ANESTHESIOLOGY

Prolonged Perioperative Use of Pregabalin and Ketamine to Prevent Persistent Pain after Cardiac Surgery

Sibtain Anwar, M.D., Ph.D., Jackie Cooper, Ph.D., Junia Rahman, M.D., Chhaya Sharma, M.D., Richard Langford, M.D.

ANESTHESIOLOGY 2019; 131:119–31

ABSTRACT

Background: Persistent postsurgical pain is common and affects quality of life. The hypothesis was that use of pregabalin and ketamine would prevent persistent pain after cardiac surgery.

Methods: This randomized, double-blind, placebo-controlled trial was undertaken at two cardiac surgery centers in the United Kingdom. Adults without chronic pain and undergoing any elective cardiac surgery patients *via* sternotomy were randomly assigned to receive either usual care, pregabalin (150 mg preoperatively and twice daily for 14 postoperative days) alone, or pregabalin in combination with a 48-h postoperative infusion of intravenous ketamine at 0.1 mg · kg^{-1} · h^{-1}. The primary endpoints were prevalence of clinically significant pain at 3 and 6 months after surgery, defined as a pain score on the numeric rating scale of 4 or higher (out of 10) after a functional assessment of three maximal coughs. The secondary outcomes included acute pain, opioid use, and safety measures, as well as long-term neuropathic pain, analgesic requirement, and quality of life.

Results: In total, 150 patients were randomized, with 17 withdrawals from treatment and 2 losses to follow-up but with data analyzed for all participants on an intention-to-treat basis. The prevalence of pain was lower at 3 postoperative months for pregabalin alone (6% [3 of 50]) and in combination with ketamine (2% [1 of 50]) compared to the control group (34% [17 of 50]; odds ratio = 0.126 [0.022 to 0.5], $P = 0.0008$; and 0.041 [0.0009 to 0.28], $P < 0.0001$, respectively) and at 6 months for pregabalin alone (6% [3 of 50]) and in combination with ketamine 0% (0 of 5) compared to the control group (28% [14 of 50]; odds ratio = 0.167 [0.029 to 0.7], $P = 0.006$; and 0.000 [0 to 0.24], $P < 0.0001$). Diplopia was more common in both active arms.

Conclusions: Preoperative administration of 150 mg of pregabalin and postoperative continuation twice daily for 14 days significantly lowered the prevalence of persistent pain after cardiac surgery.

(ANESTHESIOLOGY 2019; 131:119–31)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Cardiac surgery is associated with a significant rate of chronic postoperative pain
- Few proven strategies exist to reduce chronic postoperative pain

What This Article Tells Us That Is New

- The administration of pregabalin (14 days) with or without ketamine (2 days) postoperatively reduced the prevalence of pain at 3 and 6 months
- Side effects from pregabalin and ketamine administration were generally mild

Persistent postsurgical pain is common and has long-term effects on quality of life.[1] Defined as a new pain developing postoperatively in and around the incision site and persisting for at least 3 months after surgery, it is difficult to treat once established. Prevention of this phenomenon therefore seems attractive given the considerable impact on quality of life.

Up to half of all patients undergoing any type of surgery to the chest may be at risk, and over half of these cases will demonstrate features of neuropathic pain.[2] Postoperative pain can persist for many years—for at least 5 yr after breast surgery, for example—with effects on quality of life.[3,4] Long-term data for pain after cardiac surgery are limited, but level 1 clinical trial data reveal a prevalence of 27 to 41% at 3 postoperative months.[5–7]

Surgical incision is believed to cause hyperalgesia and sensitize the central nervous system.[1] The gabapentinoids are effective in neuromodulating these processes during the treatment of established neuropathic pain.[8] They have also been shown to suppress central sensitization in other centrally driven processes, such as chronic cough, leading to reduced symptoms as well as improved quality of life.[9]

Studies of the preventive effects of gabapentinoids have been limited in terms of duration of perioperative administration, rarely extending beyond a few days.[10] Pregabalin has improved bioavailability, efficacy, and tolerability, as

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication October 23, 2018. Accepted for publication March 22, 2019. From the Department of Perioperative Medicine, Barts Heart Centre, London, United Kingdom (S.A.); National Institutes of Health Research Biomedical Research Centre at Barts, London, United Kingdom (S.A., J.C.); and Pain and Anaesthesia Research Centre, St. Bartholomew's Hospital, London, United Kingdom (S.A., J.R., C.S., R.L.).

 Anesthesiology 2019; 131:119–31. DOI: 10.1097/ALN.0000000000002751

<zdoi;10.1097/ALN.0000000000002751>

compared to gabapentin, which may be important when considering its prolonged and prophylactic use in pain-free surgical patients.[11] The concept of preventive or *protective* analgesia is better established with some neuromodulating analgesics, such as ketamine,[12] but surprisingly few studies have taken the approach of combining agents, even in established neuropathic pain, although the exceptions have stood out for their efficacy.[13–15]

Not all surgical patients are destined to develop persistent pain. Predicting a patient's susceptibility may inform the risk: benefit evaluation of any mitigating strategy or medication, especially if the latter has potential for side effects. Preoperative challenges to the nervous system with experimental pain may predict the subsequent development of pain persistence.[16] Sensory testing can also be repeated after surgery to examine putative mechanisms for the transition to persistent pain states.

The aim of this study was to assess the effect of a prolonged regimen of preventive analgesia on chronic pain outcomes, as well as to determine risk factors and potential predictors for this phenomenon. We hypothesized that the use of pregabalin alone or in combination with ketamine would lower the prevalence of persistent pain after cardiac surgery, as compared to usual care.

Materials and Methods

Study Design

The Heart Surgery and Persistent Postsurgical Pain (Heart PPPAIN) study was a prospective, double-blind, randomized, parallel arm, three-group, placebo-controlled trial of preventive analgesia alongside a mechanistic study for persistent pain. The objective of the trial was to test the superiority of pregabalin used alone or in combination with ketamine compared to usual care in preventing pain at 3 and 6 months after cardiac surgery. We screened patients, aged 18 to 80 yr, scheduled to undergo elective surgery *via* sternotomy, at the two London heart centers of St. Bartholomew's Hospital and the London Chest Hospital.

Study Participants

We excluded patients who had undergone sternotomy previously, who gave a history of chronic pain, and who regularly used pain medication (other than paracetamol and nonsteroidal antiinflammatory drugs). As pregabalin is renally cleared, we used an estimated glomerular filtration rate of less than 60 ml/min to exclude patients or to withhold single postoperative doses, based on twice-daily blood testing. If this value was less than 30 or renal replacement therapy was required, we withdrew patients from the study.

All participating patients gave written, informed consent for this clinical trial, conducted in accordance with the original protocol, available on request from the authors and approved by the UK National Research Ethics Service and the Medicines and Healthcare Products Regulatory Authority. The study was registered on ClinicalTrials.gov (NCT01480765).

Randomization and Blinding

As set out in figure 1, 150 patients were recruited and block-randomized 1:1:1 (in groups of 30) to one of the following three treatment groups, using a computer-generated randomization sequence, created and managed in a blinded manner by the Barts Trials Pharmacy:

1. **Usual care:** received usual care of regular paracetamol and patient-controlled morphine analgesia and 1 preoperative day and 14 postoperative days of placebo capsules, as well as 48 postoperative hours of placebo (normal saline) intravenous infusion.
2. **Pregabalin group:** received usual care and 1 preoperative day and 14 postoperative days of 150-mg pregabalin capsules, alongside 48 postoperative hours of placebo (normal saline) infusion.
3. **Pregabalin and ketamine combined group:** received usual care and 1 preoperative day and 14 postoperative days of 150-mg pregabalin capsules, alongside 48 postoperative hours of ketamine infusion at 0.1 mg · kg^{-1} · h^{-1}.

Allocation concealment was achieved by the use of study capsules and intravenous infusions with identical appearance for active and placebo drugs. Pregabalin study capsules were supplied by Pfizer (Surrey, UK) with no other contribution to the design, conduct, analysis, or publication of this trial. Sealed 50-ml syringes containing clear ketamine or placebo (0.9% saline) solution were prepared in a blinded manner by the clinical trials unit at St. Bartholomew's Hospital, with no other involvement in patient care. Per-patient release of drug to the research assistants (after evaluation of eligibility, informed consent, and enrolment of participants) ensured

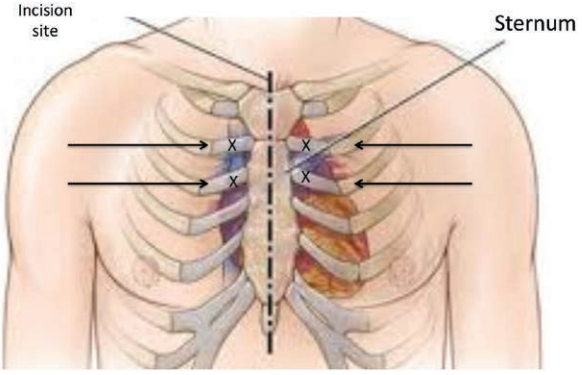

Fig. 1. Sensory testing sites. *X* marks four testing sites 5 cm from the midline on the second and third rib bilaterally. *Arrows* indicate lateral starting points for zone of hyperalgesia testing, followed by 1-cm incremental steps towards the X point.

that blindness was maintained throughout until all follow-up assessments were completed, and the data sets were locked and submitted to the trials pharmacy for release of the randomization code.

Study Procedures and Drug Administration

All patients completed baseline questionnaires of Quality of Life: EQ-5D (EuroQOL, The Netherlands), the Spielberger State Anxiety, and the Pain Catastrophizing Scale, as potential risk factors for the development of persistent pain.[17,18] On the day before surgery, we tested sensory responses to painful stimuli as set out below. This was done in a quiet environment with patients in a comfortable semireclined position and with both eyes closed. Four reference points were used for sensory testing of the planned incision site (5 cm from the midline of the sternum, at the level of the second and third rib bilaterally; marked as Xs in figure 1). Remote sensory testing was performed on the right forearm at the midpoint between the wrist and the elbow as a surrogate measure of central processing of pain.

Pressure Pain Measures

This test measures sensitivity of pain pathways to increasing mechanical pressure. We used a handheld pressure algometer (fig. 2; Somedic AB, Sweden) to measure the pain pressure threshold at the same four standardized testing points on the chest, as well as the remote site. The diameter of the contact tip was 1 cm.[2] A standard pressure of 30 kPa/s. We took the mean of four, random-ordered, measurement points as the pain pressure threshold.

Conditioned pain modulation is the physiologic engagement of the endogenous analgesic system to reduce pain intensity or increase threshold to pain detection.[19] We calculated the conditioned pain modulation effect as the difference in algometer-derived pain pressure threshold readings, with and without the application of a conditioning remote noxious stimulus.

Fig. 2. Pressure algometer (Somedic AB, Sweden).

Ischemic arm pain was used as the conditioning stimulus. A blood pressure cuff was manually inflated to 250 mmHg to achieve an arm pain score on the numeric rating scale of 5/10. In refractory cases, after 15 min of inflation, the cuff was further inflated in 10-mmHg increments to attain this pain score. Pain pressure threshold measurements were repeated at this point to record the conditioned pain modulation effect.

Tactile Pain Measures

We used 20 progressively stiffer monofilament von Frey fibers (Ugo Basile, Italy) to determine tactile pain detection thresholds at the sites described above. Ascending fibers were applied perpendicular to the skin for 1 s, to the point of deformation of the fiber, until the patient described pain, with the tactile pain detection threshold defined as the least force that elicits a sensation of pain on buckling of the standardized filament. This was determined by repetitive testing of ascending fiber sizes, until the same von Frey fiber elicits two similar responses in succession. All measurements were repeated at the remote site on the right arm.

Temporal summation to tactile stimulation is an indicator of a sensitized pain system.[20] We used the von Frey fiber one reading below the tactile pain detection threshold and stimulated at a frequency of 2 Hertz for 60 s on all test points. Pain score increases of more than 1 point were reported as positive temporal summation, as described in the literature.[21,22]

We retested pain responses at the sternotomy site, as well as remotely, on postoperative day 4 to assess for new postsurgical summation and changes in pain pressure threshold. In addition, a dynamic assessment of spreading sensitization was carried out to give an indication of zone of secondary hyperalgesia. We used the tactile pain detection threshold fiber but starting from an area free of pain—the lateral chest—and moved toward and perpendicular to the midline sternotomy. The fiber was advanced in 1-cm increments until the first sensation of pain was achieved. This distance from the midline sternotomy was measured using a disposable tape measure, and we used the sum of the four recordings as a measure of zone of secondary hyperalgesia.[20]

Clinical Management of Perioperative Care

Nursing staff administered the first study capsule (containing either 150 mg of pregabalin or placebo lactose) to all patients 2 h before surgery. Anesthesia was induced with propofol and fentanyl (restricted to a total intraoperative dose of 7.5-20 μg/kg) and maintained with isoflurane, before cardiopulmonary bypass, before converting to intravenous infusion of propofol for the remainder of the perioperative period. Remifentanil was prohibited in this study.

Cardiopulmonary bypass was established on all patients using moderate hypothermia (30° to 34°C), a membrane oxygenator, and a centrifugal pump. The intravenous infusion (of ketamine or placebo) was started at the end of cardiac surgery, once sternal closure with wires had commenced.

All patients remained sedated and ventilated for transfer to the cardiac intensive care unit after surgery, and extubation took place as per unit protocol. In addition to the trial regimen, all patients received the usual care of patient-controlled analgesia (morphine at 1 mg/ml per bolus with a lockout period of 5 min) and regular paracetamol at 1 g every 6 h for the duration of the hospital stay. During the recovery from surgery, study capsules were continued twice daily for 10 continuous days, followed by a dose reduction to 75 mg for days 11 and 12 and then 50 mg for days 13 and 14.

Chest drains were removed, as per usual care, with provision of patient-controlled morphine analgesia up to this point. Supplementary regular oral codeine was provided after drain removal, and in addition, oral tramadol was available on demand for breakthrough pain.

If patients were discharged from hospital before completion of the 14-day capsule regimen, any remaining doses were dispensed by the trials pharmacy for the patients to complete the course at home. Any unused capsules were returned to the trial pharmacy and recorded. Details of any missed doses during in-patient stay or early withdrawal from either drug were also recorded.

Outcomes

The primary outcome was the proportion of patients with clinically meaningful pain at 3 and 6 months after cardiac surgery. This was defined as a pain score on the numeric rating scale of greater than 3 out of a maximum score of 10, indicating moderate to severe pain intensity, after a functional assessment of three maximal coughs.[23] This was changed before the start of the study from pain scores alone, at rest and with cough, to better capture functional recovery and quality of life at 3 and 6 months.

Secondary outcomes included clinically meaningful acute pain scores at the sternotomy and saphenectomy sites (numeric rating scale of more than 3, after three maximal coughs and dorsiflexion, respectively) alongside total morphine consumption, both measured at 24 h after surgery. Recovery from surgery was assessed in terms of sedation and nausea scores at 24 h (Likert scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe), time to extubation, times to readiness for discharge from intensive care and hospital, and safety measures of respiratory rate and arterial carbon dioxide partial pressure at 24 h after surgery and any episode of inpatient diplopia, a common transient side effect of pregabalin use in naïve patients. Changes in sensory testing after surgery were also recorded as secondary outcomes, as well as potential biomarkers of drug efficacy.

During the final study assessment at 6 months after cardiac surgery, we assessed the presence of neuropathic pain (Leeds Assessment of Neuropathic Symptoms and Signs [S-LANSS] score above 12), EQ-5D–based quality of life index, and any medication use or sleep disturbance attributable to pain over the previous 7 days. In addition to baseline anxiety and catastrophizing scores, we also collected patient age, sex, weight, baseline EQ-5D index, duration of surgery, and the need to harvest the left internal mammary artery as biologically plausible risk factors for the development of persistent postsurgical pain.

Statistical Analysis

This study was powered to detect a two-thirds decrease in the percentage of patients with persistent postsurgical pain. Pilot observational data from 312 consecutive patients undergoing elective sternotomy in our center over a 6-month period revealed a persistent pain prevalence of 39.7%. Based on an α of 5% and a power of 80%, we therefore calculated a sample size per group of 43 patients to allow a detectable difference of 39.7% *versus* 13.2% (odds ratio [OR] = 0.231). To allow for early withdrawals and loss to follow-up, we recruited 50 patients per group.

Patients were included in the final analysis of outcomes and safety on an intention-to-treat basis, with imputation of missing data on the basis of average values for the group. Sensitivity analysis for the primary outcome was also undertaken, assuming that patients lost to follow-up had pain at 3 and 6 months, which is the most conservative possible outcome. All data was entered using two-pass verification, and analysis was performed using Stata (version 14, StataCorp, USA).

We descriptively compared the baseline characteristics across the three treatment groups. All primary and secondary outcomes are reported as frequency and percentages or medians and interquartile range. In the case of the primary outcome, this is also reported as number needed to treat (inverse of the absolute risk reduction). For the primary outcome, we used exact logistic regression to estimate ORs and CI comparing each active treatment group to the usual care group. ORs were presented using the rule of four to determine the number of decimal places with CI presented with less precision.[24] For ordinal score data, we used an ordinal logistic regression model, with the proportional-odds assumption tested by an approximate likelihood ratio test. If the continuous secondary outcomes were not normally distributed, we used quantile regression to compare medians between the groups, estimating the difference in medians along with bootstrap CI. Because the groups were balanced in terms of covariates and because sparse data may result in bias if too many variables are included in the model, the main analysis focused on unadjusted results. For the primary outcome we also ran a multivariable model to adjust for age, sex, weight, preoperative EQ-5D index, state anxiety, pain catastrophizing, and the duration and type of surgery as a sensitivity analysis to the main result. A Firth

logistic regression model was used for this to obtain bias corrected estimates.

Identifying patients at risk of developing persistent pain is particularly important given the possibility of diplopia and sedation after initiation of pregabalin in pain-free patients, and therefore the association of each predictor variable with pain was examined using Firth logistic regression with adjustment for randomization group (treatment adjusted univariate associations). To examine whether the effect of any predictor was stronger in the treatment groups we tested for interaction. We used the numeric rating scale score as a continuous dependent variable for this to increase the power, and an ordinal logistic regression model was fitted for each predictor along with treatment group and the interaction term. The area under the receiver characteristic operating characteristic curve was calculated for each variable using the control group to allow assessment of predictive ability.

A two-sided Bonferroni corrected significance level of 0.0125 was used for the primary outcome to allow for multiple comparisons (two treatment groups *vs.* control at two time points). Secondary outcomes were considered as supportive and exploratory and were tested using a two-sided α level of 0.05. Results from all tests are shown, allowing secondary outcome results to be interpreted in light of the number of tests made.

Results

We screened 362 patients to recruit 150 patients for the Heart Surgery and Persistent Postsurgical Pain (Heart PPPAIN) study from January 2012 to February 2014 (fig. 3). Three- and six-month assessments were completed on 148 patients. Two patients were lost to follow-up: one due to death on day 7 after surgery and one due to emigration. The data were imputed for these two patients, assuming no pain at follow-up, because this was the most likely outcome for the treatment groups.

Additional withdrawals from treatment also took place for delayed recovery from cardiac surgery, drug intolerance, or patient choice, as set out in figure 1. All patients were approached for 3 and 6 month follow-up, and any missing data for unresponsive patients was imputed on an "average for the group" basis, allowing analysis for all 150 patients. Baseline patient characteristics were similar among the three groups (table 1).

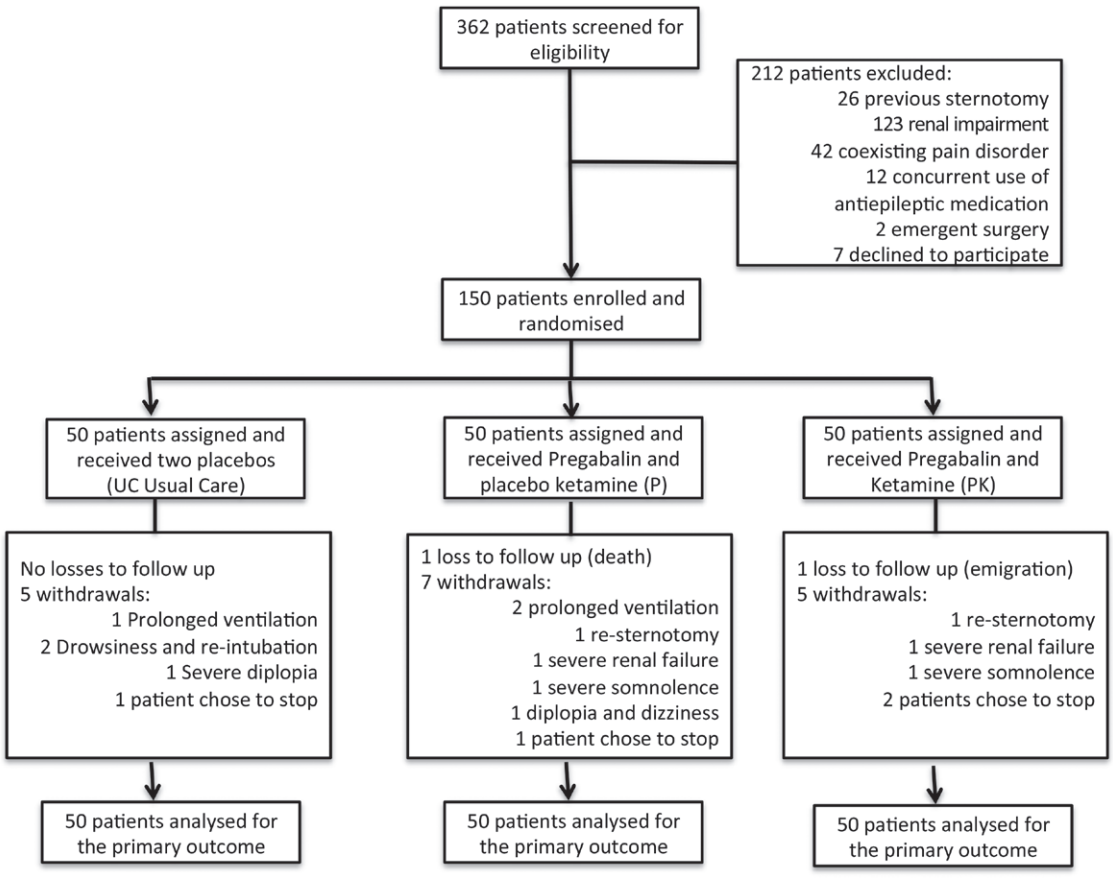

Fig. 3. Consolidated Standards of Reporting Trials diagram. P, pregabalin and placebo; PK, pregabalin and ketamine; UC, usual care.

Table 1. Baseline Characteristics of Patients as per Randomization Group

	Intervention Arm		
	Usual Care	Pregabalin Alone	Pregabalin and Ketamine
Male sex, n/N (%)	36/50 (72)	41/50 (82)	40/50 (80)
Age, median [IQR], yr	68 [52–72]	68 [59–73]	64 [54–72]
Weight, kg	81 [70–92]	76 [68–84]	77 [66–89]
Preoperative EQ-5D index	0.721 [0.395–0.784]	0.687 [0.395–0.768]	0.686 [0.382–0.776]
Anxiety: Spielberger score	38 [31–47]	39 [32–44]	40 [33–50]
Catastrophizing: Pain Catastrophizing Scale score	15 [6–26]	14 [5–24]	13 [7–28]
Duration of surgery, min	285 [225–320]	275 [245–330]	288 [250–315]
LIMA dissection	35/50 (70%)	39/50 (78%)	37/50 (74%)

The data are presented as portion (percentages) or median [IQR].
IQR, interquartile range; LIMA, left internal mammary artery.

Primary Outcome

As set out in table 2, pregabalin alone and in combination with ketamine lowered the likelihood of developing pain at 3 postoperative months from 34% (17 of 50) in the control group to 6% (3 of 50) and 2% (1 of 50), respectively (OR = 0.126 [0.022 to 0.5], number needed to treat = 3.6; and 0.041 [0.0009 to 0.28], number needed to treat = 3.1, respectively) and at 6 months from 28% (14 of 50) to 6% (3 of 50) and 0% (0 of 50; OR = 0.167 [0.029 to 0.7], number needed to treat = 4.5; and 0.0381 [0 to 0.24], number needed to treat = 3.6).

These effects remained significant after adjustment for possible confounders using a multivariable model (Supplemental Digital Content, http://links.lww.com/ALN/B934). CIs for the two active arms for the primary outcome reveal no difference in efficacy. No further comparison is therefore made between the active arms.

Sensitivity analysis assuming both patients who withdrew from the treatment arms went on to experience pain at 3 and 6 months demonstrated that the findings were robust with ORs (95% CI) for pregabalin and combined pregabalin–ketamine groups, respectively, of 0.172 (0.039 to 0.6), $P = 0.003$; and 0.083 (0.009 to 0.39), $P = 0.0002$ at 3 months; and 0.227 (0.05 to 0.8), $P = 0.017$; and 0.054 (0.0012 to 0.38), $P = 0.0004$ at 6 months.

Secondary Outcomes

Both pregabalin alone and the combined pregabalin–ketamine group lowered the likelihood of clinically meaningful acute pain scores at 24 postoperative h, for sternotomy (OR = 0.244 [0.09 to 0.6], number needed to treat = 3.1; and 0.208 [0.08 to 0.5], number needed to treat = 2.8, respectively) and saphenectomy (OR = 0.112 [0.024 to 0.4], number needed to treat = 2.4; and 0.283 [0.09 to 0.8], number needed to treat =3.4, respectively). At this time point, these values were associated with median decreases in morphine requirement of 29 mg (interquartile range = 8 to 50) and 33 mg (interquartile range = 12 to 54), respectively, for the pregabalin and pregabalin–ketamine combined groups compared to a median of 52 mg (interquartile range = 830) for patients receiving the usual care, with improved nausea scores in both active arms (table 3).

We found an increase in pain pressure threshold in both active arms but only when tested at a site remote to the incision (table 4). By contrast, the control group showed a decrease in the pain pressure threshold. When we tested at

Table 2. Baseline Sensory Measurements

	Intervention Arm		
	Usual Care	Pregabalin Alone	Pregabalin and Ketamine
PPT sternotomy site, kPa	214 [160 to 294]	266 [214 to 337]	243 [193 to 363]
PPT remote, kPa	208 [180 to 312]	289 [215 to 352]	264 [176 to 397]
Change in PPT with CPM, %	19.4 [–1.8 to 67.0]	23.8 [2.1 to 47.8]	16.3 [–2.5 to 48.6]
Presence of preoperative temporal summation at sternotomy site	17/50 (34%)	15/50 (30%)	14/50 (28%)
Presence of remote temporal summation (forearm)	10/50 (20%)	9/50 (18%)	9/50 (18%)

The data are presented as medians [IQR] or proportions (%).
CPM, conditioned pain modulation; PPT, pressure pain threshold.

Table 3. Primary and Secondary Outcomes

		Intervention Arm		
		Usual Care	Pregabalin Alone	Pregabalin and Ketamine
Primary outcomes				
Prevalence of moderate to severe pain at 3 months after surgery	N (%)	17/50 (34)	3/50 (6)	1/50 (2)
	Odds ratio (95% CI)*	1.00	0.126 (0.022 to 0.5)	0.041 (0.0009 to 0.28)
	P value	—	0.0008	< 0.0001
Prevalence of moderate to severe pain at 6 months after surgery	N (%)	14/50 (28)	3/50 (6)	0/50 (0)
	Odds ratio (95% CI)	1.00	0.167 (0.029 to 0.7)	0.000 (0 to 0.24)
	P value	—	0.006	< 0.0001
Secondary outcomes				
Prevalence of moderate to severe acute sternotomy pain at 24 h after surgery	N (%)	39/50 (78)	23/50 (46)	21/50 (42)
	Odds ratio (95% CI)	1.00	0.244 (0.09 to 0.6)	0.208 (0.08 to 0.5)
	P value	—	0.002	0.0004
Prevalence of moderate to severe acute saphenectomy pain at 24 h after surgery	N (%)	19/36 (53)	4/37 (11)	9/38 (24)
	Odds ratio (95% CI)	1.00	0.112 (0.024 to 0.4)	0.283 (0.09 to 0.8)
	P value	—	0.0002	0.019
Total morphine consumption at 24 h, mg	Median [IQR]	52 [33–83]	26 [15–36]	22 [14–31]
	B (95% CI)†	0.00	−29 (−50 to −8)	−33 (−54 to −12)
	P value	—	0.007	0.002
Extubation time, min	Median [IQR]	373 [245–540]	365 [270–540]	398 [235–555]
	B (95% CI)†	0.00	−15 (−107 to 77)	25 (−83 to 133)
	P value	—	0.749	0.647
Length of stay in cardiac intensive care, h	Median [IQR]	18 [14–24]	15 [10–21]	15 [10–24]
	B (95% CI)‡	0.00	−3 (−7 to 1)	−3 [−7 to 1]
	P value	—	0.097	0.093
Sedation score at 24 h (none/mild/moderate/severe)	Median [IQR]	2 [2–2]	2 [2–2]	2 [1–2]
	Odds ratio (95% CI)‡	1.00	0.382 (0.15 to 1.0)	0.262 (0.10 to 0.7)
	P value	—	0.042	0.005
Nausea score at 24 hours (none/mild/moderate/severe)	Median [IQR]	2 [0–2]	0 [0–0]	0 [0–1]
	Odds ratio (95% CI)‡	1.00	0.083 (0.033 to 0.21)	0.2227 (0.10 to 0.5)
	P value	—	< 0.0001	0.0002
Prevalence of diplopia throughout inpatient stay	N (%)	4/50 (8)	12/50 (24)	15/50 (30)
	Odds ratio (95% CI)	1.00	3.58 (1.0 to 17)	4.9 (1.4 to 22)
	P value	—	0.054	0.010
Respiratory rate at 24 h, breaths/min	Median [IQR]	12 [9–15]	15 [12–18]	14 [12–17]
	B (95% CI)‡	0.00	3 (1 to 5)	2 (−0 to 4)
	P value	—	0.008	0.071
Arterial carbon dioxide partial pressure at 24 hours, kPa	Median [IQR]	5.79 [5.05–6.43]	5.14 [4.8–5.6]	5.28 [4.54–5.8]
	B (95% CI)†	0.00	−0.57 (−1.04 to −0.10)	−0.52 (−0.99 to −0.05)
	P value	—	0.019	0.032
Length of stay in hospital, days	Median [IQR]	8 [6–14]	7 [5–9]	6 [5–8]
	B (95% CI)†	0.00	−1 [−5 to 1]	−2 [−6 to 0]
	P value	—	0.180	0.034
Quality of life at 6-month follow-up (EQ-5D Index)	Median [IQR]	0.53 [0.01–0.72]	0.80 [0.58–0.81]	0.77 [0.73–0.81]
	B (95% CI)†	0.00	0.27 (0.07 to 0.44)	0.24 (0.05 to 0.42)
	P value	—	0.011	0.014
Prevalence of neuropathic pain at 6-month follow-up	N (%)	8/38 (21.1)	2/43 (4.7)	0/41 (0)
	Odds ratio (95% CI)	1.00	0.187 (0.018 to 1.0)	0.068 (0 to 0.5)
	P value	—	0.055	0.003
Analgesics required for persistent postsurgical pain at 6-month follow-up	N (%)	21/50 (42.0)	5/50 (10.0)	1/50 (2.0)
	Odds ratio (95% CI)	1.00	0.156 (0.04 to 0.5)	0.0290 (0.0007 to 0.20)
	P value	—	0.0005	< 0.0001
Sleep disturbed as a result of persistent postsurgical pain at 6-month follow-up	N (%)	18/50 (36.0)	4/50 (8.0)	1/50 (2.0)
	Odds ratio (95% CI)	1.00	0.157 (0.04 to 0.5)	0.0373 (0.0009 to 0.26)
	P value	—	0.001	< 0.0001

The data are presented as proportions or medians [IQR].

*Odds ratio from exact logistic regression model. †B (95% CI) from quantile regression represents group differences in medians. ‡Odds ratio from ordinal logistic regression model representing the odds of having a higher score category.

IQR, interquartile range.

Table 4. Postoperative Sensory Changes Dependent on Treatment Arm

		Intervention Arm		
		Usual Care	Pregabalin Alone	Pregabalin and Ketamine
Change in PPT sternotomy site from baseline	Median [IQR]	−38 [−89 to 11]	−2 [−84 to 37]	−42 [−94 to 9]
	B (95% CI)*	0.00	42.9 (−7.8 to 93.6)	7.8 (−32.2 to 47.8)
	P value	—	0.097	0.701
Change in PPT remote from baseline	Median [IQR]	−46 [−112 to 15]	16 [−12 to 57]	28 [−2 to 86]
	B (95% CI)*	0.00	91 (25 to 158)	83 (19 to147)
	P value	—	0.008	0.012
New TS at sternotomy site	N (%)	16/50 (32.0)	3/50 (6.0)	2/50 (4.0)
	Odds ratio (95% CI)†	1.00	0.138 (0.024 to 0.5)	0.091 (0.010 to 0.4)
	P value	—	0.002	0.0004
New TS at remote site	N (%)	16/50 (32.0)	5/50 (10.0)	3/50 (6.0)
	Odds ratio (95% CI)†	1.00	0.240 (0.06 to 0.8)	0.138 (0.024 to 0.5)
	P value	—	0.013	0.002
Loss of TS at sternotomy site	N (%)	4/50 (8.0)	4/50 (8.0)	7/50 (14.0)
	Odds ratio (95% CI)	1.00	1.00 (0.18 to 6)	1.86 (0.4 to 9)
	P value	—	1.00	0.52
Loss of TS at remote site	N (%)	2/50 (4.0)	6/50 (12.0)	5/50 (10.0)
	Odds ratio (95% CI)†	1.00	3.24 (0.5 to 34)	2.64 (0.4 to 29)
	P value	-	0.269	0.436
Zone hyperalgesia	Median [IQR]	37.5 [14.8 to 48]	12.3 [9.5 to 29]	10.3 [6.5 to 20]
	B (95% CI)*	0.00	−21.3 (−28.4 to −14.2)	−23.8 (−31.2 to −16.4)
	P value	-	< 0.0001	< 0.0001

Data is presented as portions (%) or medians [IQR].
*B (95% CI) from quantile regression adjusted for baseline PPT. †Odds ratio (95% CI) from exact logistic regression model
IQR, interquartile range; PPT, pressure pain threshold; TS, temporal summation.

the site of sternotomy, there were no statistically significant postoperative changes in pain pressure threshold after surgery. New temporal summation was lower in both active arms, at the incision site as well as remotely, as was the zone of hyperalgesia, when compared to usual care.

In terms of the potential sedating effects of the pregabalin and ketamine in the active arms, there were no statistically or clinically significant differences in time to extubation or length of stay on the intensive care unit. Safety was assessed in terms of adverse events of inpatient diplopia, revealing an increased likelihood in both active arms with numbers needed to harm of 6.3 for pregabalin alone and 4.5 for the combined PK group. This was transient in all cases and resolved with omission of a single capsule dose. Median sedation scores were 2 in all groups but with statistically significant increases in sedation in both active arms, although the respiratory rate and arterial carbon dioxide tension revealed no clinically meaningful differences.

Length of stay in the hospital was significantly shorter in the group receiving pregabalin and ketamine, as compared to usual care. CI indicated no statistically significant difference between both active arms with a median difference of 0.5 days. At the final study assessment, at 6 postoperative months, patients in both active arms demonstrated differences in EQ-5D indices of quality of life, as well as in the likelihood of developing neuropathic pain, requiring analgesics or describing sleep disturbance as a result of persistent postsurgical pain (table 3).

Associations with Persistent Postsurgical Pain

Analysis of risk factors for pain was carried out for all 150 patients with adjustment for randomization group to allow assessment of the relationship between patient or surgical factors and long-term outcomes (independent of treatment allocation). Preoperative measures of anxiety, catastrophizing, and poor quality of life were associated with poor persistent pain outcomes (table 5), as were lower responses to conditioned pain modulation. Surgical duration and technique seems to have less impact. Postoperative reductions in pain pressure threshold remote to the sternotomy were associated with persistent pain alongside the development of new temporal summation, either at the sternotomy site or remotely. Although the zone of hyperalgesia may indicate efficacy of preventive analgesia, it is not independently associated with persistent pain in this study. No significant interactions with treatment group were found, but the study has low power to detect these effects.

Discussion

Our study demonstrates the potential to predict and prevent new postoperative pain at 3 and 6 months after cardiac surgery. We found that the use of a prolonged regimen of

Table 5. Association of Factors with Persistent Pain at 3 Months

Predictor		Odds Ratio (95% CI) Adjusted for Randomization Group	*P* Value	Area under ROC Curve (95% CI)*
Age	Per 10-y increase	0.75 (0.5–1.1)	0.146	0.64 (0.47–0.81)
Sex	Male:female	1.14 (0.36–3.6)	0.825	0.53 (0.40–0.66)
Weight	Per 1 SD increase (15 kg)	1.08 (0.7–1.8)	0.743	0.54 (0.36–0.72)
Preoperative Eq-5D index	Per 1 SD increase (0.3)	0.51 (0.32–0.8)	0.005	0.70 (0.54–0.86)
Spielberger State Anxiety	Per 1 SD increase (11 units)	1.98 (1.2–3.3)	0.010	0.73 (0.57–0.88)
Catastrophizing	Per 1 SD increase (12 units)	3.80 (2.0–7)	< 0.0001	0.86 (0.75–0.97)
PPT change with CPM	Per 1 SD increase (42)	0.329 (0.15–0.7)	0.005	0.75 (0.62–0.89)
Preoperative presence of TS sternotomy site	Yes:no	2.35 (0.9–7)	0.099	0.55 (0.41–0.70)
Preoperative presence of TS remote	Yes:no	2.09 (0.7–7)	0.208	0.53 (0.40–0.65)
Duration of surgery, min	Per 1 SD increase (85min)	1.37 (0.9–2.1)	0.167	0.63 (0.45–0.80)
Surgical technique	LIMA absent:present	0.54 (0.19–1.5)	0.247	0.54 (040-0.68)
Postoperative change in PPT at sternotomy site	Per SD increase (106)	0.52 (0.24–1.1)	0.097	0.67 (0.51–0.84)
Postoperative change in PPT at remote site	Per SD increase (146)	0.383 (0.17–0.9)	0.018	0.62 (0.41–0.82)
New TS sternotomy site	Yes:no	3.20 (1.0–10)	0.043	0.66 (0.52–0.80)
New TS remotely	Yes:no	3.94 (1.3–12)	0.01	0.66 (0.52–0.80)
Zone of hyperalgesia	Per SD increase (18)	1.61 (1.0–2.7)	0.071	0.64 (0.48–0.80)

Odds ratios with 95% CI, derived from Firth logistic regression modeling (*P* value).

*The area under the ROC curve for each variable calculated using the control group.

CPM, conditioned pain modulation; LIMA, left internal mammary artery; PPT, pain pressure threshold; ROC, receiver characteristic operating characteristic; TS, temporal summation.

pregabalin during the entire perioperative period protected patients from pain persistence, although the addition of ketamine in a multimodal manner failed to confer additional advantage. Decreases in pain scores seemed to translate into improvements in quality of life.

Over and above the cost of this additional medication, not all patients will tolerate centrally acting analgesic drugs, preoperatively or for a prolonged postoperative period, and side effects such as somnolence or dizziness have the potential to limit mobilization and return to functioning.[11,25] It may be best to identify the patients most at risk of developing persistent pain, and hence we evaluated patient phenotypes, namely those with poor preoperative quality of life, state anxiety, and pain catastrophizing. In addition, it may be possible to predict susceptibility by challenging patients to experimental pain before surgery with the conditioned pain modulation platform.[26]

Countering the argument for using these drugs in high-risk patients only is the potential to spare the use of high-dose opioids in all patients. Perioperative opioid use may delay recovery as well as increase the risks of long-term use and dependence in the postoperative period.[27,28] In other surgical models, such as thoracic surgery, local anesthetic techniques (*e.g.*, thoracic epidural or paravertebral block) are frequently used as part of a multimodal analgesic regimen. In contrast, cardiac surgery has traditionally relied on large doses of intra- and postoperative opioids as the mainstay of analgesic treatment.[29] Given that nonsteroidal antiinflammatory drugs are also avoided in this group of patients, an alternative opioid-sparing regimen such as in this trial may decrease sensitization of the central nervous system[30,31] and confer long-term outcomes benefits.

The opioid-sparing properties of pregabalin are well known,[25] but the potential to reduce the length of stay in hospital and provide lasting improvements in quality of life to 6 months are new findings, requiring corroboration in large multicenter trials. The latter is particularly surprising given the large improvements in EQ-5D index of more than 0.2. This suggests more than a simple decrease in pain intensity and more likely a system-wide benefit of opioid sparing, perhaps even a neurocognitive effect.[27,32,33]

There is some debate in the noncardiac surgery literature regarding the preventive effects of pregabalin where smaller doses or shorter durations of treatment are used, especially for less painful incisions, or where treatment is started late in the postoperative period once sensitization of the nervous system has begun.[12,34] Another explanation for differing outcomes from various surgical incisions is the varying tissue injury, pain intensity, and pain mechanisms underlying these different procedures. This has led to consensus agreement on the need for procedure specific studies of pain persistence.[10]

We tested pregabalin specifically for the prevention of pain after surgical incisions on the chest, an area where persistence is highly prevalent. Pesonen *et al.*[5] conducted a randomized trial of low-dose pregabalin for 5 days, to assess acute pain scores and opioid requirement. They demonstrated opioid sparing as well as less confusion on intensive care after cardiac surgery. Although not powered for long-term outcomes, they did report improved pain scores on movement at 3 months in the pregabalin arm compared to usual care but not at earlier time points.

Identifying the patient at risk of developing persistent pain is particularly important given the possibility

of diplopia and sedation after initiation of pregabalin in pain-free patients.[25,35] Our study suggests that preoperative assessments of quality of life, state anxiety, and pain catastrophizing, combined with conditioned pain-modulation response, could potentially predict high-risk patients. With this in mind, simplified scoring and tests suitable for routine care should be evaluated. Another putative risk factor for pain in other studies is young age,[36,37] but we failed to corroborate this, likely as a result of the small numbers of younger patients in this relatively elderly population (median age of 66 yr).

The relationship between preexisting anxiety and catastrophizing and both acute and chronic pain is established for other surgical incisions.[17,18] Further study is required to determine whether these risk factors are fixed or whether some (*e.g.*, state anxiety) can be modified, for example, by pregabalin.

A unique opportunity exists to translate the findings of this study into clinical practice, because cardiac surgery is the only adult discipline that still routinely administers anxiolytic premedication to patients before transfer to the operating room. Currently these are benzodiazepine or opioid-based, but with pregabalin ranked first in terms of patient tolerability in a recent meta-analysis of anxiolytics,[38] our study could strengthen the case for such a change in clinical practice.

Generalizability and Study Limitations

This study was pragmatic and relatively unrestrictive in terms of the types of cardiac surgeries included and therefore generalizable to other institutions. However, it does reflect the processes and challenges unique to surgery in central London teaching hospitals in the United Kingdom.[39]

Our work has several further limitations. Identical-dose oral pregabalin was administered to all patients rather than titrating for body weight. Although the multivariable model (Supplemental Digital Content, http://links.lww.com/ALN/B934) included weight, there remains a possibility of under- or overdosing in some subjects. This may explain the sedation and diplopia in both active arms and justifies a dose-finding study with smaller doses than the 300 mg/day of pregabalin used in this trial.

Although there was a statistically significant difference in sedation between usual care and both active arms, it could be argued that is unlikely to be of clinical significance (median differences of 0.38 and 0.26). The use of a limited four-point Likert scale may have lowered the sensitivity of measurement for this important side effect. Blinding questionnaires for participant and research assistants would have determined the effectiveness of blinding to treatment allocation and is a limitation of our study design.[40]

The powerful effect of pregabalin in preventing persistent pain made the combined pregabalin–ketamine arm of this trial redundant. A ketamine-only arm might have proved useful in determining the contribution of ketamine to this effect.[12]

Conclusions

We provide evidence for the protective effect of a prolonged regimen of perioperative pregabalin on pain at 3 and 6 months after cardiac surgery. We also present data suggesting that patients with state anxiety, feature of pain catastrophizing, low preoperative quality of life, or decreased response to conditioned pain modulation may be at increased risk of persistent pain. This may warrant focused discussion during informed consent as well as the use of pregabalin, in spite of its potential for short-term side effects.

In addition, postoperative *de novo* signs of new temporal summation and decreased pain thresholds at a site remote to incision may be early warning signs of hyperalgesia and central nervous system sensitization. These signs could also trigger early intervention to prevent pain persistence. Further studies should screen and target these features as a potential means of risk identification and mitigation in all surgical patients.

Research Support

Supported by the European Association of Cardiothoracic Anaesthesiologists (Rome, Italy).

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: s.anwar@qmul.ac.uk. Raw data available at: s.anwar@qmul.ac.uk.

Correspondence

Address correspondence to Dr. Anwar: Barts Heart Centre, King George V Building. St. Bartholomew's Hospital. London EC1A 7BE, United Kingdom. s.anwar@qmul.ac.uk.

References

1. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367:1618–25
2. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS: The neuropathic component in persistent postsurgical pain: A systematic literature review. Pain 2013; 154:95–102
3. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H: Prevalence of and factors associated with

persistent pain following breast cancer surgery. JAMA 2009; 302:1985–92
4. Mejdahl MK, Andersen KG, Gärtner R, Kroman N, Kehlet H: Persistent pain and sensory disturbances after treatment for breast cancer: Six year nationwide follow-up study. BMJ 2013; 346:f1865
5. Pesonen A, Suojaranta-Ylinen R, Hammarén E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH: Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: A randomized placebo-controlled trial. Br J Anaesth 2011; 106:873–81
6. Choinière M, Watt-Watson J, Victor JC, Baskett RJ, Bussières JS, Carrier M, Cogan J, Costello J, Feindel C, Guertin MC, Racine M, Taillefer MC: Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: A 2-year prospective multicentre study. CMAJ 2014; 186:E213–23
7. Turan A, Karimi N, Zimmerman NM, Mick SL, Sessler DI, Mamoun N: Intravenous acetaminophen does not decrease persistent surgical pain after cardiac surgery. J Cardiothorac Vasc Anesth 2017; 31:2058–64
8. Turk DC, Wilson HD, Cahana A: Treatment of chronic non-cancer pain. Lancet 2011; 377:2226–35
9. Ryan NM, Birring SS, Gibson PG: Gabapentin for refractory chronic cough: A randomised, double-blind, placebo-controlled trial. Lancet 2012; 380:1583–9
10. Kehlet H, Rathmell JP: Persistent postsurgical pain: The path forward through better design of clinical studies. Anesthesiology 2010; 112:514–5
11. Gilron I: Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: Current evidence and future directions. Curr Opin Anaesthesiol 2007; 20:456–72
12. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev. 2013; 7:CD008307
13. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL: Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. Lancet 2009; 374:1252–61
14. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL: Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005; 352:1324–34
15. Gilron I, Jensen TS, Dickenson AH: Combination pharmacotherapy for management of chronic pain: From bench to bedside. Lancet Neurol 2013; 12:1084–95
16. Johansen A, Schirmer H, Stubhaug A, Nielsen CS: Persistent post-surgical pain and experimental pain sensitivity in the Tromsø study: Comorbid pain matters. Pain 2014; 155:341–8
17. Kalkman CJ, Visser K, Moen J, Bonsel GJ, Grobbee DE, Moons KG: Preoperative prediction of severe postoperative pain. Pain 2003; 105:415–23
18. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA: Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain 2012; 28:819–41
19. Yarnitsky D: Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010; 23:611–5
20. Woolf CJ: Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2011; 152(3 Suppl):S2–15
21. Weissman-Fogel I, Granovsky Y, Crispel Y, Ben-Nun A, Best LA, Yarnitsky D, Granot M: Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. J Pain 2009; 10:628–36
22. Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, Bittner R, Kehlet H: Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010; 112:957–69
23. Moore RA, Straube S, Aldington D: Pain measures and cut-offs: "No worse than mild pain" as a simple, universal outcome. Anaesthesia 2013; 68:400–12
24. Cole TJ: Setting number of decimal places for reporting risk ratios: Rule of four. BMJ 2015; 350:h1845
25. Mishriky BM, Waldron NH, Habib AS: Impact of pregabalin on acute and persistent postoperative pain: A systematic review and meta-analysis. Br J Anaesth 2015; 114:10–31
26. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M: Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain 2008; 138:22–8
27. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN: Rates and risk factors for prolonged opioid use after major surgery: Population based cohort study. BMJ 2014; 348:g1251
28. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, Fox KP, Knecht DB, McMahill-Walraven CN, Palmer N, Kohane I: Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: Retrospective cohort study. BMJ 2018; 360:j5790
29. Landoni G, Isella F, Greco M, Zangrillo A, Royse CF: Benefits and risks of epidural analgesia in cardiac surgery. Br J Anaesth 2015; 115:25–32
30. Martinez V, Fletcher D: Prevention of opioid-induced hyperalgesia in surgical patients: Does it really matter? Br J Anaesth 2012; 109:302–4
31. Colvin LA, Fallon MT: Opioid-induced hyperalgesia: A clinical challenge. Br J Anaesth 2010; 104:125–7

32. Angst MS, Clark JD: Opioid-induced hyperalgesia: A qualitative systematic review. Anesthesiology 2006; 104:570–87
33. Kwanten LE, O'Brien B, Anwar S: Opioid-based anesthesia and analgesia for adult cardiac surgery: History and narrative review of the literature. J Cardiothorac Vasc Anesth 2019; 33:808–16
34. Gilron I, Kehlet H: Prevention of chronic pain after surgery: New insights for future research and patient care. Can J Anaesth 2014; 61:101–11
35. 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
36. Bruce J, Krukowski ZH: Quality of life and chronic pain four years after gastrointestinal surgery. Dis Colon Rectum 2006; 49:1362–70
37. Bruce J, Thornton AJ, Powell R, Johnston M, Wells M, Heys SD, Thompson AM, Cairns Smith W, Chambers WA, Scott NW; Recovery Study Group: Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. Pain 2014; 155:232–43
38. Baldwin D, Woods R, Lawson R, Taylor D: Efficacy of drug treatments for generalised anxiety disorder: Systematic review and meta-analysis. BMJ 2011; 342:d1199
39. Wong DJN, Harris SK, Moonesinghe SR; SNAP-2: EPICCS collaborators; Health Services Research Centre, National Institute of Academic Anaesthesia; Study Steering Group; Net Solving Limited; Trainee Research Networks; Abertawe Bro Morgannwg University Health Board; Aintree University Hospitals NHS Foundation Trust; Airedale NHS Foundation Trust; Aneurin Bevan Health Board; Ashford and St. Peters NHS Foundation Trust; Barking, Havering and Redbridge University Hospitals NHS Trust; Barnsley Hospital NHS Foundation Trust; Barts Health NHS Trust; Basildon and Thurrock University Hospitals NHS Foundation Trust; Bedford Hospital NHS Trust; Belfast Health and Social Care Trust; Betsi Cadwaladr University Health Board; Birmingham Women's NHS Foundation Trust; Blackpool Teaching Hospitals NHS Foundation Trust; Bolton Hospital NHS Foundation Trust; Bradford Teaching Hospitals NHS Foundation Trust; Brighton and Sussex University Hospitals NHS Trust; Buckinghamshire Healthcare NHS Trust; Burton Hospitals NHS Foundation Trust; Calderdale and Huddersfield NHS Foundation Trust; Cambridge University Hospitals NHS Foundation Trust; Cardiff and Vale University Health Board; Central Manchester University Hospitals NHS Foundation Trust; Chelsea and Westminster Hospital NHS Foundation Trust; Chesterfield Royal Hospital NHS Foundation Trust; Christie Hospital NHS Foundation Trust; City Hospitals Sunderland NHS Foundation Trust; Colchester Hospital University NHS Foundation Trust; Countess of Chester NHS Foundation Trust; County Durham and Darlington NHS Foundation Trust; Croydon Health Services NHS Trust; Cwm Taf University Health Board; Dartford and Gravesham NHS Trust; Derby Hospitals NHS Foundation Trust; Doncaster and Bassetlaw Hospitals NHS Foundation Trust; Dorset County Hospital NHS Foundation Trust; Dudley Group NHS Foundation Trust; East and North Hertfordshire NHS Trust; East Kent Hospitals University NHS Foundation Trust; East Lancashire Hospitals NHS Trust; East Sussex Healthcare NHS Trust; Epsom and St. Helier University Hospitals NHS Trust; Frimley Health NHS Foundation Trust; Gateshead Health NHS Foundation Trust; Gloucestershire Hospitals NHS Foundation Trust; Great Western Hospitals NHS Foundation Trust; Guy's and St. Thomas' NHS Foundation Trust; Hampshire Hospitals NHS Foundation Trust; Harrogate and District NHS Foundation Trust; Heart Of England NHS Foundation Trust; Hillingdon Hospitals NHS Foundation Trust; Homerton University Hospital NHS Foundation Trust; Hull and East Yorkshire Hospitals NHS Trust; Hywel Dda Health Board; Imperial College Healthcare NHS Trust; Ipswich Hospital NHS Trust; Isle of Wight NHS Trust; James Paget University Hospitals NHS Foundation Trust; Kettering General Hospital NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Kingston Hospital NHS Foundation Trust; Lancashire Teaching Hospitals NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust; Lewisham and Greenwich NHS Trust; Liverpool Women's NHS Foundation Trust; Luton and Dunstable University Hospital NHS Foundation Trust; Medway NHS Foundation Trust; Mid Cheshire Hospitals NHS Foundation Trust; Mid Essex Hospital Services NHS Trust; Mid Yorkshire Hospitals NHS Trust; Milton Keynes University Hospital NHS Foundation Trust; Newcastle upon Tyne Hospitals NHS Foundation Trust; NHS Ayrshire and Arran; NHS Dumfries and Galloway; NHS Fife; NHS Greater Glasgow and Clyde; NHS Highland; NHS Lanarkshire; NHS Lothian; NHS Scotland Special Board; NHS Shetland; NHS Tayside; Norfolk and Norwich University Hospitals NHS Foundation Trust; Northampton General Hospital NHS Trust; North Bristol NHS Trust; North Cumbria University Hospitals NHS Trust; Northern Devon Healthcare NHS Trust; Northern Health and Social Care Trust; Northern Lincolnshire and Goole Hospitals NHS Foundation Trust; North Middlesex University Hospital NHS Trust; North Tees and Hartlepool NHS Trust; Northumbria Healthcare NHS Foundation Trust; North West Anglia NHS Foundation Trust;

Nottingham University Hospitals NHS Trust; Oxford University Hospitals NHS Foundation Trust; Papworth Hospital NHS Foundation Trust; Pennine Acute NHS Trust; Plymouth Hospitals NHS Trust; Poole Hospital NHS Foundation Trust; Portsmouth Hospitals NHS Trust; Princess Alexandra Hospital NHS Trust; Queen Elizabeth Hospital NHS Foundation Trust; Queen Victoria Hospital NHS Foundation Trust; Robert Jones and Agnes Hunt Orthopaedic Hospital Foundation Trust; Rotherham NHS Foundation Trust; Royal Berkshire NHS Foundation Trust; Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust; Royal Cornwall Hospitals NHS Trust; Royal Devon and Exeter NHS Foundation Trust; Royal Free London NHS Foundation Trust; Royal Liverpool and Broadgreen University Hospitals NHS Trust; Royal Marsden NHS Foundation Trust; Royal National Orthopaedic Hospital NHS Trust; Royal Orthopaedic Hospital NHS Foundation Trust; Royal Surrey County Hospital NHS Foundation Trust; Royal United Hospitals Bath NHS Trust; Royal Wolverhampton Hospitals NHS Trust; Salford Royal NHS Foundation Trust; Salisbury NHS Foundation Trust; Sandwell and West Birmingham Hospitals NHS Trust; Sheffield Teaching Hospitals NHS Foundation Trust; Shrewsbury and Telford Hospital NHS Trust; South Eastern Health and Social Care Trust; Southport and Ormskirk Hospital NHS Trust; South Tees Hospitals NHS Foundation Trust; South Tyneside NHS Foundation Trust; South Warwickshire NHS Foundation Trust; St. George's Healthcare NHS Trust; St. Helens and Knowsley Teaching Hospitals NHS Trust; Stockport NHS Foundation Trust; Surrey and Sussex Healthcare NHS Trust; Tameside Hospital NHS Foundation Trust; Taunton and Somerset NHS Foundation Trust; Torbay and South Devon NHS Foundation Trust; United Lincolnshire Hospitals NHS Trust; University College London Hospitals NHS Foundation Trust; University Hospital of North Midlands NHS Trust; University Hospital of South Manchester NHS Foundation Trust; University Hospitals Birmingham NHS Foundation Trust; University Hospitals Bristol NHS Foundation Trust; University Hospitals Coventry and Warwickshire NHS Trust; University Hospitals of Leicester NHS Trust; University Hospitals of Morecambe Bay NHS Foundation Trust; University Hospital Southampton NHS Foundation Trust; Walsall Healthcare NHS Trust; Warrington and Halton Hospitals NHS Foundation Trust; Western Health and Social Care Trust; Western Sussex Hospitals NHS Foundation Trust; West Herts Hospitals NHS Trust; Weston Area Health NHS Trust; West Suffolk NHS Foundation Trust; Whittington Hospital NHS Trust; Wirral University Teaching Hospital NHS Foundation Trust; Worcestershire Acute Hospitals NHS Trust; Wrightington, Wigan and Leigh NHS Foundation Trust; Wye Valley NHS Trust; Yeovil District Hospital NHS Foundation Trust; York Teaching Hospital NHS Foundation Trust: Cancelled operations: A 7-day cohort study of planned adult inpatient surgery in 245 UK National Health Service hospitals. Br J Anaesth 2018; 121:730–8

40. Vase L, Amanzio M, Price DD: Nocebo *vs.* placebo: The challenges of trial design in analgesia research. Clin Pharmacol Ther 2015; 97:143–50