limitations

This trial was conducted in order to expand our regimen for the treatment of acute pain in the perioperative period and the prevention of persistent post-thoracotomy pain development following tissue healing. We attempted to study the unique contribution of gabapentin by holding constant, as much as possible, all other determinants of the outcome. In addition to the current (best available) standardized treatment, including co-administration of epidural and systemic analgesia, patients in the control group also received a placebo. The negative findings of the present trial must be interpreted cautiously, since the absence of evidence of treatment effect is not the same as evidence of the absence of treatment effect. Possible reasons for the lack of significant differences

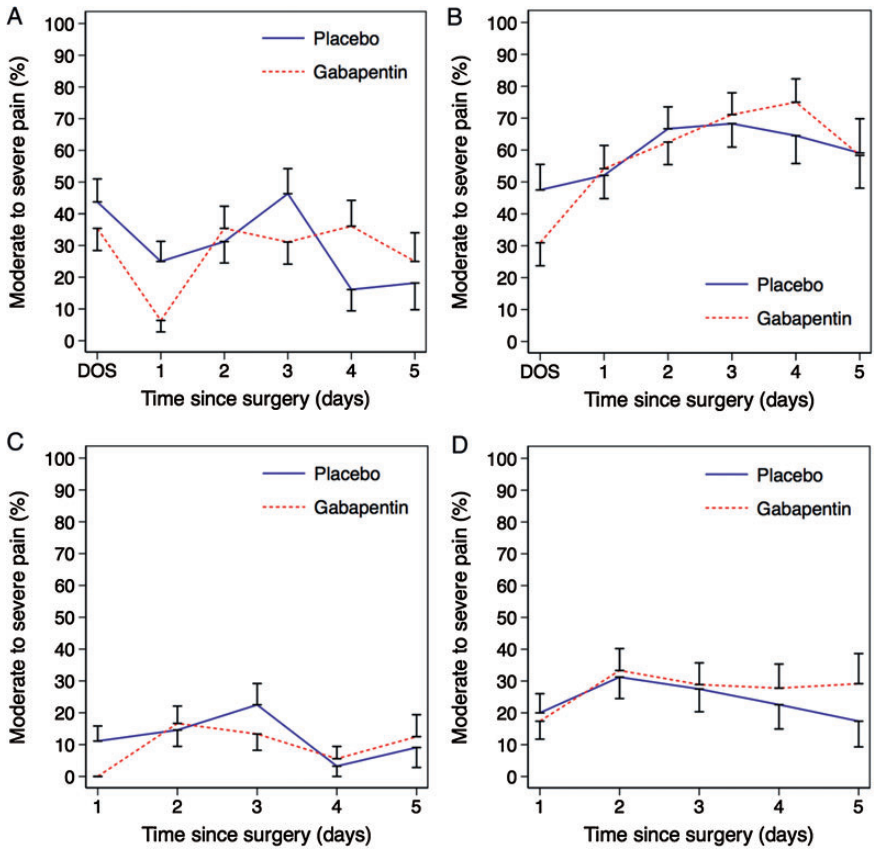


**Figure 2:** Daily risk of moderate to severe postoperative pain. Proportions of placebo- and gabapentin-treated patients with moderate to severe postoperative pain during the 5-day treatment period. Values are plotted as percentages ± standard error of the mean. There were no differences between treatment groups in terms of daily risk of clinically relevant (**A**) pain at rest, OR: 0.83 (95% CI 0.50–1.38), $P = 0.5$; (**B**) pain upon cough, OR: 0.94 (95% CI 0.55–1.50), $P = 0.8$; (**C**) shoulder pain at rest, OR: 0.71 (95% CI: 0.28–1.79), $P = 0.5$; and (**D**) shoulder pain upon abduction, OR: 1.14 (95% CI 0.52–2.50), $P = 0.7$.

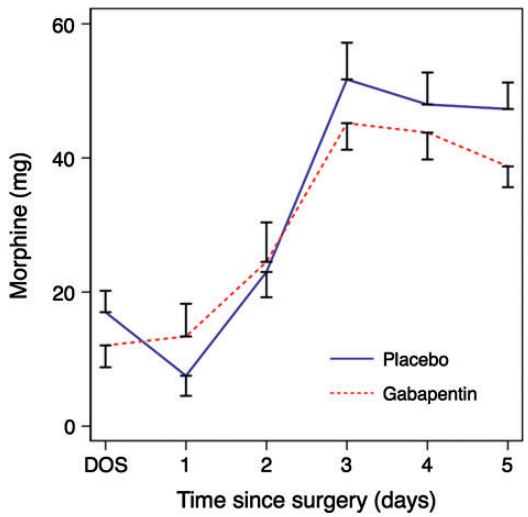


**Figure 3:** Mean daily morphine consumption of placebo- and gabapentin-treated patients during the 5-day treatment period. Values are plotted as means (mg) ± standard error of the mean. There was no difference between treatment groups in postoperative morphine consumption ($P = 0.6$).

between treatment groups include inappropriate choice of dose, frequency or duration of administration. To date, available evidence does not support the efficacy of pharmacological treatment in the prevention of persistent postoperative pain [24]. Hence, in most studies, the duration of treatment was rarely extended beyond the duration of the surgery-induced inflammatory response. The vast majority of published studies of gabapentin have involved single preoperative doses ranging from 300 to 1200 mg administered 1–2(½) h before surgery. Fewer studies have administered a preoperative dose followed by repeated multiple daily doses of 300–1800 mg/day from the day of surgery and up to 30 days postoperatively [24, 25]. We acknowledge that the duration of sensitization may extend far beyond the duration of a 5-day gabapentin treatment. We cannot rule out that ongoing long-term gabapentin treatment would have affected the incidence of persistent post-thoracotomy pain. We planned our treatment to ensure adherence and increase the likelihood of implementation into daily clinical practice if proved effective. Ideally, patients could have been discharged following thoracotomy with prescription medication to continue treatment for several weeks to months, thus providing the opportunity for sustained inhibition of the nociceptive activity. However, several of our patients were not discharged to their own home, but transferred to local hospitals for further recovery after specialized thoracic surgical care was discontinued. The implementation of long-term treatment would likely have caused major logistic problems and affected compliance negatively. Another potential source of bias in this trial was the overall amount of missing questionnaire forms during follow-up, with more patients leaving the gabapentin group. The attrition rate was high for obvious reasons; however, the reason why forms were missing was unknown in ∼15% of patients. These missing

**Table 4:** Exercise and lung function capacities at 3 and 14 days postoperatively by treatment group

| | Group | Preop. score | 3 days | | 14 days | |
|---|---|---|---|---|---|---|
| | | | Change | Difference | Change | Difference |
| 6MWT | P | 419 (385 to 453) | −143 (−203 to −82) | −19 (−98 to 60) | −45 (−117 to 27) | 1 (−89 to 92) |
| | G | 384 (351 to 417) | −124 (−180 to −68) | | −46 (−106 to 14) | |
| FVC (l) | P | 3.2 (2.9 to 3.4) | −1.3 (−1.6 to −1.0) | −0.1 (−0.4 to 0.2) | −0.8 (−1.0 to −0.6) | −0.3 (−0.6 to 0.0) |
| | G | 3.0 (2.8 to 3.3) | −1.2 (−1.4 to −1.1) | | −0.5 (−0.8 to −0.3) | |
| FVC (%) | P | 85 (79 to 90) | −30 (−41 to −20) | 4 (−8 to 15) | −22 (−27 to −16) | −8 (−17 to 1) |
| | G | 87 (81 to 93) | −34 (−40 to −27) | | −14 (−21 to −6) | |
| FEV-1 (l) | P | 2.5 (2.2 to 2.7) | −0.7 (−1.0 to −0.3) | 0.1 (−0.3 to 0.5) | −0.6 (−0.8 to −0.4) | −0.2 (−0.5 to 0.0) |
| | G | 2.2 (2.0 to 2.4) | −0.8 (−0.9 to −0.6) | | −0.4 (−0.5 to −0.2) | |
| FEV-1 (%) | P | 80 (74 to 85) | −26 (−33 to −19) | 0.3 (−11 to 11) | −17 (−23 to −11) | −6 (−13 to 2) |
| | G | 77 (71 to 82) | −26 (−34 to −19) | | −11 (−16 to −6) | |
| PEF ($l\ s^{-1}$) | P | 5.0 (4.4 to 5.6) | −0.9 (−1.9 to 0.1) | 0.5 (−0.6 to 1.6) | −0.7 (−1.3 to −0.2) | −0.1 (−0.8 to 0.7) |
| | G | 4.3 (3.8 to 4.8) | −1.4 (−1.9 to −0.9) | | −0.7 (−1.3 to −0.1) | |
| PEF (%) | P | 67 (60 to 74) | −17 (−27 to −7) | 1 (−12 to 14) | −10 (−18 to −2) | −2 (−14 to 10) |
| | G | 62 (56 to 68) | −18 (−26 to −9) | | −8 (−18 to 1) | |

Values are presented as means with 95% CI for those patients available at that specific time point.
P: placebo group; G: gabapentin group; Preop. Score: baseline preoperative score; Change: change from baseline preoperative score; Difference: placebo group minus gabapentin group; 6MWT: six-minute walk test; FVC: forced vital capacity; FEV-1: forced expiratory volume exhaled in 1 s; PEF: peak expiratory flow; (%): percent of predicted values.

**Table 5:** Predefined analgesia-related side effects during the 5-day treatment period by treatment group

| | Group | POD 1 | | POD 2 | | POD 3 | | POD 4 | | POD 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *x/n* | % (95% CI) | *x/n* | % (95% CI) | *x/n* | % (95% CI) | *x/n* | % (95% CI) | *x/n* | % (95% CI) |
| Confusion | P | 1/44 | 2 (0 to 12) | 3/48 | 6 (13 to 17) | 5/42 | 12 (4 to 26) | 4/31 | 13 (4 to 30) | 1/22 | 5 (0 to 23) |
| | G | 1/47 | 2 (0 to 11) | 2/48 | 4 (1 to 14) | 0/45 | 0 (0 to 8)[a] | 0/36 | 0 (0 to 10) | 1/24 | 4 (0 to 21) |
| Sedation | P | 3/39 | 8 (2 to 21) | 4/49 | 8 (2 to 20) | 0/48 | 0 (0 to 8)[a] | 1/36 | 3 (0 to 16) | 0/21 | 0 (0 to 16)[a] |
| | G | 1/39 | 3 (0 to 14) | 6/48 | 13 (5 to 25) | 0/48 | 0 (0 to 7)[a] | 2/36 | 5 (0 to 19) | 2/26 | 8 (0 to 25) |
| Hallucination | P | 11/45 | 24 (13 to 40) | 14/48 | 29 (17 to 44) | 7/42 | 17 (7 to 31) | 5/37 | 16 (6 to 34) | 3/22 | 14 (3 to 35) |
| | G | 4/46 | 9 (2 to 21) | 7/48 | 15 (6 to 28) | 8/45 | 18 (8 to 32) | 4/36 | 11 (3 to 26) | 3/24 | 13 (3 to 32) |
| Nausea | P | 14/45 | 31 (18 to 47) | 22/48 | 46 (31 to 61) | 19/42 | 45 (30 to 61) | 17/31 | 55 (36 to 73) | 10/23 | 44 (23 to 66) |
| | G | 11/46 | 24 (13 to 39) | 19/48 | 40 (26 to 55) | 18/45 | 40 (26 to 56) | 17/36 | 47 (30 to 65) | 12/24 | 50 (29 to 71) |
| Vomiting | P | 14/45 | 31 (18 to 47) | 8/48 | 17 (8 to 30) | 5/42 | 12 (4 to 26) | 5/31 | 16 (6 to 34) | 1/23 | 4 (0 to 22) |
| | G | 16/46 | 35 (21 to 50) | 10/48 | 21 (11 to 35) | 2/45 | 4 (0 to 15) | 8/35 | 23 (10 to 40) | 6/24 | 25 (10 to 47) |
| Itching | P | 25/44 | 57 (41 to 72) | 26/48 | 54 (39 to 69) | 14/40 | 35 (21 to 52) | 7/31 | 23 (10 to 41) | 6/23 | 26 (10 to 48) |
| | G | 22/46 | 48 (33 to 63) | 20/48 | 42 (28 to 57) | 11/45 | 24 (13 to 40) | 5/36 | 14 (5 to 30) | 2/24 | 8 (1 to 27) |
| Dizziness | P | 30/44 | 68 (52 to 81) | 26/48 | 54 (39 to 69) | 24/42 | 57 (41 to 72) | 13/31 | 42 (25 to 61) | 8/23 | 35 (16 to 57) |
| | G | 34/47 | 72 (57 to 84) | 35/48 | 73 (58 to 85) | 28/45 | 62 (47 to 76) | 21/36 | 58 (41 to 74) | 16/24 | 67 (45 to 84) |
| Hypotension | P | 1/45 | 2 (0 to 12) | 4/48 | 8 (2 to 20) | 3/41 | 7 (2 to 20) | 0/31 | 0 (0 to 11)[a] | 0/23 | 0 (0 to 15)[a] |
| | G | 1/47 | 2 (0 to 12) | 5/48 | 10 (3 to 23) | 5/45 | 11 (4 to 24) | 1/35 | 3 (0 to 15) | 1/24 | 4 (0 to 21) |
| Respiratory depression | P | 0/45 | 0 (0 to 8)[a] | 0/48 | 0 (0 to 7)[a] | 0/42 | 0 (0 to 8)[a] | 0/31 | 0 (0 to 11)[a] | 0/23 | 0 (0 to 15)[a] |
| | G | 0/46 | 0 (0 to 8)[a] | 0/48 | 0 (0 to 7)[a] | 0/45 | 0 (0 to 8)[a] | 0/36 | 0 (0 to 10)[a] | 0/24 | 0 (0 to 14)[a] |
| Fatigue | P | 41/44 | 93 (81 to 99) | 42/48 | 88 (75 to 95) | 39/42 | 86 (71 to 95) | 26/31 | 84 (66 to 95) | 20/23 | 87 (66 to 97) |
| | G | 41/47 | 87 (74 to 95) | 42/48 | 88 (75 to 95) | 36/45 | 87 (73 to 95) | 33/36 | 92 (78 to 98) | 23/24 | 96 (79 to 99) |

Values are presented as numbers and proportions (%) with binominal exact 95% CIs in parentheses.
*x*: number of events (patients with recurrent daily events are counted only once); *n:* number of non-missing patients at risk at that time point;
POD: postoperative day; P: placebo group; G: gabapentin group.
[a]One-sided, 97.5% CI.

cases could, if they were different from those providing data, have biased the estimate of the rate of persistent post-thoracotomy pain. We performed a sensitivity analysis based on best case/worst case scenarios (i.e. absence/presence of persistent pain in non-respondents) to assess the effects of potential bias. In the worst case, if all of the non-respondents who did not provide data on the primary outcome had persistent post-thoracotomy pain, the incidence would have been 57% in the placebo group versus 58% in the gabapentin group. If, on the other hand, none of these patients had persistent post-thoracotomy pain, the incidence would have been 41% for placebo-treated patients compared with 37% for gabapentin-treated patients. Therefore,

even if the worst possible bias had been present, inability to get the data would not have considerably changed any of the effect measures.

## Future implications

It remains unclear whether there is causality between acute postoperative pain and pain persistence. Predisposing factors, preoperative pain, insufficient perioperative analgesia and neuroplastic changes are all probable risk factors for postoperative pain persistence; their interaction, however, is scarcely investigated. Future well-designed prospective procedure-specific research with long-term follow-up should thus aim at classifying all preoperative, perioperative and postoperative risk factors contributing to severe acute postoperative pain, impaired functional recovery and/or the transition from acute pain to persistent postoperative pain. Additionally, it should be assessed whether such factors may be eliminated or modified by preventive patient-specific multidimensional therapeutic interventions, including psychological treatments. Psychophysical and neurophysiological assessments in the preoperative, perioperative and postoperative phases may provide valuable insights into pain processing associated with the development of persistent postoperative pain, and may also be essential for improving diagnosis, prognosis, treatment and prevention of persistent postoperative pain. Accordingly, multidisciplinary collaboration is mandatory in order to be able to correctly identify patients at risk of developing persistent post-thoracotomy pain and to properly evaluate the effectiveness of preventive strategies.

## CONCLUSION

In summary, we found no evidence of statistical significance or likely clinical importance suggesting the superiority of gabapentin over placebo for the treatment of acute pain following thoracotomy or for the prevention of the development of persistent post-thoracotomy pain.

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**Conflict of interest**: none declared.

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