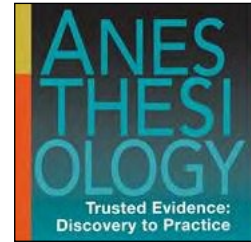


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Gabapentin for pain management following major surgery: a placebo controlled, double blind, randomized clinical trial (The GAP Study)



Sarah Baos, PhD, Mandy Lui, MSc, Terrie Walker-Smith, BSc, Maria Pufulete, PhD, David Messenger, FRCS, Reyad Abbadi, FRCS, Tim Batchelor, FCRS, Gianluca Casali, FRCS, Mark Edwards, MD FRCA, Nick Goddard, FRCA, Mohammed Abu Hilal, FRCS, Aiman Alzetani, FRCS, Marius Vaida, FRCA, Petr Martinovsky, FRCA, Palinikumar Saravanan, FRCA, Tim Cook, FRCA, Rajiv Malhotra, FRCA, Anna Simpson, PhD FRCA, Ross Little, FRCA, Sarah Wordsworth, PhD, Elizabeth Stokes, DPhil, Jingjing Jiang Eu-HEM, Barnaby Reeves, PhD, Lucy Culliford, PhD, Laura Collett, MSc, Rachel Maishman, PhD, Nilesch Chauhan, FRCA, Liz McCullagh, MPharm, Holly McKeon, MRes, Samantha Abbs, MPharm, Jenny Lamb, BA, Anna Gilbert, BSc, Chloe Hughes, David Wynick, PhD FRCP, Gianni Angelini, MD FRCS, Mike Grocott, MD FRCA FFICM FRCP, Ben Gibbison, MD FRCA FFICM, Chris A Rogers, PhD

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Gabapentin for pain management following major surgery: a placebo controlled, double blind, randomized clinical trial (The GAP Study)

Sarah Baos PhD (University of Bristol), Mandy Lui MSc (University of Bristol), Terrie Walker-Smith BSc (University of Bristol), Maria Pufulete PhD (University of Bristol), David Messenger FRCS (University Hospitals Bristol and Weston NHS Foundation Trust), Reyad Abbadi FRCS (University Hospitals Bristol and Weston NHS Foundation Trust), Tim Batchelor FRCS (University Hospitals Bristol and Weston NHS Foundation Trust), Gianluca Casali FRCS (University Hospitals Bristol and Weston NHS Foundation Trust), Mark Edwards MD FRCA (University of Southampton), Nick Goddard FRCA (University Hospital Southampton NHS Foundation Trust), Mohammed Abu Hilal FRCS (University Hospital Southampton NHS Foundation Trust), Aiman Alzetani FRCS (University Hospital Southampton NHS Foundation Trust), Marius Vaida FRCA (Somerset Hospitals Foundation NHS Trust), Petr Martinovsky FRCA (University Hospitals Blackpool NHS Trust), Palinikumar Saravanan FRCA (University Hospitals Blackpool NHS Trust), Tim Cook FRCA (Royal United Hospitals, Bath NHS Trust), Rajiv Malhotra FRCA (University Hospitals Liverpool NHS Trust), Anna Simpson PhD FRCA (University Hospitals Bristol and Weston NHS Foundation Trust), Ross Little FRCA (University Hospitals Liverpool NHS Trust), Sarah Wordsworth PhD (University of Oxford), Elizabeth Stokes DPhil (University of Oxford), Jingjing Jiang Eu-HEM (University of Oxford) Barnaby Reeves PhD (University of Bristol), Lucy Culliford PhD (University of Bristol), Laura Collett MSc (University of Bristol), Rachel Maishman PhD (University of Bristol), Nilesh Chauhan FRCA (University Hospitals Bristol and Weston NHS Foundation Trust), Liz McCullagh MPharm (University Hospitals Bristol and Weston NHS Foundation Trust), Holly McKeon MRes (University of Bristol), Samantha Abbs MPharm (University of Bristol), Jenny Lamb BA (University of Bristol), Anna Gilbert BSc (University of

Bristol), Chloe Hughes (University of Bristol), David Wynick PhD FRCP (University of Bristol and University Hospitals Bristol and Weston NHS Foundation Trust), Gianni Angelini MD FRCS (University of Bristol), Mike Grocott MD FRCA FFICM FRCP (University of Southampton), Ben Gibbison MD FRCA FFICM (University of Bristol), Chris A Rogers PhD (University of Bristol) **for the GAP Investigators**

Corresponding Author Dr Ben Gibbison Department of Anaesthesia Level 7, Bristol Royal Infirmary Marlborough Street Bristol, BS2 8HW +44 117 455 1272 Email: ben.gibbison@bristol.ac.uk

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Abbreviated Title: Gabapentin for post-surgical pain

Summary Statement: In this randomized controlled trial of gabapentin versus placebo in 1196 patients undergoing major surgery, the addition of gabapentin to usual care did not affect length of stay, pain, opiate use or quality of life.

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Conflicts of Interest: TB has received speaker fees / advisory board fees from: JnJ, Medtronic and Bristol Myers Squibb. ME has received an honorarium for a lecture from Edwards Lifesciences. MG declares the following conflicts of interest: Edwards Lifesciences (consultancy/medical advisory board);

GC left employment at the institution at which the study was being conducted during the trial. He is now employed by JnJ Med Tech.

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Abbreviations and acronyms: BPI – Brief Pain Index

CI – Confidence Interval

EQ-5D-5L - 5 Level EQ-5D

IQR – Interquartile range

IV - Intravenous

MedDRA – Medical Dictionary for Regulatory activities

NHS – National Health Service

NICE – National Institute of Health and Care Excellence

NRS – Numerical Rating Score

SAE – Serious Adverse Event

SF-12 - Short-form-12

UK – United Kingdom

US – United States of America

ABSTRACT

Background

Gabapentin is an anticonvulsant medication with approval for use in neuropathic pain and epileptic disorders. It is frequently added to multimodal analgesic regimens during and after surgery to reduce opioid use while controlling pain effectively. There is little evidence to show its effectiveness in major surgery.

Methods

In this multicenter, double blinded, randomized controlled trial, adults undergoing major cardiac, thoracic or abdominal surgery were randomized to receive either gabapentin (600mg before surgery, 300mg twice daily for 2 days after surgery) or placebo. The primary outcome was length of hospital stay. Secondary outcomes included acute and chronic pain, total opioid use, adverse health events and health related quality of life. Patients were followed up daily in-hospital until discharge and then at 4-weeks and 4 months after surgery.

Results

1196 participants were randomized (500 underwent cardiac, 346 thoracic and 350 abdominal surgery); 596 were allocated to placebo and 600 were allocated to gabapentin. Median length of hospital stay was similar in the two groups (gabapentin 5.94 (IQR 4.08-8.04) days, placebo 6.15 (IQR 4.22 – 8.97) days; hazard ratio 1.07, 95%CI 0.95-1.20, $p=0.26$). Overall, 384 participants experienced one or more serious adverse events (gabapentin 189/596, 31.7%; placebo 195/599, 32.6%), with some variation across surgical specialties.

Conclusions

Among patients undergoing major cardiac, thoracic and abdominal surgery, adding gabapentin to multimodal analgesic regimes did not alter the length of hospital stay, or the number of serious adverse events.

INTRODUCTION

Gabapentin is an anticonvulsant medication with US and UK regulatory approval to treat partial seizures and neuropathic pain. It reduces voltage-gated calcium channel activity in the central neurons and therefore reduces neuronal firing and neurotransmitter release¹⁻³. It is widely used “off license” in the peri-operative setting as an adjunct to opioid analgesia, and its use in this setting has risen substantially in many countries⁴⁻⁶. Opioids are the mainstay for managing moderate to severe pain after major surgery, but they have poor efficacy for movement-associated pain and up to 80% of patients experience side-effects including confusion, nausea, vomiting, itching, constipation and respiratory depression⁷. The rationale for using gabapentin is that it reduces opioid use, and hence opioid-related adverse effects and promotes rapid early recovery and discharge. However, there have been concerns about the trade-off between the potential adverse effects of gabapentinoids (e.g. risk of abuse and respiratory depression) and their clinical benefits⁸⁻¹³.

More than 280¹⁴ randomized controlled trials have compared gabapentin with placebo in different surgical populations. Most are small and highly heterogeneous, both statistically and clinically. Gabapentin can reduce opiate use by around 20% in the first 24 hours after surgery¹⁴. However, there is inadequate information regarding the number and impact of adverse events and Quality of Life, preventing policy decisions being made¹⁵. This has led to varying guidance: Gabapentin is included as a “strong recommendation” as a component of multi-modal analgesia for the management of postoperative pain in the US¹⁶, but not in Europe¹⁷.

In the GAP Study, we tested the hypothesis that gabapentin reduces opioid use after surgery and speeds up recovery, therefore reducing post-operative hospital stay compared to standard multimodal analgesia (usual care).

MATERIALS and METHODS

Trial design and oversight

The GAP study was a multicenter parallel group, placebo-controlled, pragmatic randomized controlled trial to compare the effectiveness, cost-effectiveness and safety of gabapentin as an adjunct to standard multimodal analgesia. Participants, clinical care teams and research teams were blinded to the treatment allocation. The trial protocol has been published previously¹⁸ and was approved by a National Health Service (NHS) Research Ethics Committee (Sheffield, UK), the UK Health Research Authority and the Medicines and Healthcare products Regulatory Authority. It was registered with the ISRCTN (ISRCTN63614165). All participants provided written informed consent.

Patients

Adults aged 18 years or older undergoing non-emergency cardiac, thoracic or abdominal surgery were screened. Patients were expected to require a postoperative hospital stay of at least 2 days and be able to swallow during the intervention delivery period. Patients who were already taking anti-epileptic medication (including gabapentinoids), had a known allergy to gabapentin, renal impairment (an estimated glomerular filtration rate <30 mL/min/1.73) or weighed less than 50kg were excluded.¹⁸

Trial procedures

Participants were allocated in a 1:1 ratio to gabapentin or placebo using a secure internet-based randomization system. Randomization was stratified by surgical specialty and site to ensure approximately equal allocation to gabapentin and placebo in each specialty and site. Allocations were permuted blocks of varying sizes, i.e. blocks of 4, 6 or 8..

The gabapentin group received 600mg gabapentin preoperatively (as close to surgery as possible) and 600 mg/day (300 mg twice daily) postoperatively for 2 days, once able to swallow (i.e. following extubation). The placebo group were given identical capsules at the same dosing intervals. The dose and timing of the treatment were informed by the findings and recommendations from the most recent

systematic review available at the time the study was designed¹⁹. Dosing windows were classified as 6 hours either side of the prescribed time-point. Other analgesia prescribed (i.e. the standard multimodal regimen used) was at the discretion of the treating clinician.

Outcomes

Patients were followed up daily whilst *in-hospital* and then at 4 weeks and 4 months after the surgery. The primary outcome was length of hospital stay, defined as time from end of surgery to hospital discharge. Secondary outcomes were: i) opioid consumption from surgery until hospital discharge, and from discharge until 4 months – all were converted to intravenous (IV) morphine equivalents; ii) acute pain assessed using the numerical rating scale (NRS) completed at 1, 4 and 12 hours postoperatively, and then twice daily until discharge; iii) chronic pain measured at baseline, 4 weeks and 4 months using the Brief Pain Inventory²⁰; iv) adverse health events (any unfavorable or unintended health event) recorded from randomization to discharge and serious adverse events (SAEs, which resulted in death or prolonged hospitalization, were life-threatening, or resulted in persistent or significant disability/incapacity) from randomization until 4 months post-operatively; and v) health-related quality of life measured using the EQ-5D-5L²¹ and Short-form-12 (SF-12)²² questionnaires completed at baseline and 4 weeks and 4 months. Resource use data were also collected to support the cost-effectiveness analyses (reported separately).

Statistical analysis and Sample size

The planned sample size was 1500 participants (750 per group), with a minimum 376 participants per surgical specialty, which provided 90% power to detect a 12.5% difference in the proportion of participants discharged by the median specialty-specific length of hospital stay (i.e. 50% in the placebo group versus 62.5% in the gabapentin group). The sample size was reduced to a minimum of 340 participants per surgical specialty (1020 participants) following recruitment difficulties due to the

COVID-19 pandemic. This provided 80% power to detect the target 12.5% difference, allowing for an observed non-compliance rate of 27%.

Analyses were by intention-to-treat. The primary outcome was compared between groups using Cox proportional hazards regression, stratified by specialty and site. *In-hospital* deaths were censored at the specialty-specific maximum observed time-to-discharge for survivors. Withdrawals before discharge were censored at withdrawal. Model assumptions were assessed graphically (see supplement for further detail, <https://links.lww.com/ALN/E128>).

Secondary outcome models included baseline values (where measured), specialty, treatment group and the specialty by treatment group interaction as fixed effects. Longitudinal models also included time, time by treatment group and specialty by time by treatment group as fixed effects, with site and participant fitted as random effects. For NRS scores, the fixed effect for time was modelled using fractional polynomial functions and time (at the participant level) was also included as a random effect. Linear mixed models were used to compare NRS and quality of life scores and a two-part mixed model was used for the Brief Pain Inventory; logistic regression comparing occurrence of pain and log-linear regression for the pain score, when pain is present. Opioid consumption to discharge and from discharge to 4 months were compared between groups using log-linear and linear models respectively. The incidence of one or more SAEs was compared using generalized linear models to obtain risk differences and risk ratios. Results for the whole study (i.e. all specialties combined) are presented when a treatment group by specialty interaction was not indicated. Similarly, for longitudinal outcomes an overall treatment difference is given if differences over time were not indicated.

Subgroup analyses of the primary outcome by sex, minimally invasive versus open surgery, and randomization before or after the start of COVID-19 pandemic, were performed by adding subgroup and a subgroup by treatment group interaction to the model. Sensitivity analyses of the primary outcome excluded ineligible participants and participants from one site where there were concerns over data

quality. The placebo is the reference group for all analyses. Results are presented as treatment effects with 95% confidence intervals without adjustment. All statistical analyses were performed using Stata software, version 17.0 (StataCorp, College Station, Texas). Further analytical details are given in the supplement.

RESULTS

Participants

Between April 2018 and May 2022, 3405 patients were assessed for eligibility in seven UK NHS hospitals, of whom 2209 were excluded. Reasons for exclusion can be found in the Supplementary Material. Therefore, 1196 participants were randomized into the study (596 allocated to placebo and 600 to gabapentin, Figure 1). Follow-up data at 4 weeks and 4 months were available for 1153/1196 (96.4%) and 1120/1196 (93.6%) randomized participants respectively. Baseline characteristics were well balanced across the groups; the median age was 68 (interquartile range [IQR] 60 to 74) years, male sex 794/1195, 66.4%, 1174/1193, 98.4% white/Caucasian ethnicity and median body mass index, 27.3 (24.4 to 30.9) kg/m² (Table 1 and Supplementary Table 1, <https://links.lww.com/ALN/E128>).

One participant withdrew consent for their data to be used. The analysis population was therefore 1195 participants. In total, 957/1195 (80.1%) participants received all trial medication per protocol (487/596, 81.7% in the placebo group and 470/599, 78.5% in the gabapentin group). The most common protocol deviation was participants receiving fewer than the prescribed 6 capsules of trial medication or receiving medication outside of the dosing window (99/596, 16.6% placebo, 124/599, 20.7% gabapentin).

In total, 27 participants withdrew after randomization; 13 participant decisions after surgery (one participant moved to a non-participating institution and 12 withdrew from follow-up), two due to clinicians deeming the participant no longer eligible and 12 did not undergo surgery in the trial.

Length of Hospital Stay

Six participants died before discharge, 4 in the cardiac specialty (1 placebo, 3 gabapentin) and 2 in the thoracic specialty (both gabapentin). Those in the placebo group stayed a median 6.15 (IQR 4.22 to 8.97) days, and those in the gabapentin group stayed a median 5.94 (IQR 4.08 to 8.04) days post-operatively (hazard ratio 1.07, 95% Confidence Interval [CI] 0.95 to 1.20, $p=0.26$, Figure 2a). The hazard ratio for hospital discharge was similar across the 3 surgical specialties ($p=0.94$). The target of a 12.5% difference in the proportion discharged within 5 days (cardiac and abdominal specialties) or 3 days (thoracic specialty) between the groups was not met in any specialty (Table 2). The sensitivity analyses did not impact the conclusion (Supplementary Table 2, <https://links.lww.com/ALN/E128>) and no subgroup differences were identified (Figure 2b -2d, Supplementary Table 3, <https://links.lww.com/ALN/E128>).

Opioid consumption

In participants undergoing cardiac surgery, there was no difference in the use of opioids, either immediately post-operatively or during follow-up. In patients undergoing thoracic surgery, participants in the gabapentin group used less opioid medication than those in the placebo group on the day of surgery and for the first 2 post-operative days (day 1: geometric mean 9.4mg versus 13.4mg IV morphine equivalents; ratio 0.73, 95%CI 0.54, 0.99), but not thereafter. Except for day 3, participants undergoing abdominal surgery used less opioid medication post-operatively (day 1: 8.5mg versus 13.8mg IV morphine equivalents; ratio 0.67, 95%CI 0.50, 0.90) but not following hospital discharge (Figure 3 and Supplementary Table 4, <https://links.lww.com/ALN/E128>). A summary of all analgesics and adjuvants used by study participants is contained in Supplementary Table 6 (<https://links.lww.com/ALN/E128>).

Pain

The maximum differences in pain measured using the NRS were within the first 24 hours after surgery. The gabapentin group had pain scores of -0.81 (95%CI -1.12 to -0.51) points lower at rest and -0.82 (95%CI -1.20 to -0.44) points lower on movement at 1 hour after the surgery. This difference reduced towards zero thereafter. At 120 hours after the surgery, mean differences were -0.040 (95%CI -0.19 to 0.11) points at rest and 0.032 (95%CI -0.15 to 0.22) points on movement. The pattern was the same across the three surgical specialties (Supplementary Table 5, <https://links.lww.com/ALN/E128>).

The number of participants reporting pain after hospital discharge was higher in the gabapentin group compared to the placebo group at both 4 weeks (63.4% versus 53.3%) and 4 months (40.6% versus 33.2%) after the surgery. However, where pain was reported, the severity of the pain was similar in the two groups (geometric mean ratio 0.99, 95% CI 0.90 to 1.08). (Supplementary Table 6, <https://links.lww.com/ALN/E128>).

Quality of life

The gabapentin group had a similar EQ-5D-5L utility score to the placebo group at 4 weeks and 4 months (mean difference -0.014, 95%CI -0.033 to 0.005) and a -0.87 (95%CI -1.71 to -0.04) point lower SF-12 physical component score. For the SF-12 mental the component the mean difference was 0.74 (95%CI -0.39 to 1.87) points at 4 weeks and -0.55 (95%CI -1.61 to 0.51) at 4 months (Supplementary Table 7, <https://links.lww.com/ALN/E128>).

Safety

Overall, 1453 adverse events were reported in 433 participants in the placebo group compared to 1488 adverse events in 420 participants in the gabapentin group. In addition to these adverse events, 414 SAEs in 189 ((31.7%) participants were reported in the placebo group and 505 SAEs in 195 (32.5%) participants were reported in the gabapentin group. Three SAEs (loss of consciousness, respiratory depression, and vomiting) in the gabapentin group were classified as possible serious adverse reactions

to the intervention. All resolved without sequelae. The remaining SAEs were classified as “not related” (565, 61.5%) or “unlikely to be related” (350, 38.1%). There were 18 deaths: 8 in the placebo group and 10 in the gabapentin group. Details of all adverse events are available in Supplementary Tables 8 and 9 (<https://links.lww.com/ALN/E128>).

DISCUSSION

Statement of principal findings

The GAP Study has shown that among patients undergoing major surgery, the addition of gabapentin (600mg pre-operatively and 300mg twice a day postoperatively two days) to multimodal analgesic regimes did not reduce hospital length of stay or improve quality of life after surgery. Participants in the gabapentin group used one-quarter to one-third less opioid medication in-hospital and reported slightly less pain in the first 24 hours after surgery, although the reduction in pain was well below the minimal clinically important difference. The small reductions in opioid use did not translate into fewer adverse events. There was no difference in opioid consumption after discharge. Participants who took gabapentin had a higher incidence of pain at 4-months, but where pain was reported, at a similar severity to the placebo group.

Interpretation in the context of existing / other evidence

The most recent comprehensive meta-analysis¹⁴, including 281 trials (24,682 participants), showed no clinically meaningful benefit of gabapentinoids on acute or chronic pain after surgery. Only 17/281 (2,463 participants) trials in this meta-analysis examined length of hospital stay. Length of stay is important, as it is reflective of all harms and benefits in the peri- and post-operative period, which are important to both patients and healthcare providers²³. Whilst many studies of gabapentin in the peri-operative period (including the GAP study) report statistically significant differences in pain scores or opioid use, very few show *clinically important* differences in pain (10mm difference on a 100mm visual analogue score²⁴) or time to cessation of pain²⁵. The mean NRS scores in the GAP study were lower in

the gabapentin group at all in-hospital time points. However, at no time-point and in no specialty, at rest or on movement, was the mean difference in NRS more than 1 point on a 10-point scale. Gabapentin also did not improve the incidence of, or the experience of longer-term pain.

The GAP study showed reductions of around one-quarter to one-third in the use of opioids for those undergoing thoracic and abdominal surgery in-hospital. These reductions were most marked during the period of intervention (i.e. for the first 2 days after surgery). However, these reductions were modest when viewed as absolute reductions in opioid use (maximum observed difference: Abdominal surgery, Day 2 post-operatively: Placebo median 21.8 (IQR 9.9 - 40.3) mg IV morphine equivalents versus gabapentin 14.5 (IQR 4.4 - 32.1) mg IV morphine equivalents). The most cited risks of gabapentin in the postoperative period are somnolence and respiratory depression, particularly when combined with opioids. No serious adverse events of somnolence or respiratory depression were reported. Somnolence occurred in four participants (0.7%) randomised to placebo and 11 participants (1.8%) randomised to Gabapentin during the trial. Respiratory depression was reported in three participants overall, one in placebo group (0.2%) and two in Gabapentin group (0.3%). The number of adverse events in the neurological and respiratory MedDRA classes was broadly similar (and inconsistently distributed) between the gabapentin and placebo groups.

Strengths and weaknesses of the study

The major strengths of this study are that it was pragmatic, at low risk of bias and integrated in existing usual care pathways for major surgery across a number of centers. It was also conducted in three major surgical specialties, ensuring findings are generalizable to all major body cavity surgery. No other study of gabapentin in the peri-operative setting has included such a wide variety of surgery types^{14 25}. Most previous studies were limited to a single specialty and in many cases a single operation (e.g. hysterectomy, single joint replacement). Although more participants were recruited from the cardiac (500) than the thoracic (346) and abdominal (350) surgery specialties, the numbers of patients from the

latter two specialties met the minimum number needed to achieve 80% power to detect the target difference in hospital length of stay in each specialty. Therefore, this imbalance in recruitment has no impact on the conclusions.

The GAP study did not test the application of gabapentin to other major non-body cavity surgery (e.g. joint replacement), or non-major (e.g. day-care) surgery. Care pathways and analgesic regimens for these other types of surgery are different and therefore we cannot fully assess the impact of the addition of gabapentin to them. However, given the minimal impact of gabapentin on pain scores within the GAP study, we would not anticipate postoperative pain would be significantly improved in other settings as indicated by the most recent meta-analysis¹⁴.

Other limitations of the trial include the non-variable dose of gabapentin and the restricted period of the intervention. Therefore, we cannot assess the impact of a higher gabapentin dose on pain or the impact of a reduced dose on adverse effects in vulnerable populations such as the elderly and frail. However, since the NRS at rest were below 2/10 (below the acceptable pain score at rest of 3²⁴) and pain scores on movement were below 4/10 from 48 hours after surgery, the impact of prolonged treatment with gabapentin beyond the time-period assessed is likely to be limited.

Implications for clinicians or policymakers

Guidance for use of gabapentin in the peri-operative setting varies: Gabapentin is included as a “strong recommendation” as a component of multi-modal analgesia for the management of postoperative pain in the US¹⁶, but not in Europe¹⁷. The UK National Institute for Health and Care Excellence (NICE) issued a “recommendation for research” for the place of gabapentin in the peri-operative setting¹⁵. The findings of this study, taken together with previous research¹⁴ suggest that gabapentin should not be part of standard peri-operative analgesic regimens for unselected patients undergoing major body-cavity surgery as it provides little benefit for either patients or care providers.

Unanswered questions and future research

The GAP study was not designed to test the place of gabapentin as “rescue” therapy for those whose pain is not controllable using conventional multi-modal analgesia. The place of gabapentin in those with pre-existing and persistent post-surgical pain must also be answered. Therefore, there is potential for studies to investigate the place of gabapentin in this setting. However, the differences in NRS between gabapentin and placebo at rest and on movement were small and clinically insignificant. It is therefore unlikely that it will be effective at controlling pain after major surgery – even as a rescue therapy.

Conclusion

In conclusion, among participants undergoing major cardiac, thoracic and abdominal surgery, the addition of gabapentin to multimodal analgesic regimes did not result in a clinically important change in hospital length of stay, opioid use, acute pain, nor quality of life. Participants who took gabapentin had a higher incidence of pain at 4-months.

Data sharing

Following publication, anonymised individual participant data will be made available upon request to the corresponding author for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council Policy on Data Sharing regarding scientific quality, ethical requirements, and value for money. Only data from participants who have consented for their data to be shared with other researchers will be provided.

Supplemental Digital Content

The GAP Study Protocol, <https://links.lww.com/ALN/E126>

The GAP Study Statistical Analysis Plan (SAP), <https://links.lww.com/ALN/E127>

The GAP Study Supplementary Tables and Acknowledgments, <https://links.lww.com/ALN/E128>

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Table and Figure Legends

Table 1 Recipient characteristics

Data are n/N (%) or median and interquartile range

+ Missing (placebo, gabapentin): cardiac (1, 0) ^ Missing (placebo, gabapentin): cardiac (1, 1)

* Codeine, tramadol, fentanyl, morphine (short acting or prolonged release), oxycodone (short acting or prolonged release), dihydrocodeine, or buprenorphine

ASA = American Society of Anesthesiologists, GI = gastrointestinal, DM = diabetes mellitus

Table 2: Time to hospital discharge after surgery

Hazard ratio for time to discharge from hospital after surgery

N = number, IQR = interquartile range, CI = confidence interval

¹ median length of stay assumed when the study was designed

Figure 1 Participant flow through the trial

Figure 2 Primary outcome – time from surgery to discharge from hospital

Panel a) shows time to discharge by treatment group and surgical speciality. Panels b) to d) show hazard ratios with 95% confidence intervals for time to discharge for the gabapentin group versus the placebo group by sub-group (panel b) – open and minimally invasive surgery, panel c) – male and female recipients, panel d) – surgery pre and post the COVID-19 pandemic).

Figure 3 Opioid consumption following surgery to discharge and during follow-up

GMR = geometric mean ratio, CI = confidence interval

Panels a) to c) show geometric mean ratios with 95% confidence intervals for opioid consumption in the first 5 days following surgery for the gabapentin group versus the placebo group by surgical speciality (panel a) cardiac, panel b) thoracic, panel c) abdominal). Panel d) compares opioid consumption during follow up in the different specialties.

Table 1 Recipient characteristics

	Cardiac (n=499)		Thoracic (n=346)		Abdominal (n=350)		Overall (n=1195)	
Characteristic	Randomized to Placebo (n=249)	Randomized to Gabapentin (n=250)	Randomized to Placebo (n=172)	Randomized to Gabapentin (n=174)	Randomized to Placebo (n=175)	Randomized to Gabapentin (n=175)	Randomized to Placebo (n=596)	Randomized to Gabapentin (n=599)
Demographics								
Age (years) ⁺	70.0 (62, 76)	69.0 (61, 74)	69.0 (60, 75)	67.0 (59, 74)	66 (57, 73)	66 (57, 72)	69 (60, 75)	68 (59, 74)
Male sex	190/249 (76.3%)	196/250 (78.4%)	95/172 (55.2%)	94/174 (54%)	103/175 (58.9%)	116/175 (66.3%)	388/596 (65.1%)	406/599 (67.8%)
White/Caucasian	242/248 (97.6%)	242/249 (97.2%)	171/172 (99.4%)	173/174 (99.4%)	172/175 (98.3%)	174/175 (99.4%)	585/595 (98.3%)	589/598 (98.5%)
Asian/Asian British	3/248 (1.2%)	2/249 (0.8%)	1/172 (0.6%)	0/174 (0.0%)	0/175 (0.0%)	0/175 (0.0%)	4/595 (0.7%)	2/598 (0.3%)
Black/Black British	1/248 (0.4%)	0/249 (0.0%)	0/172 (0.0%)	0/174 (0.0%)	2/175 (1.1%)	1/175 (0.6%)	3/595 (0.5%)	1/598 (0.2%)
Mixed/Multiple/Other ethnic group	2/248 (0.8%)	5/249 (2.0%)	0/172 (0.0%)	1/174 (0.6%)	1/175 (0.6%)	0/175 (0.0%)	3/595 (0.5%)	6/598 (1.0%)
Body mass index [^]	27.4 (24.3,31.3)	27.8 (25.3,30.8)	26.8 (24.1,30.8)	26.2 (23.1,29.7)	27.8 (24.9,31.5)	27.3 (24.6,30.7)	27.4 (24.4, 31.2)	27.1 (24.5, 30.5)
ASA grade								
I	5/245 (2.04%)	1/249 (0.4%)	5/171 (2.9%)	7/174 (4.0%)	8/174 (4.6%)	5/175 (2.9%)	18/590 (3.1%)	13/598 (2.2%)

	Cardiac (n=499)		Thoracic (n=346)		Abdominal (n=350)		Overall (n=1195)	
Characteristic	Randomized to Placebo (n=249)	Randomized to Gabapentin (n=250)	Randomized to Placebo (n=172)	Randomized to Gabapentin (n=174)	Randomized to Placebo (n=175)	Randomized to Gabapentin (n=175)	Randomized to Placebo (n=596)	Randomized to Gabapentin (n=599)
II	22/245 (9.00%)	26/249 (10.4%)	106/171 (62.0%)	104/174 (59.8%)	125/174 (71.8%)	125/175 (71.4%)	253/590 (42.9%)	255/598 (42.6%)
III	203/245 (82.9%)	210/249 (84.3%)	60/171 (35.1%)	63/174 (36.2%)	40/174 (23.0%)	45/175 (25.7%)	303/590 (51.4%)	318/598 (53.2%)
IV	15/245 (6.1%)	12/249 (4.8%)	0/171	0/174	1/174 (0.6%)	0/175	16/590 (2.7%)	12/598 (2.0%)
Medical history								
Non-diabetic	203/248 (81.9%)	204/249 (81.9%)	147/172 (85.5%)	154/173 (89%)	151/175 (86.3%)	151/175 (86.3%)	501/595 (84.2%)	509/597 (85.3%)
DM - oral medication	26/248 (10.5%)	28/249 (11.2%)	15/172 (8.7%)	10/173 (5.8%)	9/175 (5.1%)	12/175 (6.9%)	50/595 (8.4%)	50/597 (8.4%)
DM - injected medication	9/248 (3.6%)	8/249 (3.2%)	6/172 (3.5%)	6/173 (3.5%)	5/175 (2.9%)	9/175 (5.1%)	20/595 (3.4%)	23/597 (3.9%)
DM - diet controlled	10/248 (4.0%)	9/249 (3.6%)	4/172 (2.3%)	3/173 (1.7%)	10/175 (5.7%)	3/175 (1.7%)	24/595 (4.0%)	15/597 (2.5%)
Non-smoker	124/248 (50%)	124/249 (49.8%)	54/172 (31.4%)	52/174 (29.9%)	98/175 (56%)	92/175 (52.6%)	276/595 (46.4%)	268/598 (44.8%)
Ex smoker > 1 month	105/248 (42.3%)	97/249 (39%)	91/172 (52.9%)	83/174 (47.7%)	62/175 (35.4%)	69/175 (39.4%)	258/595 (43.4%)	249/598 (41.6%)

	Cardiac (n=499)		Thoracic (n=346)		Abdominal (n=350)		Overall (n=1195)	
Characteristic	Randomized to Placebo (n=249)	Randomized to Gabapentin (n=250)	Randomized to Placebo (n=172)	Randomized to Gabapentin (n=174)	Randomized to Placebo (n=175)	Randomized to Gabapentin (n=175)	Randomized to Placebo (n=596)	Randomized to Gabapentin (n=599)
Current smoker	19/248 (7.7%)	28/249 (11.2%)	27/172 (15.7%)	39/174 (22.4%)	15/175 (8.6%)	14/175 (8%)	61/595 (10.3%)	81/598 (13.5%)
Medication at baseline								
Any analgesia	120/248 (48.4%)	132/249 (53.0%)	65/172 (37.8%)	70/174 (40.2%)	65/175 (37.1%)	45/175 (25.7%)	250/595 (42.0%)	247/598 (41.3%)
Opioids*	12/120 (10.0%)	20/132 (15.2%)	34/65 (52.3%)	25/70 (35.7%)	21/65 (32.3%)	16/45 (35.6%)	67/250 (26.8%)	61/247 (24.7%)
Anti-depressants	29/248 (11.7%)	26/249 (10.4%)	20/172 (11.6%)	34/174 (19.5%)	19/175 (10.9%)	19/175 (10.9%)	68/595 (11.4%)	79/598 (13.2%)
Surgery received								
Lower GI surgery	-	-	-	-	137/175 (78.3%)	132/175 (75.4%)	137/596 (11.5%)	132/599 (11.0%)
Upper GI surgery	-	-	-	-	38/175 (21.7%)	43/175 (24.6%)	38/596 (3.2%)	43/599 (3.6%)
Open surgery	247/247 (100%)	248/248 (100%)	64/169 (37.9%)	60/173 (34.7%)	93/173 (53.8%)	101/174 (58.0%)	404/589 (68.6%)	409/595 (68.7%)

	Cardiac (n=499)		Thoracic (n=346)		Abdominal (n=350)		Overall (n=1195)	
Characteristic	Randomized to Placebo (n=249)	Randomized to Gabapentin (n=250)	Randomized to Placebo (n=172)	Randomized to Gabapentin (n=174)	Randomized to Placebo (n=175)	Randomized to Gabapentin (n=175)	Randomized to Placebo (n=596)	Randomized to Gabapentin (n=599)
Minimal access surgery	-	-	105/169 (62.1%)	113/173 (65.3%)	80/173 (46.2%)	73/174 (42.0%)	185/589 (31.4%)	186/595 (31.3%)

Data are n/N (%) or median and interquartile range

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* Codeine, tramadol, fentanyl, morphine (short acting or prolonged release), oxycodone (short acting or prolonged release), dihydrocodeine, or buprenorphine

ASA = American Society of Anesthesiologists, GI = gastrointestinal, DM = diabetes mellitus

Table 2: Time to hospital discharge after surgery

Time from surgery to hospital discharge (days)	Randomised to placebo	Randomised to gabapentin	Hazard Ratio (95% CI)	P value
All participants (N)	589	593		
Median (IQR)	6.15 (4.22 – 8.97)	5.94 (4.08 – 8.04)	1.07 (0.95 – 1.20)	0.26
Cardiac (N)	247	248		
Median (IQR)	7.04 (5.38 – 10.24)	6.97 (5.27 – 9.20)	1.07 (0.89 – 1.28)	
Discharged within 5 days ¹	26.3%	27.0%		
Thoracic (N)	169	171		
Median (IQR)	3.99 (2.31 – 6.21)	3.41 (2.93 – 5.25)	1.09 (0.88 – 1.36)	
Discharged within 3 days ¹	48.5%	50.9%		
Abdominal (N)	173	174		
Median (IQR)	6.15 (4.21 – 9.17)	5.35 (4.06 – 8.29)	1.03 (0.83 – 1.29)	
Discharged within 5 days ¹	44.2%	52.3%		
Treatment by specialty interaction				0.94

Hazard ratio for time to discharge from hospital after surgery

N = number, IQR = interquartile range, CI = confidence interval

¹ median length of stay assumed when the study was designed

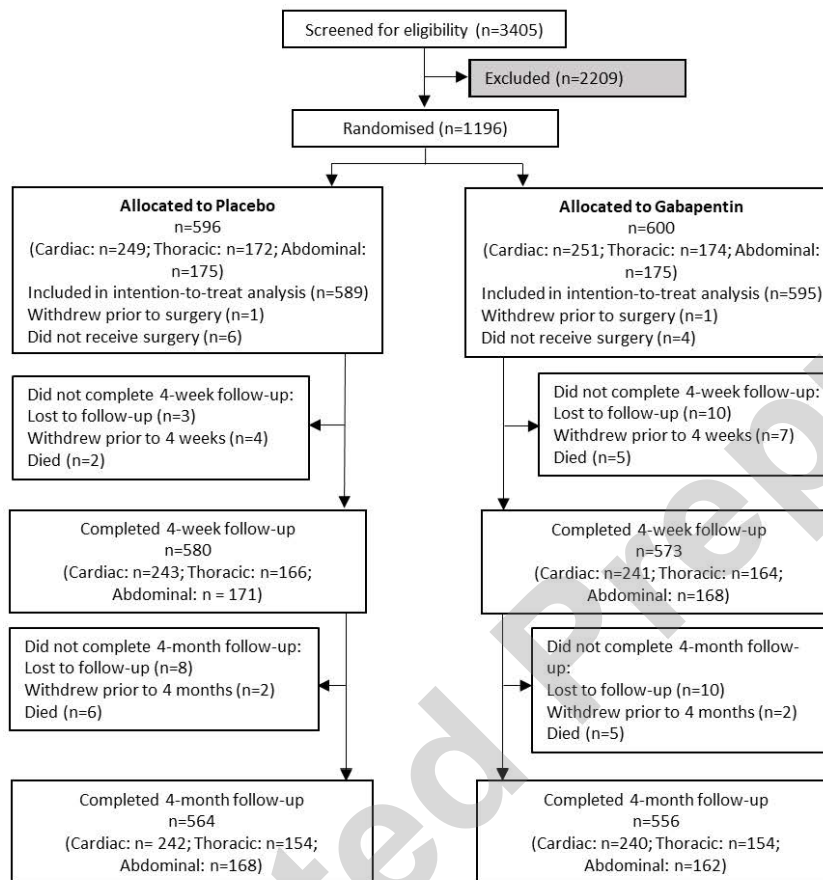


Figure 1 Participant flow through the trial

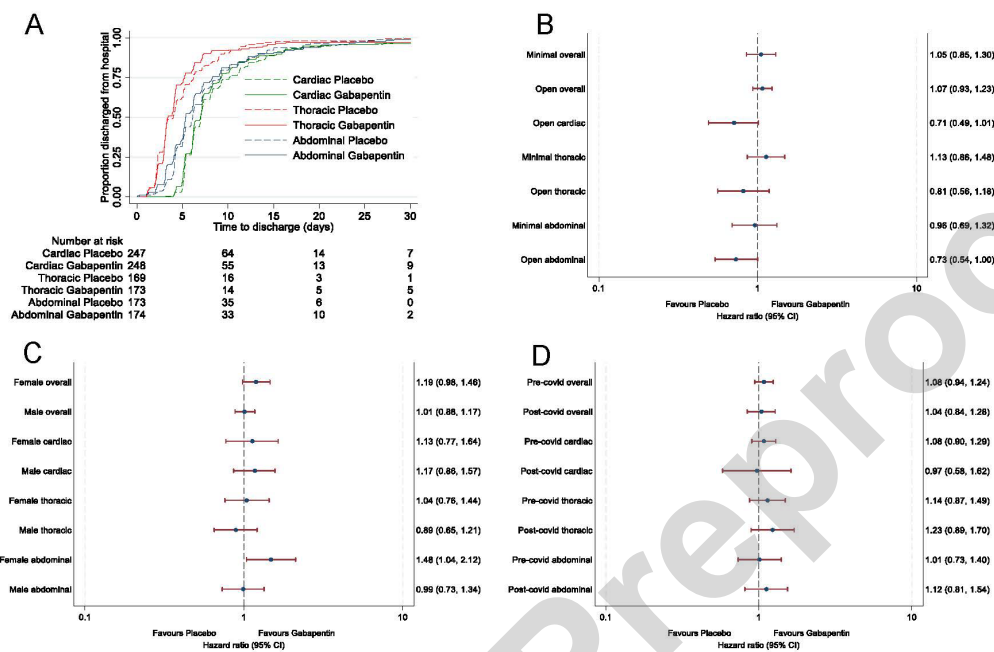


Figure 2 Primary outcome – time from surgery to discharge from hospital

Panel a) shows time to discharge by treatment group and surgical speciality. Panels b) to d) show hazard ratios with 95% confidence intervals for time to discharge for the gabapentin group versus the placebo group by sub-group (panel b) – open and minimally invasive surgery, panel c) – male and female recipients, panel d) – surgery pre and post the COVID-19 pandemic.

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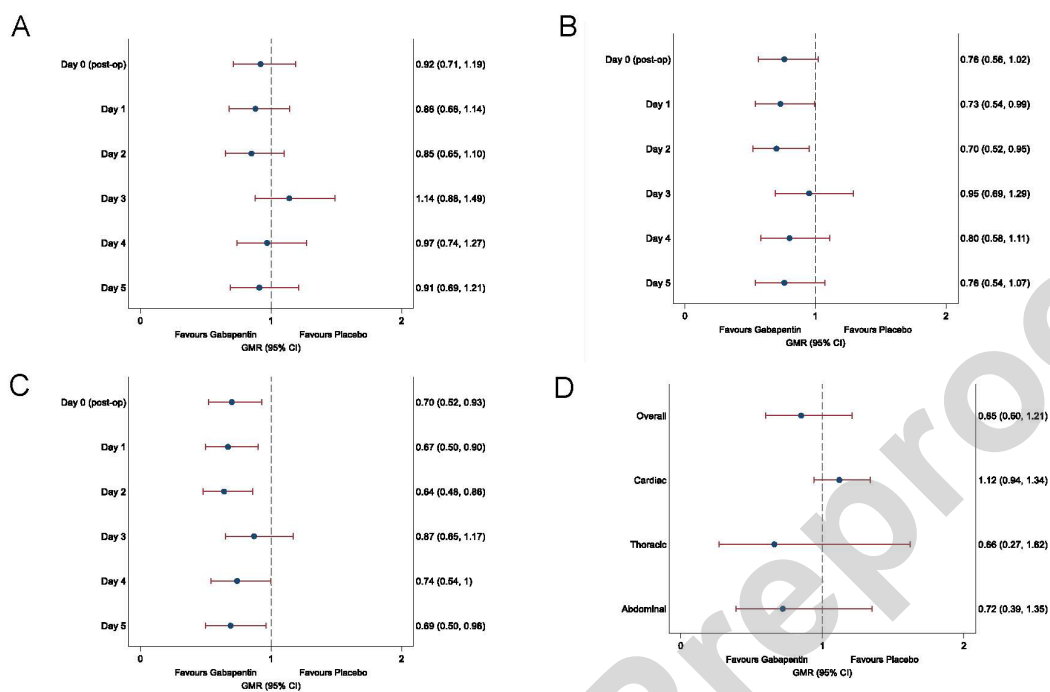


Fig 3. Opioid consumption following surgery to discharge and during follow-up

GMR = geometric mean ratio, CI = confidence interval

Panels a) to c) show geometric mean ratios with 95% confidence intervals for opioid consumption in the first 5 days following surgery for the gabapentin group versus the placebo group by surgical specialty (panel a) cardiac, panel b) thoracic, panel c) abdominal). Panel d) compares opioid consumption during follow-up by specialty.

Accepted Preproof