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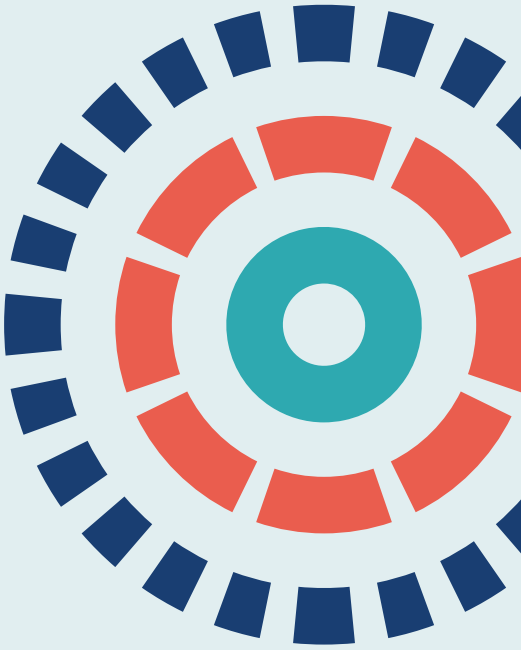

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Abstract

Gabapentin to reduce pain in women aged between 18 and 50 years with chronic pelvic pain: the GaPP2 RCT

Catherine A Hewitt,[1] Katy Vincent,[2] Lee J Middleton,[1] Liana Romaniuk,[3] Magda Koscielniak,[4] Ann M Doust,[4] Judy Birch,[5] Heather Whalley,[3] Jane P Daniels[6,7] and Andrew W Horne[4*] on behalf of the GaPP2 Collaborative Group

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Background: Chronic pelvic pain affects 2–24% of women worldwide, and evidence for medical treatments is limited. Gabapentin is effective in treating some chronic pain conditions, but its effect on central pain processing is unknown.

Objectives: To test the hypothesis that gabapentin can reduce pain and improve physical and emotional functioning in women with chronic pelvic pain. We investigated the mechanism of action of gabapentin in a subset of women.

Design: A randomised, double-blind, placebo-controlled, multicentre trial with a brain imaging substudy.

Setting: This trial took place in 39 UK hospitals.

Participants: A target of 300 women with a history of chronic pelvic pain in whom a laparoscopy revealed no obvious pelvic pathology.

Intervention: Women were randomised to receive 300 mg of gabapentin (which was escalated to a maximum of 2700 mg daily) or a matched placebo over a 4-week dose-escalation period, followed by 12 weeks on optimal dose. A mechanistic substudy was also undertaken, in which a subset of participants had a functional magnetic resonance imaging scan of their brain before and following 16 weeks of treatment.

Main outcome measures: The dual primary measure of the worst and average pelvic pain scores was assessed weekly by a numerical rating scale (0–10) in weeks 13–16 post randomisation. The secondary outcomes were patient-reported questionnaires, assessed physical functioning, fatigue, psychological health, sexual activity, work and productivity, and pain catastrophising. Health-care resource use, analgesic use and adverse events were also collected. The main outcome measure for the mechanistic study was brain activity at rest and in response to noxious stimuli.

Results: In the main trial, 306 participants were randomised. The mean worst pain score was 7.1 (standard deviation 2.6) in the gabapentin group and 7.4 (standard deviation 2.2) in the placebo group (adjusted mean difference −0.20, 97.5% confidence interval −0.81 to 0.42; $p = 0.47$). The mean average pain score was 4.3 (standard deviation 2.3) in the gabapentin group and 4.5 (standard deviation 2.2) in the placebo group (adjusted mean difference −0.18, 97.5% confidence interval −0.71 to 0.35; $p = 0.45$). No significant between-group differences were observed for any secondary outcome. A higher proportion of women experienced a serious adverse event in the gabapentin group than in the placebo group (10/153 vs. 3/153; $p = 0.04$). Dizziness, drowsiness and visual disturbances were more common in the gabapentin group than in the placebo group. In the mechanistic study, 45 participants had a baseline functional magnetic resonance imaging scan of their brain, with 25 participants returning for a scan at the end of treatment. Gabapentin significantly decreased evoked activity in the anterior cingulate cortex and cuneus. Change in anterior cingulate cortex activity after treatment related to improvement on the pain interference scale, and baseline activation of this region predicted response to treatment.

Conclusions: Gabapentin did not reduce pain and did not improve other outcomes compared with placebo over 16 weeks. Serious adverse effects were significantly higher in the gabapentin group than in the placebo group. Gabapentin reduces evoked activity in the anterior cingulate cortex, with changes of activity in this region tracking reported pain, and baseline activity predicting response to treatment.

Limitations: Primary outcome data were unavailable in 62 and 60 women for the average and worst numerical rating scale pain scores, respectively. A sensitivity analysis using imputation methods did not change the result.

Future work: Clinical trials to investigate other pharmacological interventions (monotherapy vs. combination therapy), physiotherapy and cognitive–behavioural therapy to treat women with chronic pelvic pain are needed.

Trial registration: Current Controlled Trials ISRCTN77451762 and EudraCT 2014-005035-13.

Funding: This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 7, No. 7. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of boxes

List of abbreviations

ACC	anterior cingulate cortex
AE	adverse event
BCTU	Birmingham Clinical Trials Unit
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPP	chronic pelvic pain
DMC	Data Monitoring Committee
DPMS	descending pain modulatory system
fMRI	functional magnetic resonance imaging
FOV	field of view
FWE	family-wise error rate
GHQ-12	General Health Questionnaire (short)
GP	general practitioner
IASP	International Association for the Study of Pain
IMP	investigational medicinal product
IQR	interquartile range
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
NeuPSIG	neuropathic pain special interest group of IASP
NICE	National Institute for Health and Care Excellence
NRS	numerical rating scale
PAG	periaqueductal grey matter
PCS	Pain Catastrophizing Scale
PI	principal investigator
PPSN	Pelvic Pain Support Network
RCT	randomised controlled trial
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SAQ	Sexual Activity Questionnaire
SD	standard deviation
SF-12	Short Form-12
SUSAR	suspected unexpected serious adverse reaction
TE	echo time
TR	repetition time
TSC	Trial Steering Committee
WPAIQ	Work and Productivity Activity Impairment Questionnaire

Plain English summary

What was the question?

Long-standing (chronic) pelvic pain affects over 1 million women in the UK, but there is a lack of proven treatments. If no underlying cause is found, the pain is much more difficult to treat. Gabapentin, which is used to treat other chronic pain conditions, is being increasingly prescribed. There is no evidence to show whether or not gabapentin is effective for chronic pelvic pain, so we conducted a clinical trial. We also wanted to understand whether or not we could see changes in the brains of women with chronic pelvic pain and whether or not these changes can predict response to gabapentin.

What did we do?

We involved 306 women with chronic pelvic pain, for which no cause had been found, and randomly assigned them to take gabapentin or placebo for 16 weeks. We collected information on pain, physical health and emotional well-being at the beginning and end of the study. Women scored their pain from 0 to 10 and sent this score by text message. We asked 45 participants to undergo a brain scan to look at brain activity before and during treatment.

What did we find?

Gabapentin did not reduce pain and did not improve any other aspects of the women's life compared with placebo. Side effects were more common with gabapentin than placebo. We identified areas of the brain that responded to gabapentin.

What does this mean?

Women with no obvious cause for their chronic pelvic pain should be made aware that gabapentin will not relieve their pain and may give them unpleasant side effects. More research is required to see if physiotherapy or talking therapies can help instead.

Scientific summary

Background

Long-standing (chronic) pelvic pain affects over 1 million women in the UK. It is the reason for 20% of gynaecological consultations and causes a 45% reduction in work productivity. The annual cost of caring for women in the UK with chronic pelvic pain has been estimated to be £154M.

The pathogenesis of the painful symptoms experienced by women with chronic pelvic pain is poorly understood. The painful symptoms are associated with specific pathological processes, such as endometriosis, but up to 55% of women with chronic pelvic pain appear to have no obvious underlying pathology.

The management of chronic pelvic pain is difficult because in the absence of underlying pathology no established gynaecological treatments are available.

Objectives of the main trial

The GaPP2 trial was designed to test the hypothesis that treatment with gabapentin has the potential to provide a safe, effective, convenient oral treatment that alleviates pain in women with chronic pelvic pain in the absence of any obvious pelvic pathology. We also wanted to test the hypothesis that treatment with gabapentin has the potential to improve physical and emotional functioning.

Objectives of the mechanistic substudy

The mechanistic component of the trial had the following objectives:

- determine the presence of central nervous system changes in women with chronic pelvic pain and no obvious underlying pathology
- determine the effect of gabapentin on central pain processing in women with chronic pelvic pain and no underlying pathology
- determine whether or not there are baseline functional magnetic resonance imaging measures that correlate with response to treatment
- determine whether or not there are clinical measures that correlate with response to treatment.

Design

This was a randomised, double-blind, placebo-controlled, multicentre trial with a mechanistic substudy to explore the mechanism of action of gabapentin.

Methods

Setting

The trial was conducted in 39 sites in NHS hospital settings across the UK, recruiting between 2015 and 2019. The mechanistic substudy was conducted only at the Edinburgh Imaging Facility at the University of Edinburgh.

Participants

For the main trial, informed consent was sought from women (aged between 18 and 50 years) with chronic pelvic pain and no obvious pelvic pathology at laparoscopy. For the mechanistic substudy, Edinburgh participants who consented to the main trial were approached to undergo a functional magnetic resonance imaging scan of the brain.

Interventions

Each participant received either gabapentin capsules at a dose of 300 mg three times per day (increased to a maximum dose of 2700 mg) or placebo capsules. These were commenced at randomisation and continued for a total of 16 weeks (4-week dose escalation followed by 12 weeks on the optimal dose). Optimal dosing was determined by the participants, who were instructed to increase their dose until they perceived adequate pain relief or intolerance to perceived side effects. Neither the clinician nor the participant knew which group they were allocated to throughout the study.

Screening and randomisation

Participants were asked to return numerical rating pain scores weekly for 4 weeks on both the average and the worst scales (scores range from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable). If at least three of the four pain scores were returned on both scales and at least two of the worst pain scores were ≥ 4, then the woman was considered fully eligible for the trial and was invited to attend a randomisation visit. Randomisation was performed online via a secure internet facility. Women were unblinded at the end of the treatment phase after all data were collected.

Outcome measures

Primary

Dual measures of worst and average pelvic pain scores assessed weekly by a numerical rating scale at baseline and then during the final 4 weeks of treatment (weeks 13–16 post randomisation).

Secondary

- Numerical rating score of pain: to include an examination of the proportion of women who have a 30% or 50% reduction in average and worst pain scores from baseline to the end of treatment (pain scores ranging from 0, no pain, to 10, worst pain imaginable).
- Short Form-12 quality of life: the Short Form Health Survey provides summary information on physical and mental health status.
- Brief Pain Inventory: a comprehensive instrument for pain assessment.
- Brief Fatigue Inventory: to measure the severity of fatigue in adults.
- General Health Questionnaire (short): to identify psychological distress.
- Work and Productivity Activity Impairment: a valid questionnaire for assessing impairments in paid work and activities.
- Pain Catastrophizing Scale: one of the most widely used instruments for measuring catastrophic thinking related to pain.
- Sexual Activity Questionnaire: a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort.
- PainDETECT™: a new screening questionnaire to identify neuropathic components in patients.
- Pelvic Pain and Urinary/Frequency Patient Symptom Scale (baseline only): a questionnaire that is predictive of treatment success.
- Number of attendances to health-care professionals for chronic pelvic pain.
- Use of concomitant medications was recorded to identify any reductions in analgesic use.

Mechanistic substudy

Brain activity (measured by functional magnetic resonance imaging) at rest and evoked in response to punctate stimuli.

Results

Main trial

A total of 1348 participants were approached for participation, and 414 were consented to the initial screening phase. Of these women, 306 were randomised, 153 allocated to gabapentin and 153 allocated to placebo. Ten women withdrew from GaPP2 and one woman died. In addition, primary outcome data were unavailable in 62 and 60 women for the average and worst pain scores, respectively. Sensitivity analyses using a multiple imputation approach were performed to assess the effect of missing responses.

The baseline data (age, body mass index and maternal ethnicity) of the participants were comparable in the two groups of the trial. In weeks 13–16, the mean worst pain score was 7.1 (standard deviation 2.6) in the gabapentin group and 7.4 (standard deviation 2.2) in the placebo group (adjusted mean difference −0.20, 97.5% confidence interval −0.81 to 0.42; $p = 0.47$). The mean average pain score was 4.3 (standard deviation 2.3) in the gabapentin group and 4.5 (standard deviation 2.2) in the placebo group (adjusted mean difference −0.18, 97.5% confidence interval −0.71 to 0.35; $p = 0.45$). No significant between-group differences were observed for any secondary outcome. A higher proportion of women experienced a serious adverse event in the gabapentin group than in the placebo group (10/153 vs. 3/153; $p = 0.04$). Dizziness, drowsiness and visual disturbances were more common in the gabapentin group.

Mechanistic substudy

A total of 83 women were consented in Edinburgh for the main trial. Of these, 45 consented to take part in the mechanistic study and had a baseline functional magnetic resonance imaging brain scan; 25 returned for a follow-up scan between weeks 12 and 16 of treatment. Twelve women were in the placebo group and 13 were in the gabapentin group. Whole-brain and a priori defined region of interest analyses were performed. Group mean activation included regions known to be important in the processing of pain. Compared with placebo, gabapentin reduced evoked activity in the anterior cingulate cortex and the cuneus. In the gabapentin group, changes in activity in the anterior cingulate cortex tracked with clinically meaningful improvements (Brief Pain Inventory pain interference scores); however, this was not the case for the cuneus. Baseline evoked activity in the anterior cingulate cortex was also a predictor of response, with those with the greatest activity having a greater improvement in the physical component of the Short Form-12 and reduction in their PainDETECT scores.

Conclusions

Gabapentin did not reduce pain scores and did not improve other outcomes compared with placebo over the course of 16 weeks. Serious adverse effects were significantly higher in the gabapentin group than in the placebo group. In the mechanistic study, gabapentin exerted a clinically relevant effect on the anterior cingulate cortex.

Women with chronic pelvic pain and no obvious pelvic pathology should be advised that gabapentin may not alleviate their pain and may give them unpleasant side effects. No further research is required. Questions that remain unaddressed relate to the use of other pharmacological interventions (monotherapy vs. combination therapy), physiotherapy and cognitive–behavioural therapy for treating women with chronic pelvic pain.

Trial registration

This trial is registered as ISRCTN77451762 and EudraCT 2014-005035-13.

Funding

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Chapter 1 Introduction

Clinical background

Chronic pelvic pain (CPP) is as common as asthma, migraine and back pain,[2] and affects more than 1 million women in the UK.[3] It is associated with significantly reduced quality of life[4,5] and a 45% reduction in work productivity, and it has been estimated that caring for women with CPP in the UK costs £154M annually.[6,7] CPP can be associated with an underlying pathology, such as endometriosis, but in up to 55% of women no obvious cause can be identified at laparoscopy.[7] Management of CPP is difficult when no pathology is identified, as no established gynaecological treatments are available, but careful exploration of the patient's symptoms and history may point to non-gynaecological causes of CPP for which some effective treatments exist.

Increasing evidence demonstrates that people suffering with chronic pain conditions show many physiological similarities to healthy pain-free controls, no matter what/where the underlying cause of the pain.[8–11] This has led some to argue that 'chronic pain' should be considered as a disease in its own right,[12] and at the very least points towards the use of treatments targeting central pain mechanisms in addition to disease-specific therapies.

Drugs targeting central pain mechanisms

There are three main classes of drugs that are used as adjunctive analgesics for both the treatment of neuropathic pain and the treatment of conditions thought to have a central component (e.g. fibromyalgia):[13,14] tricyclic antidepressants, gabapentinoids and selective serotonin and noradrenaline reuptake inhibitors. However, much of this use is currently 'off-licence', as the specific indications for which each drug is licensed varies. At the time of the design of the pilot study for this trial (GaPP1),[1,15] there was an increase in the prescription of these adjunctive analgesics for CPP in both primary and secondary care[16] owing to their effectiveness in managing other chronic pain conditions. The rate of patients newly treated with gabapentinoids in primary care tripled from 2007 to 2017 and, by 2017, 50% of gabapentinoid prescriptions were for an off-label indication. We also observed at the time that there was considerable use of gabapentin for CPP (largely because of its perceived effectiveness in other chronic pain conditions). First, with the support of the Scottish Primary Care Research Network, we surveyed a random group of general practitioners (GPs). Of the GPs who responded to our survey, 74% said that they would consider gabapentin as a treatment option for CPP in women. Second, with the support of the Royal College of Obstetricians and Gynaecologists, we surveyed a random group of gynaecologists and 50% said that they currently prescribe gabapentin for CPP, and > 90% said that they would consider gabapentin as a treatment option for this condition. Since then, awareness and use of gabapentinoids has continued to increase in gynaecology, with the publication of reviews in this area[17] and reference within the National Institute for Health and Care Excellence (NICE) guideline for endometriosis[18] to the NICE guideline on neuropathic pain for treatment of CPP with neuromodulators.[19] This was despite the fact that there was no good-quality evidence of efficacy in CPP specifically on which to base this practice, and the fact that these drugs were not licensed for CPP. One randomised controlled trial (RCT)[20] compared the efficacy of gabapentin and amitriptyline for CPP in women with a range of pelvic pathologies; however, this study was open label, there was no placebo group, the population had a mixed aetiology of pain symptoms and

the numbers analysed were small ($n = 56$). Another placebo-controlled trial of 60 women from Egypt[21] did show a statistically, and potentially clinically, significant difference in patient-reported pain after 12 weeks of treatment, but the variability of the patient responses was considerably lower than all previous studies of CPP and not generalisable outside that population. The trial was not powered to detect meaningful differences and had substantial attrition.[21] Our own pilot trial (GaPP1)[1] was not powered to detect meaningful differences and experienced significant attrition. There were no studies investigating pregabalin or duloxetine for this indication. Interestingly, there was one RCT of pregabalin for treating CPP in men that showed no benefit of treatment over placebo after a 6-week course of treatment.[22] During the course of our trial a subsequent paper was published (albeit a retrospective database analysis rather than a clinical trial) that reported greater benefit of gabapentin than pregabalin for CPP in men.[23] To date, to our knowledge, there remain no studies investigating duloxetine for this indication in men or women. Given the benefit of gabapentin over amitriptyline in the one existing study of CPP in women,[20] this was the adjunctive analgesic chosen for further investigation in GaPP1 and subsequently the full trial reported here (GaPP2).

Although there is limited evidence of the efficacy of gabapentin in CPP, there is proven benefit of the efficacy of gabapentin in other chronic pain conditions. A systematic review showed that the number needed to treat against placebo to be 5.8 [95% confidence interval (CI) 4.3 to 9.0] to achieve at least 50% pain-intensity reduction in painful diabetic neuropathy (829 patients); 7.5 (95% CI 5.2 to 14) to achieve at least 50% pain-intensity reduction in postherpetic neuralgia (892 patients); and 5.4 (95% CI 2.9 to 31) to achieve at least 30% pain-intensity reduction in fibromyalgia (150 patients).[16] Furthermore, gabapentin is a drug that is very well tolerated: all-cause withdrawal rates are similar to placebo (gabapentin, 20%; placebo, 19%; $n = 17$ studies; $n = 3063$ participants).[16]

Recent safety concerns regarding gabapentinoids

Despite clinical trial data suggesting gabapentin to be well tolerated, there have been significant concerns regarding the risk of both abuse and dependence associated with the use of gabapentinoids, both their use clinically and their illicit use recreationally. There is certainly good evidence of misuse of gabapentin in the population as a whole, and this seems to be particularly the case for individuals with a history of substance abuse and if there is concomitant opiate or benzodiazepine use.[24,25] Of relevance to GaPP2, it does appear that men may be more vulnerable to these effects than women.[26] Nonetheless, given that gabapentinoids are commonly prescribed for symptoms that are significantly more prevalent in women (chronic pain, anxiety and climacteric symptoms), large data sets will be required to discern with certainty whether or not a sexual dimorphism exists. However, in April 2019 (while GaPP2 was recruiting), gabapentin and pregabalin were reclassified as controlled drugs under the Misuse of Drugs Act 1971[27] as class C substances, and scheduled under the Misuse of Drugs Regulations 2001 as 'schedule 3'.[28]

Recently, there has also been increased concern of the side-effect profile of gabapentinoids.[29] A large, retrospective, cohort study identified an increased risk of suicidal behaviour, unintentional overdoses, head/body injuries and road–traffic incidents and offences with gabapentinoids. The risks were, however, significantly higher for pregabalin than for gabapentin, and associations with adverse outcomes were mainly seen in the 15–24 years age group. In fact, gabapentin was not associated with an increased risk of suicidal behaviour and was associated with a decreased risk of road–traffic incidents and offences, and violent crime. These data suggest that the risks of pregabalin, particularly in adolescents, may have been underestimated; however, these data are reassuring for gabapentin, except when combined with opiates or for those with a history of substance abuse.

Potential mechanism of action of gabapentin in chronic pelvic pain

The gabapentinoids are thought to exert their analgesic effect by binding to the alpha-2/delta subunit of voltage-gated calcium channels on primary afferent neurons, thereby reducing the release of neurotransmitters from their central terminals.[30–32] In line with the observed centrally mediated adverse effects (somnolence, dizziness and nausea) of gabapentin, neuroimaging studies have also demonstrated gabapentin to exert an effect on the activation of specific brain regions in both humans[33,34] and rats.[35] The preclinical study[35] looked at anaesthetised animals at rest and observed reduced activation in areas of the brain known to be involved in pain perception after infusion of gabapentin; these data were also consistent with known pharmacokinetics with respect to transport of gabapentin across the blood–brain barrier. The human studies[33,34] were both carried out on healthy volunteers, but used an induced model of central sensitisation (capsaicin induced). They show that gabapentin is able to reduce the abnormal brainstem activity in response to a mechanical stimulus associated with this sensitised state,[33] and that this effect could distinguish between gabapentin, ibuprofen and placebo.[34] Of relevance to the GaPP2 trial, the first study was undertaken in a cohort of 12 men[33] and the second in a mixed cohort of 25 subjects, 13 of whom were women.[34] There has been one study[36] exploring the central effects of pregabalin on a female cohort of fibromyalgia patients ($n = 27$). To the best of our knowledge, there are still no other studies focusing on the effects of gabapentin in a solely female cohort of chronic pain patients, except a pilot neuroimaging analysis from the GaPP1 study.[37]

Clinical research questions

1. What is the efficacy of gabapentin compared with placebo in the alleviation of pain in women with CPP without any obvious pelvic pathology?
2. Does gabapentin, compared with placebo, significantly improve physical and emotional functioning in women with CPP without any obvious pelvic pathology?

Mechanistic substudy research questions

1. Are there central nervous system changes in women with CPP and no underlying obvious pelvic pathology?
2. What is the effect of gabapentin on central pain processing in women with CPP and no underlying obvious pelvic pathology?
3. Are there any baseline functional magnetic resonance imaging (fMRI) measures that correlate to response to treatment?
4. Are there clinical measures that correlate to response to treatment?

To address these research questions, we proposed the following:

i. to conduct a high-quality, multicentre RCT comparing gabapentin with placebo in women with CPP without any obvious pathology
ii. to explore possible subgroup effects of gabapentin owing to the presence or absence of dysmenorrhoea, psychological distress and hormone treatment
iii. to conduct fMRI studies on a representative subsample of trial participants to identify changes in brain activity that are altered by gabapentin and identify potentially predictive brain activity markers of treatment response.

Chapter 2 Methods

This chapter reports the methods used to conduct the GaPP2 trial.

Trial design

The GaPP2 trial was a placebo-controlled, randomised, blinded, multicentre trial of gabapentin for the management of CPP in women with no known aetiology with a nested-mechanistic fMRI brain study (see *Chapter 4*). The trial had a favourable ethics opinion from Research Ethics Committee West Midlands – Coventry and Warwickshire (Multicentre Research Ethics Committee reference 15/MW/0036).

Recruitment

The GaPP2 trial participants were recruited from gynaecology outpatient departments in 39 participating NHS sites across the UK. The GaPP2 trial recruitment followed a two-step process (*Table 1*). Potential participants were referred, with their permission, to the local research teams by their attending clinician. All participants were told that participation in the trial was completely voluntary and that they could withdraw at any stage in the trial. This was part of the consent process. Participants were reassured that participation or withdrawal would not affect their normal clinical care. All women were approached, with permission, by researchers who were trained in Good Clinical Practice and specifically in taking consent for this trial. Potential participants were provided with a participant information sheet and given time to consider their involvement. If participants expressed an interest, written informed consent was sought and participants were invited to a screening visit at which they were assessed for eligibility. For the mechanistic substudy, eligible participants in Edinburgh only were given a separate participant information sheet and, if interested, signed a second consent form.

Eligibility criteria

Participants were assessed for eligibility by an appropriately trained doctor. The participants needed to meet the following criteria:

- women aged between 18 and 50 years
- experiencing CPP (non-cyclical with or without dysmenorrhoea or dyspareunia) of > 3 months duration
- having pain located within the true pelvis or between and below anterior iliac crests
- having no obvious pelvic pathology at laparoscopy (laparoscopy must have taken place at least 2 weeks prior to consenting to participation, but no more than 36 months prior to screening)
- using, or willing to use, effective contraception if necessary to avoid pregnancy
- able to give informed consent.

TABLE 1 Summary of trial design

Phase	Flow of participant through the trial		Outcomes collected	Time scale
Recruitment	Women with CPP		Eligibility criteria	≤ 3 years and > 2 weeks
	Laparoscopy and ultrasound: no or minimal pathology seen			
	If recent laparoscopy: information provided before discharge	If identified from patient referrals: information sent to respondent		
	Consent and screening			
Run-in	Pre randomisation		NRS	−4 weeks
			NRS	−3 weeks
			NRS	−2 weeks
			NRS	−1 week
	Randomisation ($n = 300$)		fMRI scan of the brain, PROMs	0 weeks (baseline)
	Gabapentin dispensed ($n = 150$)	Placebo dispensed ($n = 150$)		
Titration	Gabapentin commenced and escalate dose	Placebo commenced and escalate dose	AEs collected	1 week
				2 weeks
				3 weeks
				4 weeks
Treatment	Maximum-tolerated dose maintained			5 weeks
				6 weeks
				7 weeks
				8 weeks
				9 weeks
				10 weeks
				11 weeks
				12 weeks
			NRS	13 weeks
			NRS	14 weeks
			NRS	15 weeks
			NRS	16 weeks
	End of study		fMRI brain scan, PROMS	
	Unblinding			
Taper	Gabapentin taper down or remain on treatment		AEs collected	17–20 weeks

AE, adverse event; NRS, numerical rating scale; PROM, patient-reported outcome measure.

Participants could not be included if any of the following criteria were applicable:

- known pelvic pathology –
  - endometriosis (macroscopic lesions)
  - complex or > 5 cm ovarian cyst or fibroid > 3 cm
  - dense adhesions
- current malignancy under treatment
- current use of gabapentin or pregabalin
- taking gonadotropin-releasing hormone agonists, and unable or unwilling to stop
- surgery planned in the next 6 months
- history of significant renal impairment
- previous reaction to gabapentin
- breastfeeding
- pregnant
- planned pregnancy in the next 6 months
- pain suspected to be of gastrointestinal origin (positive Rome III Diagnostic Criteria)
- co-enrolment in another clinical trial of an investigational medicinal product
- metal implant/pacemaker/claustrophobia (fMRI mechanistic study only)
- receiving prohibited medications (e.g. pregabalin or high-dose opioids).

The final element of eligibility was a 4-week screening phase. Participants were asked to return numerical rating scale (NRS) pain scores weekly for 4 weeks on both the average and the worst scales (scores range from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable). If at least three of four pain scores were returned on both scales, and at least two of the worst pain scores were ≥ 4, the woman was considered fully eligible for the trial and was invited to attend a randomisation visit. No study drugs were taken during this pre-randomisation screening phase, but participants were able to remain on any analgesics they were taking.

Randomisation method and minimisation variables

Once final eligibility was confirmed and consent obtained, women were randomised to the GaPP2 trial by the research staff at sites using a secure online randomisation service provided by the Birmingham Clinical Trials Unit (BCTU) (see *Table 1*). Participants were randomised in an equal (1 : 1) ratio to gabapentin or placebo, and a bottle number was allocated. The bottle number was sent via e-mail to the local principal investigator (PI), the trial pharmacist and the research nurse undertaking the randomisation. A 'minimisation' procedure, incorporating a random element using a computer-based algorithm, was used to avoid chance imbalances in important prognostic variables. Strata used in the minimisation were:

- Presence or absence of dysmenorrhoea (yes, no); a pain score of ≥ 4 was considered as 'presence of dysmenorrhoea' (on a NRS of 0–10).
- Psychological distress measured by the General Health Questionnaire (short) (GHQ-12) (≥ 2 on a 0–12 scale).
- Use of sex hormonal treatments (yes, no) (e.g. combined oral contraceptives, progestogens and levonorgestrel-releasing intra-uterine system).
- Recruiting centre.

Investigation medicinal product information

The investigational medicinal product (IMP) was gabapentin in the form of an overencapsulated capsule. Each capsule contained 300 mg of gabapentin.

The placebo was lactose powder, which was encapsulated in the same way as the IMP to be identical in colour, shape and weight. The treatment regime was exactly the same as in the gabapentin group. For the gabapentin, it was assumed that given that the outer capsule disintegrates, the excipient falls away and exposes the original gabapentin capsule. Disintegration of the original capsule and subsequent bioavailability were not impacted by the overencapsulation.

Interventions were supplied by Sharp Clinical Services (Tredegar, UK), who procured the trial drug and manufactured the placebo capsule, overencapsulated the IMP and placebo, and dispensed into containers accordingly. This company had no role in the design, conduct, analysis or reporting of the trial.

A clinical trial pharmacist prepared the trial treatment bottle for dispense. Each trial treatment bottle contained 155 capsules. This was enough to see every participant through the dose-escalation phase. Bottles were then dispensed at each visit, depending on the optimal dose reached, up to a maximum of seven bottles.

Treatment allocations

Participants commenced the trial intervention on the day that they were randomised. They commenced on a dose of 300 mg and increased this by 300 mg every 3 days. Doses were split into three doses three times per day. Participants were given written instructions regarding dose escalation (*Table 2*). This took place in the first 4 weeks of treatment. Optimal dosing was determined by the participants, who were instructed to increase until they perceived adequate pain relief or intolerance to the perceived side effects. The optimal dose was then continued for 12 weeks. At the end of the treatment phase, the dose was reduced over a 2-week period (written instructions were provided; *Table 3*), unless there was a clinical decision to continue open-label treatment.

Blinding

Participants, investigators, research nurses and other attending clinicians all remained blind to the trial drug allocation for the duration of their participation. All participants were unblinded at the end of the trial after all data were collected. Women who perceived a benefit from gabapentin were able to discuss treatment continuance at their optimal dose on open-label treatment following discussion with their direct clinical care team.

TABLE 2 Dose escalation instructions

Day in trial	Total number of capsules per day (maximum)	Dosing	Maximum daily dose of gabapentin
1	1	One capsule at night	300 mg
2	1	One capsule at night	300 mg
3	1	One capsule at night	300 mg
4	2	One capsule twice daily	600 mg
5	2	One capsule twice daily	600 mg
6	2	One capsule twice daily	600 mg
7	3	One capsule three times daily	900 mg
8	3	One capsule three times daily	900 mg
9	3	One capsule three times daily	900 mg
10	4	One capsule twice and two capsules at night	1200 mg

TABLE 2 Dose escalation instructions (*continued*)

Day in trial	Total number of capsules per day (maximum)	Dosing	Maximum daily dose of gabapentin
11	4	One capsule twice and two capsules at night	1200 mg
12	4	One capsule twice and two capsules at night	1200 mg
13	5	Two capsules twice and one capsule once	1500 mg
14	5	Two capsules twice and one capsule once	1500 mg
15	5	Two capsules twice and one capsule once	1500 mg
16	6	Two capsules three times daily	1800 mg
17	6	Two capsules three times daily	1800 mg
18	6	Two capsules three times daily	1800 mg
19	7	Two capsules twice and three capsules at night	2100 mg
20	7	Two capsules twice and three capsules at night	2100 mg
21	7	Two capsules twice and three capsules at night	2100 mg
22	8	Three capsules twice and two capsules once	2400 mg
23	8	Three capsules twice and two capsules once	2400 mg
24	8	Three capsules twice and two capsules once	2400 mg
25	9	Three capsules three times daily	2700 mg
26	9	Three capsules three times daily	2700 mg
27	9	Three capsules three times daily	2700 mg
28–112	Remain on maximum-tolerated dose for 12 weeks (not exceeding 2700 mg or nine capsules per day). Daily dose should be divided equally into three doses		

TABLE 3 Dose reduction instructions

Number of capsules to be taken and when	Total number of capsules per day (maximum)
Three capsules three times daily (morning, afternoon and night)	9
Three capsules in the morning and two capsules in the afternoon and three capsules at night	8
Two capsules in the morning and two capsules in the afternoon and three capsules at night	7
Two capsules three times daily (morning, afternoon and night)	6
Two capsules in the morning and one capsule in the afternoon and two at night	5
One capsule in the morning and one capsule in the afternoon and two at night	4
One capsule three times daily (morning, afternoon and night)	3
One capsule in the morning and one at night	2
One capsule at night for one night	1

In case of any serious adverse event (SAE), the general recommendation was to initiate management and care of the participant as if the woman was taking gabapentin. Cases that were considered serious, unexpected and possibly, probably or definitely related to the trial intervention (see Vincent *et al.*[38]) were unblinded as appropriate. In any other circumstances, investigators, research nurses and midwives remained blind to drug allocation while the participant remained in the trial. However, if the drug allocation was specifically requested immediately to assist the medical management of a participant, clinicians could contact the relevant pharmacy department where code-break envelopes were kept for each individual bottle that held the related allocation for that bottle.

Scheduled trial appointments

Trial participants completed five trial visits in total, which comprised the initial screening visit, randomisation and three follow-up visits that were conducted at weeks 4–5 (visit 3), 8–10 (visit 4) and 16–17 (visit 5 was the end of the trial) (*Box 1*). If no resupply of the IMP was required, women were able to complete visits 3 and 4 over the telephone. At each follow-up visit, adverse events (AEs), use of rescue analgesia and any side effects were captured, and, for visit 5 only, visits to a GP and other health-care professionals were recorded. For the mechanistic substudy, participants were asked to attend for a fMRI scan at the time of their second visit (pre randomisation), and were then asked to return at the time of their fifth visit (before unblinding).

BOX 1 Schedule of trial assessments

Possible recruit identified by clinician

- Pelvic pain > 3 months.
- No pathology at laparoscopy at < 36 months and > 2 weeks.
- Not on gabapentin/pregabalin.
- Not pregnant/planning pregnancy.
- Asked permission to be approached by research staff.

Approached by research staff

- GaPP2 patient information sheet.
- fMRI substudy patient information sheet (Scotland).
- Asked permission to be contacted regarding study entry.

Visit 1 (pre-trial eligibility) (week –4)

Participant

- Informed consent.
- Pre-screening.

Research team

- Eligibility.
- Contact details.

Weekly contact (weeks –4 to –1)

- NRS worst and average scores.
- Option to withdraw.
- fMRI (Scotland only) (blood sample): visit 1A.

BOX 1 Schedule of trial assessments (*continued*)

Visit 2 (baseline: week 0)

Participant

- Screening.
- Randomised.
- Treatment diary.
- Questionnaires.
- Saliva sample.

Research team

- Confirm eligibility.
- Reviews SAEs.
- Option to withdraw.

Visit 3 (week 4)

Participant

- Collect medication (if required).

Research team

- Review treatment diary.
- Review AEs.
- Option to withdraw.

Visit 4 (week 10) (can be remote consultation)

Participant

- Collect medication (if required).

Research team

- Review treatment diary.
- Review AEs.
- Option to withdraw.

Weekly text message (weeks 13–16)

- NRS worst and average scores.
- Option to withdraw.
- fMRI (Scotland only) (blood sample): visit 4A.

Visit 5 (week 17)

Participant

- Questionnaires.
- Unblinding.

Research team

- Collect diary.
- Collect medication.
- Review AEs.
- Review treatment.

Taper down treatment (weeks 17–19)

- As required and remote consultations.

Adherence monitoring

Adherence was evaluated by two methods. First, women were asked to complete a daily treatment diary, which documented how many capsules of IMP were taken. When women provided data for at least 5 days in 1 week, the weekly median number of capsules taken was calculated. Second, the participant was asked about adherence to the study medication at their final follow-up visit (visit 5). This was asked as a categorical response with the following groups: never (0%), hardly any (1–24%), some (25–49%), most (50–74%), almost always (75–99%) and every day (100%). Women were defined as adherent if they reported taking $\geq$ 50% of their study drug at visit 5 [most (50–74%), almost always (75–99%) or every day (100%)]. Women who were considered adherent as per this definition constituted the per-protocol cohort.

Participant withdrawal

A participant was considered for withdrawal from the trial treatment if, in the opinion of the investigator or the care-providing clinician or clinical team, it was medically necessary to do so. Participants could also voluntarily withdraw from treatment at any time; however, women were encouraged to continue follow-up after withdrawal from the trial treatment to minimise attrition bias.

Participants could voluntarily withdraw their consent to study participation at any time. If a participant did not return for a scheduled visit, attempts were made to contact them and, where possible, review adherence and safety data. Reasons for withdrawal were captured where possible. If a participant explicitly withdrew consent to have any further data recorded, their decision was respected and recorded on the electronic data capture system. All communication surrounding the withdrawal was noted in the patient's medical notes, and no further data were collected for that participant.

Outcomes and assessments

Primary outcome measures

We employed dual primary outcome measures of average and worst pain scores recorded on a NRS. These were assessed and interpreted as separate outcomes. Weekly pain scores (ranging from 0, no pain, to 10, the worst pain imaginable) were recorded, during the final 4 weeks of treatment (weeks 13–16 post randomisation) in the form of (1) 'average pain this week' and (2) 'worst pain this week'. The average pain score was taken as the average of 'average pain this week' and the worst pain score as the worst response from 'worst pain this week' over the 4 weeks of assessment.

Secondary outcome measures

Secondary outcomes are as follows:

- Numerical rating score of pain – to include an examination of the proportion of women who have a 30% or 50% reduction in average and worst pain scores from baseline to the end of treatment (pain scores ranging from 0 meaning no pain to 10 being worst pain imaginable).
- Short Form-12 (SF-12) quality of life – Short Form Health Survey provides summary information on physical and mental health status.[39]
- Brief Pain Inventory (BPI) – a comprehensive instrument for pain assessment.[40]
- Brief Fatigue Inventory (BFI) – to measure the severity of fatigue in adults.[41]
- GHQ-12 – to identify psychological distress.[42]
- Work and Productivity Activity Impairment Questionnaire (WPAIQ) – a valid questionnaire for assessing impairments in paid work and activities.[43]
- Pain Catastrophizing Scale (PCS) – one of the most widely used instruments for measuring catastrophic thinking related to pain.[44]

- Sexual Activity Questionnaire (SAQ) – a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort.[45]
- PainDETECT™ – a new screening questionnaire to identify neuropathic components in patients.[46]
- Pelvic Pain and Urinary/Frequency Patient Symptom Scale (baseline only) – a questionnaire that is predictive of treatment success.[47]
- Number of attendances to health-care professionals for CPP.
- Use of concomitant medications was recorded to identify any reductions in analgesic use.

Outcome assessment details

The schedule of outcome assessments is given in *Table 4*. Details of how outcomes were generated are given in *Table 5*.

TABLE 4 Schedule of outcome assessments

Phase	Screening phase				Baseline, randomisation and treatment dispensed	Titration	Treatment				End of study and unblinding	Taper
Duration (weeks)	**−4 to −1**				**0**	**1–4**	**5–12**	**13–16**			**17**	**17–19**
Weekly worst and average NRS	✓	✓	✓	✓				✓	✓	✓	✓		
Saliva sample					✓							
SF12					✓						✓	
BPI					✓						✓	
PCS					✓						✓	
SAQ					✓						✓	
BFI					✓						✓	
GHQ-12					✓						✓	
WPAIQ					✓						✓	
PainDETECT					✓						✓	
PUF patient symptom scale					✓							
Adverse events						✓	✓	✓			✓	✓
Permitted/ concomitant medication	✓					✓	✓	✓				✓
Adherence or discontinuation						✓	✓	✓				✓
fMRI substudy[b]												
fMRI brain scan	✓							✓[a]				
Blood sample	✓							✓				

PUF, Pelvic Pain and Urinary/Frequency.
a A second fMRI scan should take place a minimum of 8 weeks following randomisation.
b 50 Scottish participants; fMRI scan carried out in Edinburgh.

TABLE 5 Details of outcome assessments

Outcome assessed	Time point	Method	Reported by
Weekly worst and average NRS pain scores	Weeks 13–16	Text-messaging service	Study participant
Quality-of-life questionnaires	Visit 5	Completed on paper forms	Study participant
Adverse events	Visits 3–5	Clinical assessment of participant at follow-up visit and medical records	Research nurse/doctor
Concomitant medication	Visits 3–5	Clinical assessment of participant at follow-up visit and medical records	Research nurse/doctor
Adherence or discontinuation	Throughout the treatment period (weeks 1–17)	Treatment diaries and clinical follow-up at visit 5	Study participant and research nurse/doctor

Relevant trial data were transcribed directly into a secure web-based database. All personal information was treated as strictly confidential. Source data comprised the case report forms, questionnaires and hospital notes. Women were encouraged to report AEs occurring between clinic visits or visits to non-participating hospitals to the research nurse. Self-reports were verified against clinical notes. Pain scores were reported by women via text messages, which were imported directly into the trial database using a third-party company called 'Textlocal' (Chester, UK). There were validation methods built into this system to ensure data consistency and quality. Any text message sent by women that did not contain only a numerical digit between 0 and 10 generated an e-mail to the GaPP2 trial mailbox for interpretation or chasing up. All worst/average pain scores were checked on entry to ensure that they were the right way round (logically worst scores should be higher than average scores). Furthermore, any scores that had been inputted into the database manually following collection of the pain score over the telephone could not be overwritten by a subsequent text message.

Adverse events and serious adverse events

All AEs, from consent to the end of treatment (including a dose reduction if required) and whether observed directly or reported by the patient, were collected and recorded. Commonly known side effects of gabapentin were not reported as AEs but were captured directly into the database at each visit. Trial participants were asked about the occurrence of AEs and SAEs at each study visit. All SAEs were e-mailed or faxed to the sponsor's office within 24 hours of the research staff becoming aware of the event. The local PI (or other nominated clinician) had to assign seriousness, severity, causality and expectedness (if deemed related) to the SAE before reporting. SAEs categorised by the local investigator as both suspected to be related to the trial drug and unexpected were classified as suspected unexpected serious adverse reactions (SUSARs), and were subject to expedited reporting. In the case of any SAEs, management and care of the participant was initiated as if they were taking gabapentin. The attending clinician and local PI were not made aware of the actual trial drug allocation.

Pregnancy reporting

Any participants who became pregnant while on treatment were withdrawn from treatment, and all pregnancies were followed up until delivery.

Statistical considerations

Sample size

The planned sample size of 240 women was estimated to provide 90% power to detect a minimally important clinical difference in NRS pain score of 1 point on a 0–10 scale,[48] assuming a standard deviation (SD) of 2.5 (GaPP1), which is equivalent to a standardised difference of 0.4.[1] To account for any increase in the risk of type-I error that may be associated with having dual outcome measures, a Bonferroni correction was applied (a two-sided alpha level of 0.025 was used). We planned to include 300 women in the trial to account for up to 20% loss to follow-up.

Statistical analysis

A comprehensive statistical analysis plan (SAP) was drawn up prior to any analysis and was provided to the independent Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) for review.

In summary, categorical baseline data were summarised with frequencies and percentages. Normally-distributed continuous variables were summarised with means and standard deviations; otherwise, medians and interquartile ranges (IQRs) were presented. In the first instance, participants were analysed in the treatment group to which they were randomised (intention to treat), irrespective of adherence with the treatment protocol. All estimates of differences between groups were presented with two-sided CIs.

For the primary outcome (average and worst pain scores), means and standard deviations were reported alongside adjusted mean differences (with 97.5% CIs) that were estimated using a linear-regression model adjusting for baseline score and the minimisation parameters (presence of dysmenorrhoea, psychological distress defined by the GHQ, current use of hormonal contraceptive and recruiting hospital). Statistical significance of the treatment group parameter was determined from the *p*-value generated by the model. A Bonferroni correction was applied for multiplicity (differences considered statistically significant at a 2.5% level). A further analysis of pain scores was examined using a repeated-measures (multilevel) model adjusting for the minimisation parameters. All assessment times were included in the model (weeks 13–16 pain scores), with baseline score included as a covariate in the model. Time was included as a continuous variable in the model. Time-by-treatment effects were explored by including the corresponding parameter in the model; if significant ($p < 0.025$), a constant treatment effect was not assumed and estimates of effect size (and 97.5% CI) were generated at each time point (weeks 13–16). A general 'unstructured' covariance structure was assumed.

For continuous secondary outcome measures [SF-12, BPI, BFI, GHQ-12, WPAIQ, PCS, SAQ and PainDETECT], means and standard deviations were reported alongside adjusted mean differences (with 99% CIs) that were estimated using a linear-regression model adjusting for baseline score and the minimisation parameters. Binary outcomes ($\geq$ 30% or 50% reduction in pain NRS pain scores) were summarised using frequencies and percentages. A log-binomial model was used to generate adjusted relative risks (and 99% CIs), adjusting for baseline score and the minimisation parameters. The number of attendances to health-care professionals for CPP and the use of concomitant medications were summarised descriptively only. Categorical data were summarised by frequencies and percentages. Continuous data were summarised by the number of responses, mean and SD if they were deemed to be normally distributed, and the number of responses, median and IQR if data appeared skewed. Formal statistical testing was not applied.

Sensitivity analysis was performed on the dual primary outcomes only. Every attempt was made to collect follow-up data from all participants. In particular, participants continued to be followed up even after protocol treatment violation where possible. Patients who returned zero or one NRS pain score were not included in the primary analysis; however, they were included in a sensitivity analysis using a multiple imputation approach. Missing responses were simulated using a Markov chain Monte Carlo method that assumes an arbitrary missing data pattern and a multivariate normal distribution.

Variables, including treatment group and the three subgroup variables (listed below), were included in the model and were used to generate 20 simulated data sets. An analysis was then performed (as per the primary analysis) on each set, with the results combined using Rubin's rules to obtain a single set of results (treatment effect estimate and CIs). Further sensitivity analyses were conducted to assess the effect of adherence; this was limited to the per-protocol cohort, as defined above, and an analysis was carried out to assess the effect of time between screening and randomisation.

Pre-planned subgroup analyses (limited to the dual primary outcome measures only) were completed for the following: (1) presence or absence of dysmenorrhoea (yes/no), (2) psychological distress measured by the GHQ-12 (0–1, 2–12) and (3) current use of hormonal contraceptives (e.g. combined oral contraceptives, progestogens and levonorgestrel intra-uterine system) (yes/no). The effects of these subgroups were examined by adding the subgroup by treatment-group interaction parameters to the linear-regression model; a chi-squared test was used to test the statistical significance of this parameter.

Interim analyses of effectiveness and safety end points were performed on behalf of the DMC (see *Acknowledgements*) on an approximately annual basis during the period of recruitment. These analyses were performed using the Haybittle–Peto principle;[49] therefore, no adjustment was made in the final *p*-values to determine significance.

Trial oversight

Study oversight was provided by a TSC that was chaired initially by Dr Jim Thornton (University of Nottingham) and then Dr Patrick Chien (NHS Tayside), and a DMC that was chaired by Professor Mary Ann Lumsden (University of Glasgow).

The TSC provided independent supervision for the trial, and provided advice to the chief investigator and co-investigators on all aspects of the trial throughout the study. The DMC adopted the DAMOCLES charter[50] to define its terms of reference and operation in relation to oversight of the GaPP2 trial.

Chapter 3 Results of the clinical trial

This chapter reports the results of the main RCT.

Recruitment

Recruitment took place over 39 months in 39 UK NHS hospitals from November 2015 to January 2019. The contribution from each site can been seen in *Table 6*.

Screening of participants commenced in November 2015, and the last participant was randomised in March 2019. The complete flow of participants through the GaPP2 trial is shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram in *Figure 1*. Initially, 1348 individuals were approached for participation, of whom 414 were initially considered eligible based on clinical criteria. Of these women, 306 women were randomised, 76 did not return for randomisation for various reasons, 20 were ineligible because they did not return sufficient pain scores and 12 were found to be ineligible following collection of pain scores. A total of 153 participants were assigned to the gabapentin group and 153 to the placebo group. Ten women withdrew from the GaPP2 trial and one woman died. In addition, primary outcome data were unavailable for 51 and 49 women for the average and worst pain scores, respectively (across both groups) (see *Figure 1*). Reasons for trial withdrawal are provided in *Table 7*.

Pregnancy

Of the 306 randomised women, four became pregnant during follow-up in the GaPP2 trial. Of these women, two withdrew from treatment and any further follow-up once pregnancy was known, one withdrew only from treatment once pregnancy was known and one had withdrawn from treatment prior to knowing she was pregnant. All babies were delivered healthy, with no reported abnormalities.

Participant characteristics

The women had a mean age of 30 years and the majority were of white ethnicity. The minimised randomisation ensured balance between groups in terms of the proportion with a dysmenorrhoea pain score of ≥ 4 out of 10 (65% in both groups), current use of sex hormones (65%) and GHQ-12 questionnaire score (mean score of 4.7). The groups were also well balanced in all other baseline characteristics (*Table 8*).

Adherence to treatment

Of those participants with available adherence data, 101 out of 112 (90%) women in the gabapentin group were considered adherent, compared with 101 out of 109 (93%) women in the placebo group. A detailed breakdown of the extent of self-reported adherence to the study drug is shown in *Table 9*.

From the participants' study drug diaries, the overall median number of capsules taken daily per week was calculated for each week by trial group and is presented in *Figure 2*. The median number of capsules taken during the dose-escalation phase was similar between the trial groups; thereafter, the gabapentin group generally took one capsule more than the placebo group throughout the treatment period. The median maximum-tolerated dose was 2100 mg (or placebo equivalent) for both groups at week 4; however, this reached 2700 mg (the maximum permitted dose) in later weeks for some women.

TABLE 6 Recruitment by centre

City/town	Centre	Number of participants randomised
Edinburgh	Royal Infirmary of Edinburgh	60
Aberdeen	Aberdeen Maternity Hospital	27
Glasgow	Queen Elizabeth University Hospital	22
Southampton	Princess Anne Hospital	18
South Tees	The James Cook University Hospital	17
Milton Keynes	Milton Keynes University Hospital	13
Burnley	Burnley General Hospital	13
Kilmarnock	Crosshouse Hospital	11
Chester	Countess of Chester Hospital	10
Yeovil	Yeovil District Hospital	9
East Kilbride	Hairmyres Hospital	9
Liverpool	Liverpool Women's Hospital	9
Sunderland	Sunderland Royal Hospital	9
Kirkcaldy	Victoria Hospital	8
North Tees	University Hospital of North Tees	8
Telford	Princess Royal Hospital	8
Birmingham	Birmingham Women's Hospital	7
Rotherham	Rotherham General Hospital	6
Crewe	Leighton Hospital	5
Birmingham	Birmingham Heartlands Hospital	5
Newcastle	The Royal Victoria Infirmary	5
Walsall	Walsall Manor Hospital	4
Glamorgan	Royal Glamorgan Hospital	4
Oxford	John Radcliffe Hospital	3
Aylesbury	Stoke Mandeville Hospital	3
South Tyneside	South Tyneside District General Hospital	2
London	West Middlesex University Hospital	2
Manchester	St Mary's Hospital	2
London	The Royal London Hospital	2
Peterborough	Peterborough District Hospital	1
Worcester	Worcestershire Royal Hospital	1
Inverness	Raigmore Hospital	1
Darlington	Darlington Memorial Hospital	1
Wrexham	Wrexham Maelor Hospital	1

Chelsea and Westminster, Poole General Hospital, Hartlepool General Hospital, University College London Hospital and University Hospital Birmingham were open to recruitment but did not randomise any participants to GaPP2.

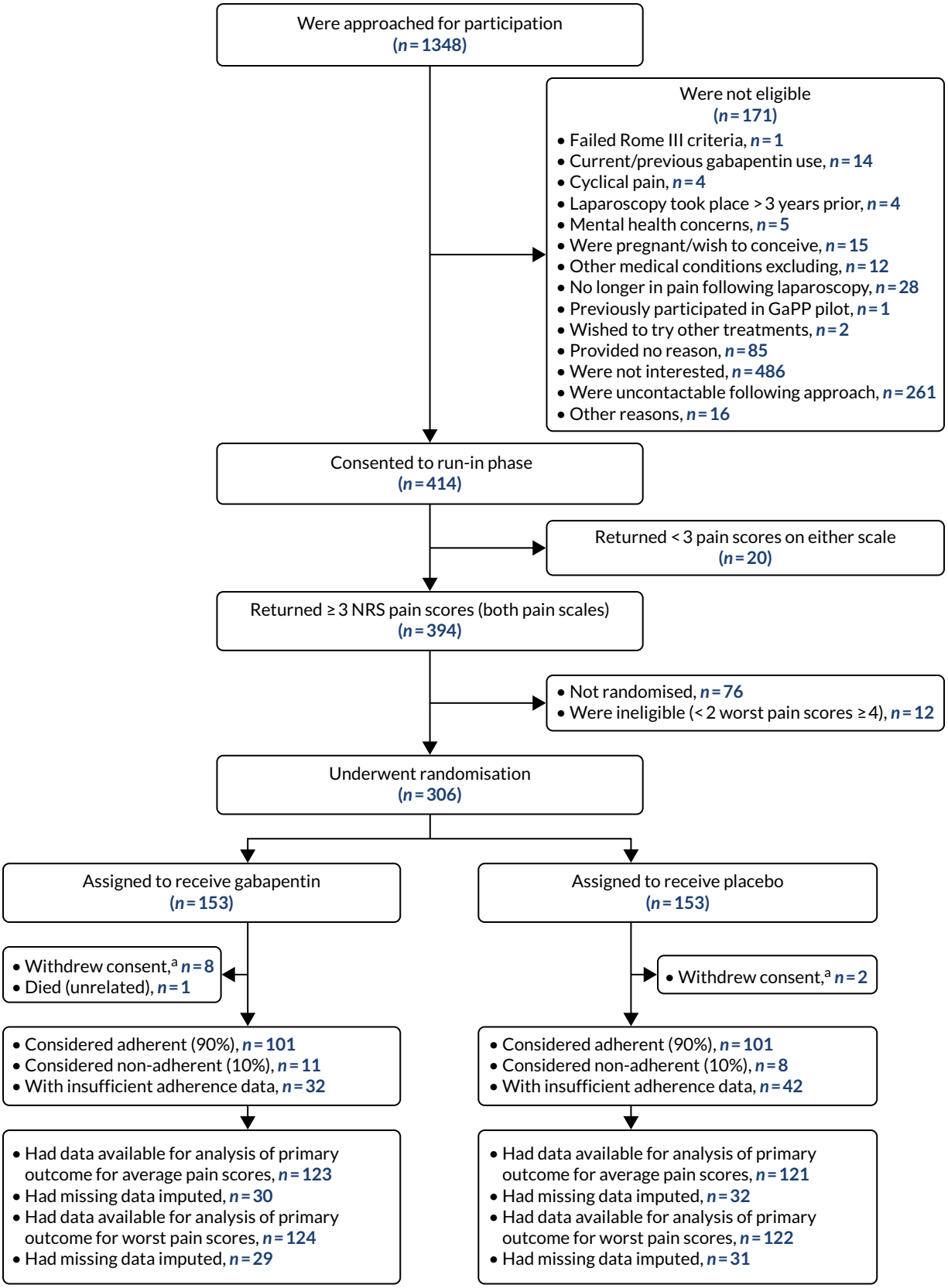

FIGURE 1 The CONSORT diagram of the flow of participants through the GaPP2 trial. a, Withdrawn consent for any further follow-up from the point of withdrawal.

TABLE 7 Withdrawals and deaths in the GaPP2 trial

Type of attrition	Trial group	
	Gabapentin (*N* = 153)	Placebo (*N* = 153)
Withdrawals,[a] **n *(%)***	***8 (5)***	***2 (1)***
Reason for withdrawal (*n*)		
Pregnancy	1	1
Withdrew consent owing to SAE	1	–
Woman feeling discomfort owing to urinary tract infection	1	–
Increased working hours and family commitments	1	–
Does not want further involvement	1	–
No reason provided	3	1
Deaths,* n *(%)	***1 (1)***	***0 (–)***
Cause of death,[b] (*n*)		
Influenza/pneumonia	1	–

a Withdrawn consent for any further follow-up from the point of withdrawal.
b The death was unrelated to trial treatment; see *Table 18* and *Box 2* for further details.

TABLE 8 Demographic and baseline characteristics of the participants

Characteristic	Trial group	
	Gabapentin (*N* = 153)	Placebo (*N* = 153)
Age (years), mean (SD); *n*	30.5 (7.7); 153	30.1 (8.6); 153
Dysmenorrhoea,[a,b] *n* (%)	100 (65)	100 (65)
GHQ-12 score for anxiety and depression,[a,c] *n* (%)	38 (25)	38 (25)
GHQ-12 total score,[c] mean (SD); *n*	4.6 (3.7); 153	4.7 (3.7); 153
Current use of sex hormones,[a] *n* (%)	99 (65)	99 (65)
Patch	2 (2)	0 (–)
Combined oral contraceptive pill	26 (26)	21 (21)
Progesterone-only pill	19 (19)	16 (16)
LNG IUS	38 (38)	45 (45)
Implant	12 (12)	12 (12)
Injection	5 (5)	8 (8)
Ethnicity, *n* (%)		
White	150 (98)	148 (97)
Black (Caribbean/African/other)	1 (1)	0 (–)
Asian (Indian/Pakistani/Bangladeshi/other)	2 (1)	4 (2)
Mixed (Caribbean/African/Asian/other)	0 (–)	1 (1)
BMI (kg/m^2), mean (SD); *n*	27.1 (5.7); 151	27.8 (5.9); 150
Education,[d] *n* (%)		
Primary	4 (3)	5 (3)
Secondary	47 (31)	46 (31)

TABLE 8 Demographic and baseline characteristics of the participants (*continued*)

Characteristic	Trial group	
	Gabapentin (*N* = 153)	Placebo (*N* = 153)
Tertiary	101 (66)	101 (66)
Missing	1	1
Menstruating, *n* (%)	109 (71)	108 (71)
Pain score during periods,[b] mean (SD); *n*	7.7 (1.6); 103	7.6 (1.7); 103
PUF Patient Symptom Scale symptom score,[e] mean (SD); *n*	9.7 (4.1); 153	10.0 (4.5); 148
PUF Patient Symptom Scale bother score,[e] mean (SD); *n*	5.3 (2.6); 153	5.4 (2.8); 150
PUF Patient Symptom Scale total score,[e] mean (SD); *n*	15.0 (6.3); 153	15.5 (7.0); 147
Rescue medications,[f] *n* (%)	114 (75)	112 (73)
NSAIDs	62 (54)	66 (59)
Opiates	78 (68)	68 (61)
Other	61 (54)	58 (52)
Neuropathic pain,[g] *n* (%)	25 (16)	26 (17)
Missing	1	4

BMI, body mass index; LNG IUS, levonorgestrel-releasing intra-uterine system; NSAID, non-steroidal anti-inflammatory drug; PUF, Pelvic Pain and Urinary/Frequency.
a Minimisation variable.
b Dysmenorrhoea is defined as a pain score during periods of ≥ 4. Pain scores range from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.
c GHQ-12 scores range from 0 to 12, where higher scores represent higher levels of mental distress. A score of 0 or 1 meets the definition of anxiety and depression.
d Education unknown (gabapentin, $n = 1$; placebo, $n = 1$).
e Pelvic Pain and Urinary/Frequency Patient Symptom Scale symptom scores range from 0 to 23, bother scores range from 0 to 12 and total scores range from 0 to 35, where low scores indicate better outcomes and high scores indicate worse outcomes.
f Rescue medication includes NSAIDs, opiates and other. Other includes paracetamol.
g Neuropathic pain defined as a PainDETECT score of > 19.

TABLE 9 Adherence

Adherence[a]	Trial group, *n* (%)	
	Gabapentin (*N* = 112)	Placebo (*N* = 109)
Never (0%)	0 (–)	2 (2)
Hardly any (1–24%)	7 (6)	1 (1)
Some (25–49%)	4 (4)	5 (5)
Most (50–74%)	10 (9)	10 (9)
Almost always (75–99%)	36 (32)	34 (31)
Every day (100%)	55 (49)	57 (52)

a How frequently women reported taking their study drug.

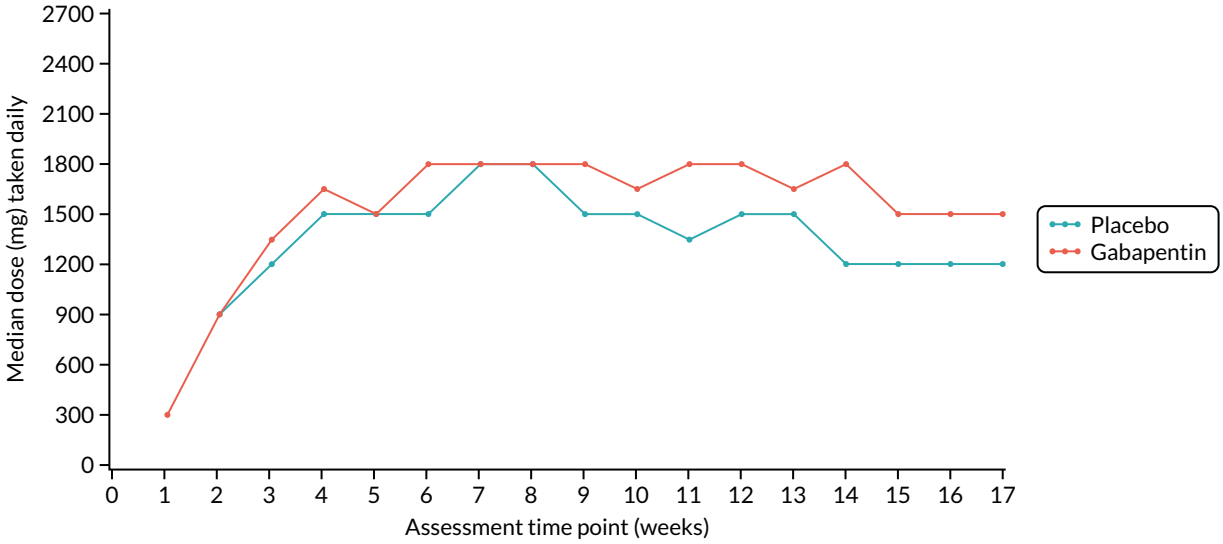

FIGURE 2 Median dose taken daily at each assessment week by trial group. Reproduced with permission from Horne *et al.*[51] © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/.

Primary outcome

There were no significant between-group differences in both the worst and the average NRS pain scores. The mean worst NRS pain score was 7.1 (SD 2.6) in the gabapentin group and 7.4 (SD 2.2) in the placebo group (adjusted mean difference −0.20, 97.5% CI −0.81 to 0.42; $p = 0.47$). The mean average NRS pain score was 4.3 (SD 2.3) in the gabapentin group and 4.5 (SD 2.2) in the placebo group (adjusted mean difference −0.18, 97.5% CI −0.71 to 0.35; $p = 0.45$) (*Table 10* and *Figure 3*).

Sensitivity analyses

In the per-protocol analysis of the primary outcome comparison, including only the 101 women defined as adherent to taking the study drug in each trial group, the mean differences for worst and average pain changed only marginally. Similarly, when multiple imputation was used to estimate missing outcome data, the point estimate and CIs were almost identical to the intention-to-treat analysis of available data. Finally, when the interval between the end of screening and randomisation, when the study drug was commenced, was taken into account in the analysis model, there was no impact on the mean difference for either pain score. These sensitivity analyses are shown in *Table 11*.

A subgroup analysis was carried out for the three prespecified variables used in the minimisation algorithm, namely the presence of dysmenorrhoea, the baseline use of sex hormones and the GHQ-12

TABLE 10 Dual primary outcome measures

	Baseline		End of study[a]		
	Gabapentin group	Placebo group	Gabapentin group	Placebo group	Mean difference[b] (97.5% CI); *p*-value
Worst NRS pain score, mean (SD); *n*	8.4 (1.3); 153	8.6 (1.2); 153	7.1 (2.6); 124	7.4 (2.2); 122	−0.20 (−0.81 to 0.42); 0.47
Average NRS pain score, mean (SD); *n*	5.5 (1.7); 153	5.5 (1.7); 153	4.3 (2.3); 123	4.5 (2.2); 121	−0.18 (−0.71 to 0.35); 0.45

a Worst and average NRS pain scores measured at weeks 13–16 post randomisation.
b Adjusted for baseline score and minimisation variables. Values of < 0 favour gabapentin. The threshold for statistical significance is $\alpha = 0.025$ owing to Bonferroni correction.

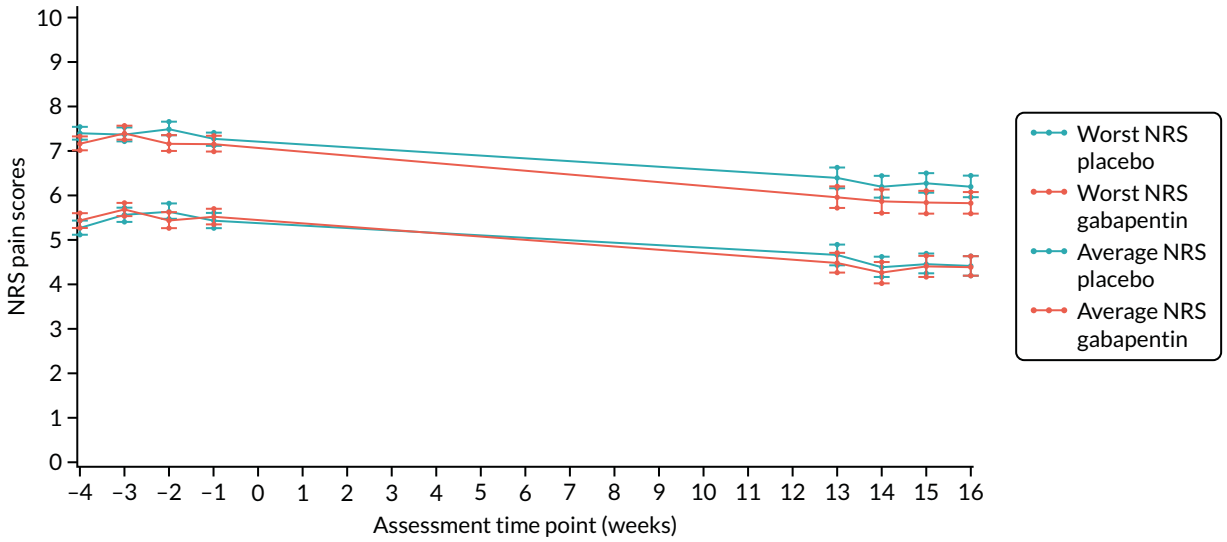

FIGURE 3 Primary outcome plot of worst and average NRS scores. Reproduced with permission from Horne *et al.*[51]

TABLE 11 Sensitivity analyses of the primary outcome

Primary outcome	Baseline		End of study[a]		
	Gabapentin group	Placebo group	Gabapentin group	Placebo group	Mean difference[b] (97.5% CI)
***Worst NRS pain scores,[c] mean (SD);* n**					
Per-protocol analysis[d]	8.5 (1.1); 101	8.6 (1.2); 101	7.3 (2.3); 98	7.5 (2.2); 97	−0.14 (−0.81 to 0.53)
Multiple imputation for missing data	–	–	–	–	−0.19 (−0.72 to 0.33)
Effect of time between screening and randomisation	8.4 (1.3); 153	8.6 (1.2); 153	7.1 (2.6); 124	7.4 (2.2); 122	−0.20 (−0.82 to 0.42)
***Average NRS pain scores,[c] mean (SD);* n**					
Per-protocol analysis[d]	5.6 (1.6); 101	5.4 (1.7); 101	4.4 (2.0); 98	4.5 (2.1); 97	−0.23 (−0.81 to 0.35)
Multiple imputation for missing data	–	–	–	–	−0.21 (−0.66 to 0.24)
Effect of time between screening and randomisation	5.5 (1.7); 153	5.5 (1.7); 153	4.3 (2.3); 123	4.5 (2.2); 121	−0.18 (−0.71 to 0.35)

a Worst and average NRS pain scores measured at weeks 13–16 post randomisation.
b Adjusted for baseline score and minimisation variables (including time between screening and randomisation, for the effect of time between screening and randomisation sensitivity analysis only). Values of < 0 favour gabapentin.
c Pain scores range from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.
d The per-protocol cohort includes only those adherent with treatment allocation (gabapentin, $n = 101$; placebo, $n = 101$).

score defining depression or anxiety. There was no evidence of varying effect in the three prespecified subgroup analyses. The mean scores for worst and average pain in each subgroup are shown in *Table 12*.

Further analysis of pain scores, examined using a repeated-measures model, demonstrated a constant treatment effect across time points for both worst and average scores. The mean scores for worst and average pain at each time point are shown in *Table 13*.

TABLE 12 Subgroup analysis of the primary outcome

Primary outcome	Trial group		Interaction *p*-value
	Gabapentin	Placebo	
***Worst NRS pain scores,[a] mean (SD);* n**			
Dysmenorrhoea			
Yes	7.2 (2.3); 79	7.4 (2.3); 78	0.7
No	6.8 (2.9); 45	7.3 (2.2); 44	
GHQ-12 score			
0–1	6.5 (2.4); 35	6.6 (2.2); 33	0.4
2–12	7.3 (2.6); 89	7.6 (2.2); 89	
Use of sex hormones			
Yes	7.2 (2.5); 81	7.1 (2.3); 81	0.1
No	6.8 (2.7); 43	8.0 (2.0); 41	
***Average NRS pain scores,[a] mean (SD);* n**			
Dysmenorrhoea			
Yes	4.5 (2.1); 79	4.4 (2.2); 77	0.3
No	3.9 (2.5); 44	4.6 (2.2); 44	
GHQ-12 score			
0–1	3.8 (2.2); 35	3.6 (2.2); 33	0.1
2–12	4.5 (2.3); 88	4.8 (2.1); 88	
Use of sex hormones			
Yes	4.5 (2.3); 81	4.3 (2.1); 81	0.3
No	3.9 (2.1); 42	4.8 (2.3); 40	

a Pain scores range from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.

TABLE 13 Repeated-measures analysis

Primary outcome	Trial group		Interaction *p*-value	Mean difference[a] (97.5% CI)
	Gabapentin	Placebo		
Worst NRS pain scores,[b] mean (SD); *n*				
Week 13	6.0 (2.7); 123	6.4 (2.5); 115	0.8	−0.29 (−0.87 to 0.29)
Week 14	5.9 (2.9); 119	6.2 (2.6); 118		
Week 15	5.8 (2.8); 118	6.3 (2.4); 118		
Week 16	5.8 (2.6); 116	6.2 (2.7); 118		
Average NRS pain scores,[b] mean (SD); *n*				
Week 13	4.5 (2.5); 122	4.7 (2.4); 114	0.8	−0.11 (−0.62 to 0.41)
Week 14	4.3 (2.5); 118	4.4 (2.5); 115		
Week 15	4.4 (2.5); 118	4.5 (2.3); 118		
Week 16	4.4 (2.4); 115	4.4 (2.4); 117		

a Adjusted for baseline score and minimisation variables. Values of < 0 favour gabapentin.

b Pain scores range from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.

Secondary outcome results

The proportion of women who reported a decrease in their pain score by at least 30% or 50% between baseline and 13–16 weeks post randomisation was calculated, and the proportions for each group compared. There were no differences in the proportion of participants achieving either percentage reduction (at least 30% or 50%) for both worst and average pain scores between the groups, as shown in *Table 14*.

The patient-reported outcomes were completed at the end of the treatment phase (weeks 16–17). No significant differences were noted in any patient-reported secondary outcomes. Summary scores and point estimates are provided in *Table 15*.

TABLE 14 Reduction in NRS pain scores from baseline

Secondary outcome	Trial group		Risk ratio[a] (99% CI)
	Gabapentin	Placebo	
Reduction in NRS score from baseline (≥ 30%), *n/N* (%)			
Worst NRS pain score	30/124 (24)	21/122 (17)	1.38 (0.72 to 2.64)
Average NRS pain score	44/123 (36)	37/121 (31)	1.12 (0.70 to 1.80)
Reduction in NRS score from baseline (≥ 50%), *n/N* (%)			
Worst NRS pain score	19/124 (15)	10/122 (8)	1.84 (0.71 to 4.75)
Average NRS pain score	27/123 (22)	19/121 (16)	1.36 (0.68 to 2.72)

a Adjusted for baseline score and minimisation variables. Values of > 1 favour gabapentin.

TABLE 15 Patient-reported outcomes

Patient-reported questionnaires	Baseline, mean (SD); *n*		End of study,[a] mean (SD); *n*		Mean difference (99% CI)
	Gabapentin group	Placebo group	Gabapentin group	Placebo group	
SF-12 mental component score	40.3 (10.8); 153	39.5 (11.3); 149	41.3 (10.6); 111	42.5 (11.1); 110	−1.11[b] (−4.60 to 2.39)
SF-12 physical component score	39.0 (9.2); 153	40.1 (9.4); 149	43.8 (10.6); 111	44.6 (10.1); 110	0.49[b] (−2.27 to 3.24)
BPI pain interference score	4.9 (2.6); 152	5.0 (2.6); 152	3.6 (2.8); 111	3.6 (2.8); 112	−0.04[c] (−0.84 to 0.77)
BFI global fatigue score	5.3 (2.4); 153	5.1 (2.3); 152	4.2 (2.5); 111	4.0 (2.7); 112	0.12[c] (−0.65 to 0.89)
GHQ-12 total score	4.6 (3.7); 153	4.7 (3.7); 153	3.8 (3.9); 111	3.0 (3.5); 111	0.72[c] (−0.49 to 1.94)
WPAIQ activity impairment score	53.4 (25.1); 153	52.1 (25.4); 151	39.3 (29.0); 110	38.6 (29.6); 111	−0.77[c] (−9.66 to 8.12)
WPAIQ absenteeism score[d]	10.9 (23.2); 117	12.0 (25.6); 121	10.8 (23.5); 83	4.9 (15.1); 89	5.32[c] (−2.06 to 12.71)

continued

TABLE 15 Patient-reported outcomes (*continued*)

Patient-reported questionnaires	Baseline, mean (SD); *n*		End of study,[a] mean (SD); *n*		Mean difference (99% CI)
	Gabapentin group	Placebo group	Gabapentin group	Placebo group	
WPAIQ presenteesism score[e]	47.1 (26.2); 109	46.5 (26.7); 104	36.4 (28.4); 72	38.0 (29.6); 79	−1.89[c] (−14.43 to 10.65)
WPAIQ work productivity loss score[e]	49.7 (27.9); 109	49.2 (28.2); 103	39.9 (31.1); 72	39.2 (30.7); 79	−0.43[c] (−13.73 to 12.87)
PCS total score	27.4 (12.9); 153	27.2 (13.0); 152	20.8 (14.6); 111	19.7 (12.5); 111	0.48[c] (−3.24 to 4.20)
SAQ pleasure score[f]	10.2 (4.1); 117	9.7 (4.8); 101	10.8 (4.5); 83	10.9 (4.1); 69	−0.14[b] (−1.84 to 1.56)
SAQ discomfort score[f]	2.9 (1.6); 117	3.1 (1.8); 100	3.6 (1.9); 84	3.3 (2.0); 68	0.17[b] (−0.55 to 0.90)
SAQ habit score[f]	0.8 (0.6); 118	0.6 (0.6); 101	1.1 (0.8); 83	0.9 (0.7); 69	0.19[b] (−0.15 to 0.53)
PainDETECT total score	13.6 (6.9); 152	13.3 (6.5); 149	12.4 (6.8); 111	10.9 (6.7); 107	1.19[c] (−0.74 to 3.12)

a Patient-reported questionnaires collected weeks 16–17 post randomisation.
b Mean difference (99% CI), adjusted for baseline score and minimisation variables. Values of > 0 favour gabapentin.
c Mean difference (99% CI), adjusted for baseline score and minimisation variables. Values of < 0 favour gabapentin.
d In women who are currently employed (baseline: gabapentin, $n = 117$, placebo, $n = 122$; week 16: gabapentin, $n = 83$, placebo, $n = 90$).
e In women who are currently employed and working hours in the last 7 days > 0 (baseline: gabapentin, $n = 109$, placebo, $n = 104$; week 16: gabapentin, $n = 73$, placebo, $n = 79$).
f In women who are currently sexually active (baseline: gabapentin, $n = 123$, placebo, $n = 105$; week 16: gabapentin, $n = 87$, placebo, $n = 74$).

Note
Worst and average NRS, BPI and BFI scores range from 0 to 10. SF-12 and WPAIQ scores range from 0 to 100. GHQ-12 scores range from 0 to 12. PCS scores range from 0 to 52. SAQ pleasure scores range from 0 to 18. SAQ discomfort scores range from 0 to 6. SAQ habit scores range from 0 to 3. PainDETECT scores range from −1 to 38.

Women in the gabapentin group reported that they were taking fewer painkillers; however, these differences were marginal and not statistically examined (*Table 16*).

No differences were noted in the number of visits to health-care professionals for CPP between the gabapentin and the placebo groups (*Table 17*).

TABLE 16 Summary of use of painkillers

Use of painkillers since taking study medication	Weeks 4–5, *n* (%)		Weeks 8–10, *n* (%)		Weeks 16–17,[a] *n* (%)	
	Gabapentin group (*N* = 118)	Placebo group (*N* = 121)	Gabapentin group (*N* = 111)	Placebo group (*N* = 108)	Gabapentin group (*N* = 103)	Placebo group (*N* = 101)
Less	65 (55)	61 (50)	57 (51)	52 (48)	52 (50)	42 (42)
Same	42 (36)	46 (38)	38 (34)	42 (39)	40 (39)	45 (44)
More	11 (9)	14 (12)	16 (15)	14 (13)	11 (11)	14 (14)

a Weeks 16–17 are the end-of-study assessment.

TABLE 17 Summary of the number of visits to health-care professionals

Number of health-care visits for CPP	Baseline[a]		End of study[b]	
	Gabapentin group	Placebo group	Gabapentin group	Placebo group
GP*, n *(%)				
Total, *N*	152	152	111	109
Zero	103 (68)	118 (78)	62 (56)	62 (57)
One	28 (18)	16 (10)	16 (14)	21 (19)
Two	12 (8)	10 (7)	16 (14)	11 (10)
Three or more	9 (6)	8 (5)	17 (16)	15 (14)
Hospital outpatients*, n *(%)				
Total, *N*	152	152	111	109
Zero	139 (91)	126 (83)	89 (80)	83 (76)
One	10 (7)	22 (14)	16 (14)	20 (18)
Two	2 (1)	3 (2)	2 (2)	4 (4)
Three or more	1 (1)	1 (1)	4 (4)	2 (2)
Practice nurse*, n *(%)				
Total, *N*	152	152	110	109
Zero	142 (93)	146 (96)	99 (90)	103 (94)
One	7 (5)	6 (4)	8 (7)	3 (3)
Two	1 (1)	0 (–)	1 (1)	1 (1)
Three or more	2 (1)	0 (–)	2 (2)	2 (2)
Physiotherapist*, n *(%)				
Total, *N*	152	152	110	109
Zero	147 (97)	151 (99)	107 (97)	105 (96)
One	5 (3)	1 (1)	1 (1)	0 (–)
Two	0 (–)	0 (–)	1 (1)	1 (1)
Three or more	0 (–)	0 (–)	1 (1)	3 (3)
Other*,[c] n *(%)				
Total, *N*	151	152	110	109
Zero	141 (93)	143 (94)	99 (90)	97 (89)
One	5 (4)	5 (4)	6 (5)	5 (4)
Two	2 (1)	2 (1)	2 (2)	3 (3)
Three or more	3 (2)	2 (1)	3 (3)	4 (4)

a Baseline: in month prior to randomisation.
b End of study (weeks 16–17): since taking trial medication.
c Includes alternative therapist, accident and emergency, occupational health, out-of-hour's doctor, health psychologist, pain specialist, massage therapist, research nurse, research midwife, hospital, dentist, paramedic, magnetic resonance imaging, eye hospital and counsellor for cognitive–behavioural therapy.

Adverse events

A higher proportion of women experienced a SAE in the gabapentin group (10/153, 7%) than in the placebo group (3/153, 2%) ($p = 0.04$) (*Table 18*). One participant, who was in the gabapentin group, died of a complication of pneumonia that was exacerbated by other comorbidities (type 2 diabetes and obesity), but this was not considered to be related to study participation. Dizziness and tiredness were the most frequently reported side effects of the study treatment, but a substantial proportion of women reported drowsiness and changes in mood and urinary patterns. Dizziness, drowsiness and visual disturbances were significantly more common in the gabapentin group than in the placebo group (see *Table 18*).

TABLE 18 Summary of reported side effects and AEs

Safety outcome	Trial group		Risk ratio[a] (99% CI)	*p*-value
	Gabapentin	Placebo		
Side effects*, n/N *(%)				
Dizziness	66/122 (54)	32/114 (28)	1.91 (1.22 to 2.99)	< 0.001
Tiredness	85/129 (66)	68/120 (57)	1.12 (0.86 to 1.44)	0.27
Drowsiness	64/124 (52)	34/116 (29)	1.71 (1.09 to 2.68)	0.002
Change in mood	55/118 (47)	43/112 (38)	1.17 (0.79 to 1.74)	0.29
Change in urinary pattern	37/114 (32)	35/111 (32)	1.00 (0.61 to 1.63)	1.0
Visual disturbances	25/113 (22)	12/110 (11)	2.25 (0.99 to 5.10)	0.01
Change in skin	31/112 (28)	23/110 (21)	1.35 (0.74 to 2.50)	0.20
Different pain	33/116 (28)	37/117 (32)	0.88 (0.53 to 1.46)	0.51
Shortness of breath	17/114 (15)	11/109 (10)	1.45 (0.57 to 3.71)	0.31
AEs				
SAEs, *n/N* (%)	10/153 (7)	3/153 (2)	–	0.04
Total number of SAEs, *n*	12	3	–	–

a Risk ratio (99% CI), adjusted for baseline score and minimisation variables. Values of < 1 favour gabapentin.

BOX 2 Details of SAEs

Gabapentin

On the third dose of medication, onset of side effects occurred within 2 hours. Generalised myalgia occurred especially lower limbs with pain in both groins. Auditory hallucinations and paranoid thoughts, medication stopped. Paraesthesia in the left foot and lower leg 48 hours later. Further weakness and myalgia of both limbs now resolving after cessation of medication.

Increased pelvic pain for a few weeks, GP prescribed oral antibiotics for a bacterial infection. Hospitalised and ultrasound revealed mirena coil had perforated uterus. Mirena coil removed by GA. Patient recovered

Pain and migraine. USS of abdo carried out, 3 cm simple cyst seen and no further treatment required. Lumbar puncture performed. Dural tear occurred, causing prolonged headache and monitoring in hospital. Antibiotics and fluids given.

BOX 2 Details of SAEs (*continued*)

Attended A&E with history of chest pain and shortness of breath for 1 week, body pain for 3 weeks and abdominal distension for 2 months. Brief respiratory arrest following morphine. Admitted to ITU, primary diagnosis pneumococcal pneumonia, acute kidney injury and brief respiratory arrest following morphine. Participants condition deteriorated, had cardiac arrest twice with successful resuscitation. Ventilated and sedated, NG tube in situ. Participant became unstable overnight, sudden loss of cardiac output, resuscitation attempted but unsuccessful. Participant died.

SAE 1:[a] Participant admitted with severe abdominal pain, IV paracetamol and morphine, discharged, booked in for ultrasound of abdomen. Scan showed gallstones, discharged with provisional diagnosis of cholecytitis.

SAE 2:[a] Participant admitted to hospital with acute right side abdominal pain radiating to back, more severe than previous episodes. Treated with analgesia and booked for elective laparoscopic cholecystectomy. Diagnosis gall stones.

Loss of consciousness, panic attacks, hallucinations, nausea, dizziness and drowsy.

SAE 1:[a] Severe left quadrant pain. Attended A&E was kept overnight, abdominal ultrasound, nil acute showed, discharged.

SUSAR 1:[a] Pain behind left eye, noticed bloodshot then eye started blistering. Diagnosed with scleritis.

Participant admitted to hospital with severe headaches, assessed for meningitis. Lumbar puncture. Resolved with no diagnosis.

Right sided pelvic pain for 1 week. Diagnostic laparoscopy performed and ruptured right sided cyst removed. Participant claimed to feel unwell and feverish. Microscopy showed *Escherichia coli* in cyst. IV antibiotics commenced. *E. coli* was laboratory error: human contamination. Participant discharged as no growth in urine.

Anaphylactic shock. Anaphylactic throat swelling and rash sudden onset. Unable to breathe. Paramedics called and treated at home. Likely cause: response to fish consumption.

Placebo

Pain felt in back on right side. Diagnosed with renal colic, nil seen on CT or ultrasound scan, treated with analgesia. Haematuria noted.

Attended hospital for cough with yellow sputum, fever, neck pain and generally feeling unwell for past 7 days. Possible chest infection. Admitted, treated with IV and oral antibiotics and IV fluids. Participant made good clinical improvement.

Dizziness with palpitations, resulting in participant collapsing, attended A&E. Participant had experienced previous episodes prior to commencing IMP. ECG performed with normal sinus arrhythmia, discharged home with a diagnosis of vertigo. Saw GP following episode and referred for cardiology for a 24/72 tape. Diagnosed with postural hypotension.

A&E, accident and emergency; CT, computerised tomography; ECG, electrocardiogram; GA, general aesthetic; ITU, intensive therapy unit; IV, intravenous; NG, nasogastric; USS, ultrasound scan.
a In patients who reported more than one SAE.

Chapter 4 Results of the mechanistic substudy

This chapter describes the mechanistic substudy of the GaPP2 clinical trial.

Introduction

Increasingly, chronic pain conditions are being acknowledged to be associated with a number of central nervous system changes that may be responsible for generating or maintaining the pain.[8] Changes within key regions, including somatosensory, emotion regulation and components of the descending pain modulatory system (DPMS) [including the anterior cingulate cortex (ACC), amygdala, periaqueductal grey matter (PAG) and rostral ventromedial medulla], have been demonstrated both in conditions with a known peripheral pathology (e.g. osteoarthritis,[52–54] shoulder impingement syndrome,[55] endometriosis-associated pain)[56,57] and in those for which no pathology can be found (e.g. fibromyalgia,[58,59] chronic back pain,[60] irritable bowel syndrome[61] and somatoform pain disorder[62]). CPP appears to be no different, with reviews[63,64] identifying similar changes in women with and without identified pathology. However, more is known about irritable bowel syndrome and internal cystitis/bladder pain syndrome than about laparoscopy-negative CPP when considering pain syndromes without identified pathology. Studies of CPP relatively consistently demonstrate widespread hyperalgesia (an increased response to a stimulus that was previously painful) and often allodynia (pain from a previously non-painful stimulus). The neuroimaging studies that have explored the correlates of these sensations implicate a variety of regions (as with other chronic pain conditions), including those involved with emotion regulation and the PAG, as potentially involving dysfunctional pain regulatory mechanisms. However, to date, there are no neuroimaging studies focusing on women with CPP of unknown cause. In addition, women with CPP from a variety of causes have been shown to have hypothalamic–pituitary–adrenal axis dysfunction, autonomic system changes and, frequently, psychological distress.[63]

Gabapentin is a neuromodulator for which there is evidence of efficacy in neuropathic pain conditions,[65] such as postherpetic neuralgia[66] and diabetic neuropathy.[67] In addition, it is also used for conditions in which there is considered to be a central component to the pain (e.g. fibromyalgia). Several animal studies have shown reductions in central sensitisation following intrathecal administration of gabapentin.[68–71] In humans, an important element of gabapentin's efficacy appears to be supraspinal, as intrathecal administrations are insufficient to induce analgesia.[72] In anaesthetised rats, gabapentin induces a dose-dependent increase in thalamic and PAG activation, as well as decreased activation of the limbic system (amygdala and entorhinal cortex).[35] Neuroimaging work in healthy humans has found that a single 1800-mg dose of gabapentin during experimentally-induced central sensitisation reduced both PAG activation and pain-induced deactivations,[33] as well as insula and mesencephalic reticular formation activation.[73] This suggests that gabapentin could constitute an effective 'antihyperalgesic', which supports its use in chronic pain syndromes. However, it remains to be established whether or not gabapentin is efficacious in CPP[17] or what factors may contribute to the likelihood of its success in treating any particular person.

Randomised controlled trials of prospective analgesics always face the hurdle of strong placebo effects. It has been proposed that we need a more mechanistic understanding of how analgesics engage pain networks, and to relate this to symptom change within the individual, to establish true efficacy.[74] Neuroimaging techniques offer a non-invasive and objective means to assess how pain networks are altered over time in the presence of a particular treatment. Within this RCT of gabapentin for CPP, we embedded a pre- and post-treatment fMRI study that examined brain responses to punctate stimuli.

The aims were to determine (1) whether or not gabapentin, in comparison with placebo, altered brain responses to pain; (2) whether or not this covaried with positive clinical responses over time; and (3) whether or not pre-treatment brain responses could predict positive clinical response. In addition to measures of subjective pain, we were concerned with our participants' mental well-being and ability to function in day-to-day life; a series of participant-reported validated questionnaires encompassing these domains were, therefore, collected at baseline and after 16 weeks of treatment.

Objectives

- Determine the presence of central nervous system changes in women with CPP and no obvious underlying pathology.
- Determine the effect of gabapentin on central pain processing in women with CPP and no underlying pathology.
- Determine whether or not there are baseline fMRI measures that correlate with response to treatment.
- Determine whether or not there are clinical measures that correlate with response to treatment.

Methods

Participants were drawn from those who were recruited to the GaPP2 trial from the Edinburgh region. In total, 45 women underwent a pre-treatment baseline MRI scan, and 25 women returned for a second scan after 12 weeks of maximum-tolerated dose of the intervention (gabapentin or placebo). *Figure 4* demonstrates group allocation and reasons for exclusion. In addition to the inclusion and exclusion criteria of the main trial, additional exclusion criteria applied to those undergoing MRI: the presence of implants not compatible with magnetic resonance, such as pacemakers, and claustrophobia.

Sample size

The sample size was based on data from our pilot study, GaPP1.[1] In that study, 12 women had a fMRI scan after the 12 weeks of treatment, with 11 usable data sets. Of these, five were using placebo and six were using gabapentin. A priori region of interest (ROI) analysis demonstrated a $> 1.2\%$ difference in the blood oxygen level-dependent signal in the PAG and a $> 1.4\%$ difference in the left posterior insula between the groups. With a power of $> 80\%$ and $p = 0.05$, we, therefore, calculated that we would need to recruit 50 women (25 per treatment group) to detect a difference in signal from key ROIs. This sample size is greater than that used in a number of other pharmacological fMRI studies.

Magnetic resonance imaging scanning

Scanning took place at the Edinburgh Imaging Facility, Queen's Medical Research Institute,[75] using a 3T Siemens Magnetom Verio scanner (Siemens Healthcare GmbH, Erlangen, Germany). Scanning constituted a high-resolution structural scan; functional imaging during both a resting state scan and the application of punctate stimuli; field map acquisitions; and pseudo-continuous arterial spin labelling. The primary outcome of interest for the mechanistic study was functional responses to punctate stimuli, and this is the focus of this chapter. Future analyses will incorporate data from the remaining sequences acquired.

The blood oxygen level-dependent functional images were acquired using an echoplanar T2* GRAPPA (generalised autocalibrating partial parallel acquisition) gradient echo pulse sequence, with a repetition time (TR) of 2500 milliseconds, an echo time (TE) of 30 milliseconds, a flip angle of 90°, a field of view

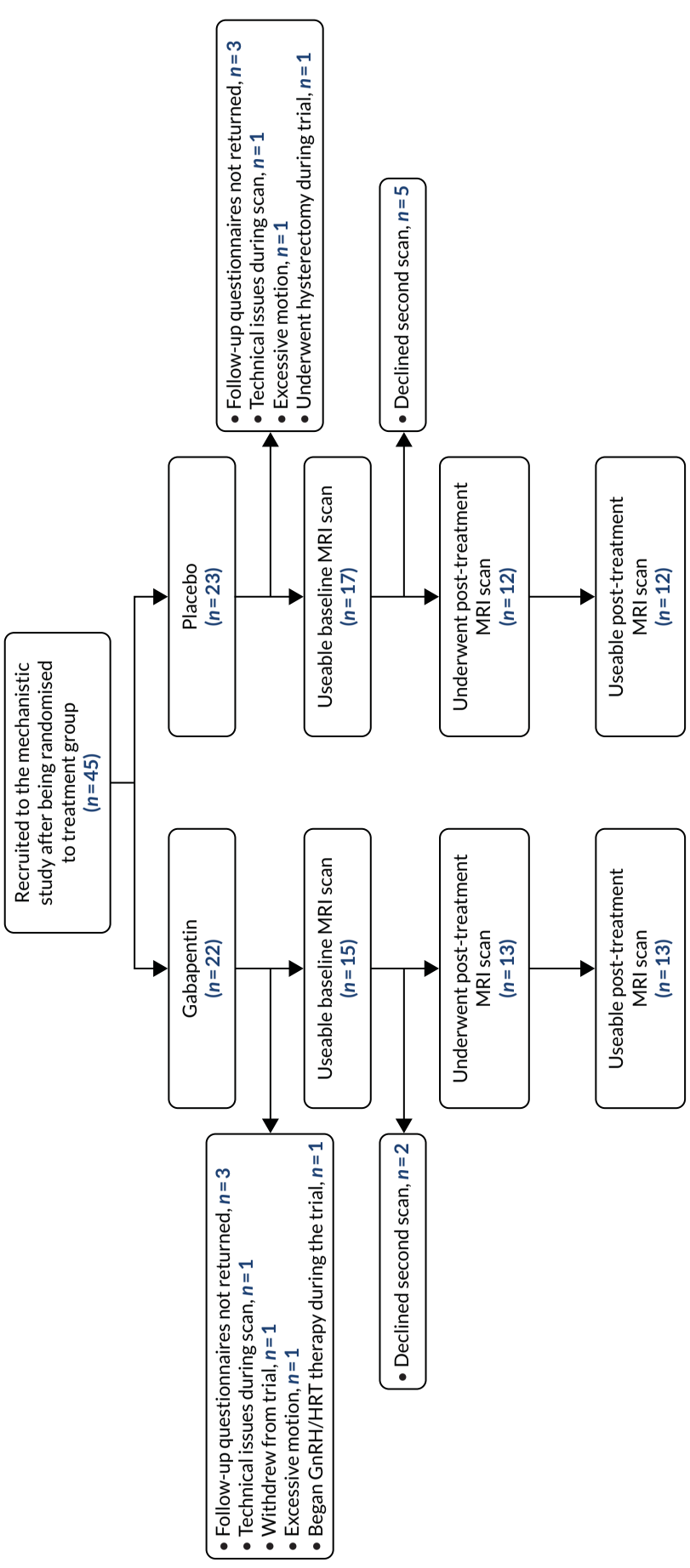

FIGURE 4 Participant group allocation and reasons for exclusion from the study analysis. GnRH, gonadotropin-releasing hormone; HRT, hormone replacement therapy.

(FOV) of 192 mm, 45 interleaved contiguous slices and a resolution of 3 × 3 × 3 mm. A T1-weighted structural image was acquired using a MPRAGE (magnetisation-prepared rapid gradient echo) sequence, with a TR of 2300 milliseconds, a TE of 2.98 milliseconds, a FOV of 256 mm, a resolution of 1 × 1 × 1 mm and a flip angle of 9°. The punctate task was 10 minutes and 50 seconds, that is 260 volumes, the first four of which were discarded to reduce T1 saturation effects. The resting state scan lasted 8 minutes and 20 seconds, with 200 volumes. The resting state scan was performed prior to the punctate scan to avoid flaring participants' pain and, thus, not truly measuring a resting state. Gradient field maps were acquired with the same dimensions as the functional data, and TE1 (echo time 1) 4.92 milliseconds, TE2 (echo time 2) 7.38 milliseconds. The pre-treatment scan occurred at visit 1 of the trial schedule, and the post-treatment scan between week 13 and week 16 (visit 5 of the trial schedule). Both scans were identical and for each participant took place during the same phase of their menstrual cycle.

The punctate scan involved the application of 39 punctate stimuli using a 300 g Touch Test von Frey filament (Ugo Basile, Gemonio, Italy) (6.65 mm) in an event-related design. These were applied by five researchers who had undergone appropriate training and were directed by timed auditory cues. The mean interstimulus interval was 16 seconds, with random jitters of 2.5 seconds. Stimuli were applied to the lower abdomen, 10 cm above the superior edge of the pubic bone. In contrast to the original grant application, pain processing at a site distant to the clinical pain was not carried out owing to the limitation of the equipment used for thermal stimulation of the left hand. Use of the thermal stimulation equipment in the magnetic resonance imaging (MRI) scanner created significant noise, which lead to distortion of the fMRI signal that was not correctable with analysis tools. We attempted to reduce this noise by altering filters between the control and the scanner rooms, but were unable to make a meaningful improvement. Thus, the thermal stimulation component of the paradigm was removed. As this was at a control site rather than the site of referral of pain, it was not the primary fMRI sequence of interest and, thus, the key data we had aimed to collect are still available (evoked pain from a referral site and resting state data).

Outcome measures

- fMRI measures of evoked pain.
- fMRI measures of resting brain activity and connectivity.
- Post-treatment minus pre-treatment difference in fMRI measures.
- Correlation of participant-reported outcomes and fMRI measures.

Statistical analysis plan

The SAP for the mechanistic substudy was agreed between the research team, including the a priori ROI and whole-brain analyses previously described. Further exploratory analyses of this rich data set will continue, to improve our understanding of the main mechanistic findings.

Covariates of interest

An a priori selection of participant-reported secondary outcomes was drawn from the clinical trial and incorporated into a series of exploratory analyses of fMRI data. NRS pain scores were taken from the pre-treatment and post-treatment assessments for average and worst pain. Physical and mental well-being measures were used from the Short Form Health Survey (SF-12) (with the mental component score and physical component score). The degree to which pain interfered with daily living was taken from the BPI. Fatigue and psychological distress were taken from the BFI and GHQ-12, respectively. Levels of rumination, pain magnification and helplessness were taken from the PCS. Neuropathic pain scores were taken from PainDETECT.

Punctate functional magnetic resonance imaging data analysis

The principal analysis of the punctate fMRI data took place within Statistical Parametric Mapping (SPM12) software [version 12 (7771); The Wellcome Centre for Human Neuroimaging, University College London, London, UK]. Data were unwarped using the field maps and realigned to a mean image, which was co-registered to each person's T1-weighted structural image. This was, in turn, segmented and warped to the Montreal Neurological Institute (MNI) space, with warp parameters applied to the co-registered functional images. The data were finally smoothed with a 5 mm full width half maximum kernel. Quality assurance procedures examined the data for slice spikes and significant motion (defined as a single-volume motion exceeding half a voxel, i.e. 1.5 mm). Volumes that demonstrated problems were replaced with a dummy volume interpolated from those acquired just before and after it, and such volumes were represented within a nuisance regressor within the affected participants' first-level design matrices. If data contained more than 10 significant movement events, the participant was excluded.

For each participant, the onset of each punctate stimulus was represented as a delta function and was convolved with the canonical haemodynamic response function, as well as its temporal and dispersion derivatives. Nuisance regressors representing motion parameters (and dummy volumes where applicable) were included, and the contrast for the canonical punctate regressor was taken forward into random-effects flexible-factorial analyses. This modelled the main effects of participant, time, treatment and the treatment group by time interaction. Incorporating the main effects of the treatment and participant would in part account for any nuisance variance between the groups at baseline. The main effects of treatment, time and the interaction were assessed, with clusters being reported as significant if they achieved a whole-brain family-wise error rate (FWE) corrected threshold of $p < 0.05$. To enhance sensitivity within the brainstem, a further analysis was restricted to within an anatomical mask of the midbrain, pons and medulla, as defined by Brodmann,[76] and implemented within the WFU Pickatlas software (version 3.0.5; Wake Forest University School of Medicine, Winston-Salem, NC, USA).[77,78]

For any regions demonstrating significant treatment-by-time interactions, the impact that this had on our covariates of interest was assessed in a series of general linear models. The first eigenvariate was extracted from significant clusters and analysed in SPSS version 24.0 (IBM SPSS Statistics for Macintosh, IBM Corporation, Armonk, NY, USA). Each participant-reported measure was the dependent variable, treatment group was a random factor and the changes in brain activation over time were entered as covariates, with covariate-by-treatment interactions being modelled.

Finally, to determine whether or not punctate activation at baseline was able to predict subsequent clinical response, the post-treatment minus pre-treatment difference for each participant-reported measure was analysed within a general linear model using SPSS. This modelled treatment as a random factor, and the pre-treatment punctate-induced responses from those regions demonstrating a treatment-by-time interaction were included as covariates.

Results

Behavioural measures

Punctate stimuli were perceived as painful by some women. Pain intensity ratings after the punctate paradigm ranged from 0 to 8 (pre-treatment scan: 3.56 ± 2.36; end-of-treatment scan: 3.12 ± 2.15). There was no significant change in pain intensity of these stimuli between the two scans for either group, and there was not a time × treatment interaction [placebo: scan 2 > scan 1, $t(11) = -0.764$, $p = 0.461$; gabapentin: scan 2 > scan 1, $t(11) = -0.672$, $p = 0.515$; time × treatment interaction $F(1,22) = 0.006$, $p = 0.938$].

The effects of punctate stimuli

To demonstrate validity of the task, the main effects of punctate stimuli across both treatment groups and visits are displayed in *Table 19* and *Figure 5*. This demonstrated activation and deactivation of regions typically associated with central pain processing, including bilateral insula, thalamus, ACC and somatosensory cortices.

Punctate validation analyses

The main effects of time (across both treatment groups) and the effects of treatment at time 1 (post allocation but pre intervention) were analysed. A lack of significant findings for these analyses would support the validity of the data as a whole. There were no main effects of time that achieved statistical significance ($p > 0.551$ FWE-corrected). Comparing the two treatment groups prior to treatment showed one region of significant difference: the left postcentral gyrus [Brodmann area = 40; MNI −36, −26, 74; peak $z = 4.98$; kE (cluster extent) = 134; cluster $p < 0.001$ FWE-corrected], which was not part of the primary somatosensory cortex.

TABLE 19 Regions demonstrating significant activation in response to punctate stimuli across groups and visits

Region	Brodmann area	MNI co-ordinates			Peak *z*	Cluster size	Cluster *p* (FWE-corrected)
Activations		***x***	***y***	***z***			
Right IFG/insula	13/44/47	48	18	−10	7.02	3025	< 0.001
Left SPL/postcentral gyrus	2/7/40	−30	−50	50	6.56	3264	< 0.001
Left IFG/insula/STG	13/22/47	−58	12	−4	5.84	963	< 0.001
Right IPL/SMG/MTG	2/22/40	64	−36	40	5.81	5725	< 0.001
Left cerebellum	–	−28	−72	−26	5.50	1560	< 0.001
Right cerebellum	–	28	−48	−50	5.37	67	0.034
Left cuneus/lingual gyrus	17/18	−6	−98	10	5.30	856	< 0.001
Right ACC/SFG	8/32	4	40	24	5.10	541	< 0.001
Left MFG/precentral gyrus	6	−50	12	42	5.07	450	< 0.001
Bilateral caudate/thalamus/SN/STN	–	−14	−10	8	5.07	1026	< 0.001
Right SFG	8	14	50	40	5.01	105	0.003
Left MFG/IFG	9/46	−44	38	32	4.62	448	< 0.001
Right ITG	37	50	−46	−22	4.60	115	0.001
Right cuneus	18	14	−84	30	4.44	74	0.020
Left ACC	32	−12	20	28	4.23	75	0.019
Deactivations							
Left pre/postcentral gyri	3/4/6	−14	−36	72	6.78	2169	< 0.001
Right medial frontal gyrus	10	2	56	−8	5.80	162	< 0.001
Left precuneus	19	−20	−86	46	4.66	124	0.001
Left postcentral gyrus	3	−38	−16	50	4.12	62	0.048

IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SN, substantia nigra; SPL, superior parietal lobule; STN, subthalamic nucleus.

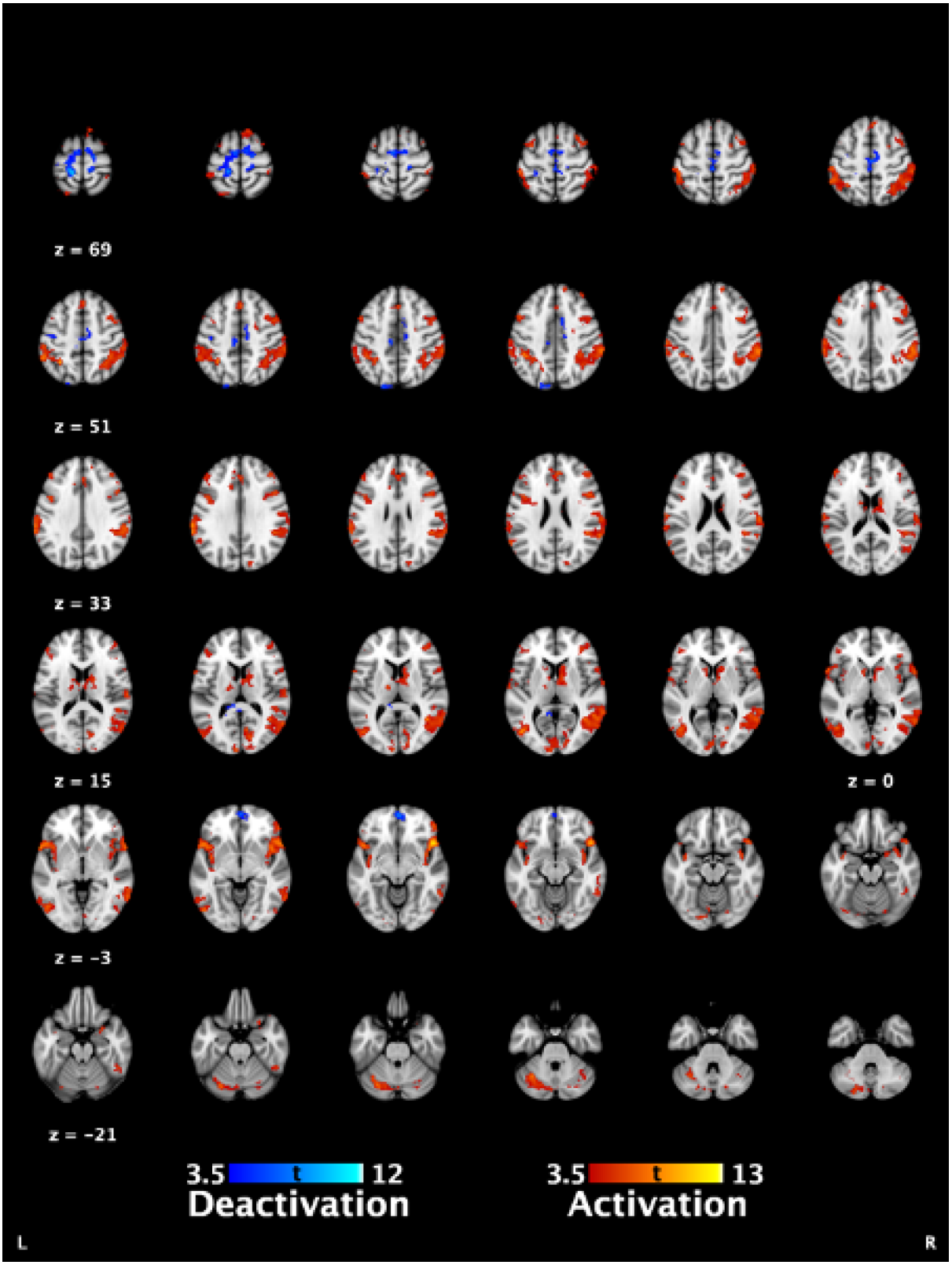

FIGURE 5 Axial slices displaying whole-brain significant punctate-induced activation and deactivation. Displayed clusters have $p < 0.05$ FWE-corrected for the whole-brain volume.

Punctate: treatment-by-time interaction

The critical contrast of interest was to establish whether or not gabapentin altered brain activity over time compared with changes seen in the placebo group. The treatment-by-time interaction showed significant effects in the ACC (pregenual and anterior midcingulate subdivisions) and cuneus (*Table 20* and *Figure 6*). Data were extracted from these regions, and post hoc *t*-tests confirmed that pain-evoked activity within the ACC significantly decreased following treatment with gabapentin [$t(12) = -5.763$; $p < 0.001$] and increased in the placebo group [$t(11) = 3.784$; $p = 0.003$]. In the cuneus, activation was significantly decreased in the gabapentin group only [$t(12) = 5.126$, $p < 0.001$, vs. $p = 0.204$ for placebo]. These results remained highly significant after covarying for baseline average pain scores within a repeated-measures analysis of covariance ($p < 0.001$). No areas demonstrated a significant interaction in the brainstem mask. These findings remained significant when the pain intensity ratings obtained after the punctate paradigm were included as a covariate.

Covariance with clinical measures of interest

The treatment-by-time interaction in ACC was related to a significant improvement in BPI pain interferences scores [$F(1,17) = 12.905$; $p = 0.002$; see *Figure 6*c). For women in the gabapentin group, those who showed larger reductions in ACC activation post treatment also had the greatest improvements

TABLE 20 Regions showing a significant treatment-by-time interaction

Region	Brodmann area	MNI co-ordinates	Peak *z*	Cluster size	Cluster *p* (FWE-corrected)
Right ACC	24/32	6, 32, 22	4.63	293	< 0.001
Right cuneus	18	16, −72, 14	4.16	66	0.013

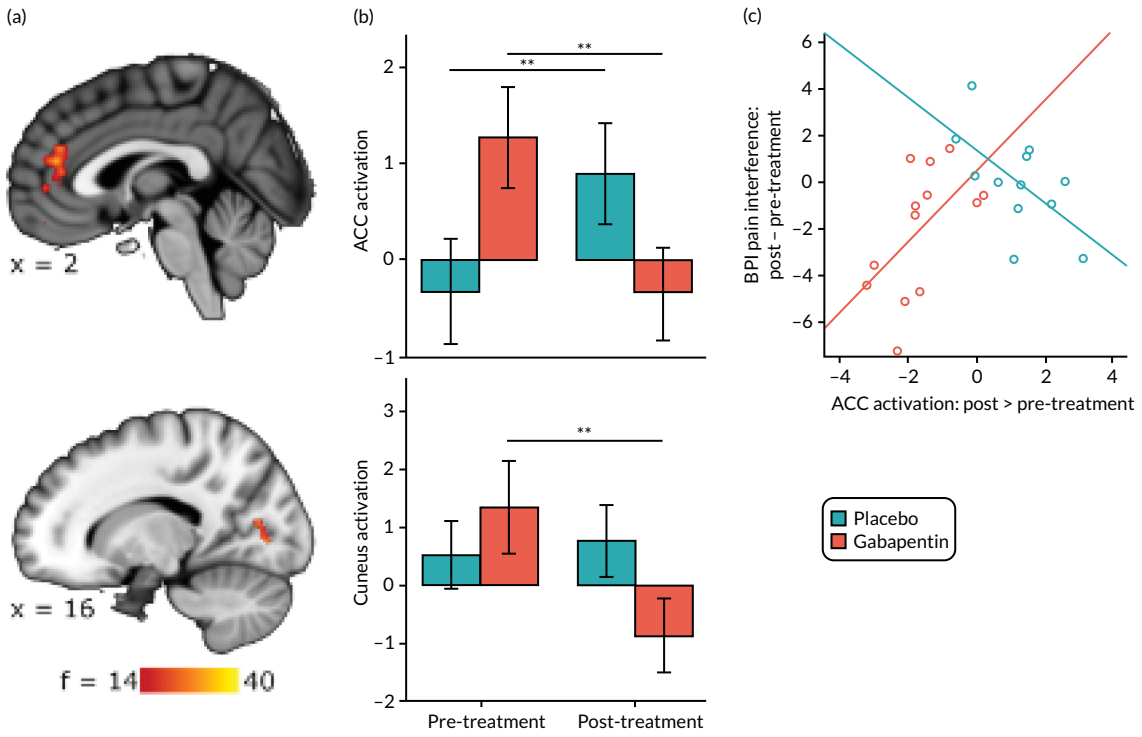

FIGURE 6 Treatment-by-time interaction punctate activation, and associated clinical correlations. (a) Sagittal slices depict the ACC and cuneus, from top to bottom. Both clusters are $p < 0.05$ FWE-corrected for the whole-brain volume; (b) extracted activation displaying the nature of the treatment-by-time interactions, ** denotes post hoc *t*-test significance of < 0.005. Error bars are 95% CI; (c) scatterplots demonstrating the relationships between changes in BPI pain interference scores and ACC activation. For BPI pain interference score, negative changes over time indicate an improvement in symptoms.

in their pain interference scores (Pearson's $r = 0.562$; $p = 0.046$). The placebo group demonstrated a markedly different pattern: the more their ACC response increased over time, the greater their improvement on the BPI pain interference score (Pearson's $r = -0.605$; $p = 0.037$). Cuneus changes were not found to differentially impact on clinical improvement.

Punctate: predicting a positive response from baseline data

The ACC activation at baseline significantly predicted improvements in the physical component of the SF-12 across both groups [physical component score, $F(1,17) = 9.341$; $p = 0.007$], but also demonstrated a significant group interaction [$F(1,17) = 5.452$; $p = 0.032$]. *Figure 7a* suggests that, although those with elevated pre-treatment ACC activation appear to improve in general, the effect is especially pronounced in the gabapentin group.

The ACC responses at baseline also predicted improvements in neuropathic pain scores as measured by PainDETECT [$F(1,17) = 7.142$; $p = 0.016$]. The pattern was similar to that seen in the physical component score (see *Figure 7b*) in that elevated pre-treatment ACC predicted better outcomes, but this was much more marked in those taking gabapentin.

In all cases, the black line represents the fit across both groups. For those in the gabapentin group, the greatest improvements in (1) physical well-being (i.e. increases in SF-12 physical component scores) and (2) neuropathic pain (i.e. decreased PainDETECT scores) are seen in those with elevated pre-treatment ACC responses. However, bivariate correlations between the pre-treatment ACC activation and the clinical measures at baseline did not show a significant positive relationship with PainDETECT scores ($r = 0.374$; $p = 0.066$).

To examine this further in the clinical trial's primary outcome measures, the study sample was split according to the median scores of average pain (post treatment minus pre treatment). Within the gabapentin group, those who showed the most improvement in average pain had elevated baseline ACC activation [$t(11) = 2.309$; $p = 0.041$] and a more pronounced reduction in ACC activation after treatment [$t(11) = 2.664$; $p = 0.022$]. This was not seen in the placebo group ($p > 0.314$). There were no such effects in the cuneus or for worst pain scores.

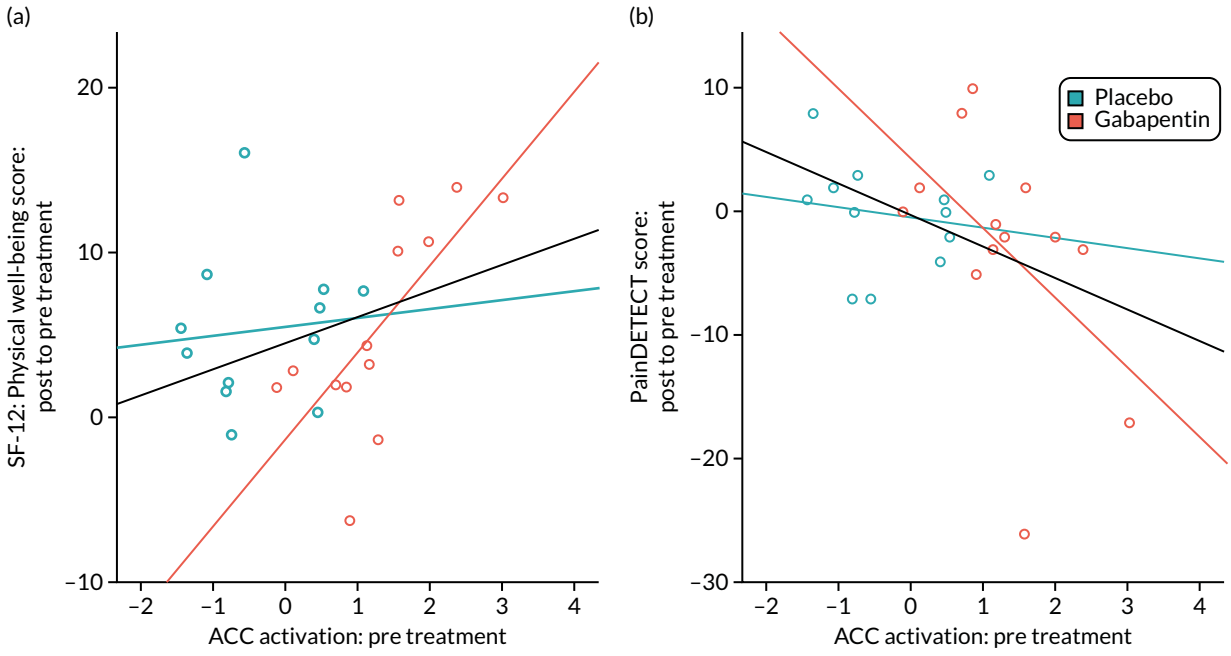

FIGURE 7 Predicting response to gabapentin using pre-treatment punctate activation. (a) SF-12 physical well-being score; and (b) PainDETECT score.

Discussion

In the mechanistic group of the GaPP2 trial, we have shown that a 12-week course of gabapentin appears to exert an effect on the ACC in women with CPP. Those taking gabapentin show a significant reduction in ACC responses to punctate stimuli after treatment, which in turn was associated with improvements in pain interference scores. ACC activity at baseline also predicted those most likely to respond to gabapentin, with participants who had the most ACC activation in response to punctate stimuli showing the largest improvements in physical well-being and neuropathic pain. Although these findings are in a small cohort only, the ability of neuroimaging to detect a signal of efficacy and disentangle treatment effects from placebo is one of the strengths of a design such as this.

The ACC is known to play a role in pain processing[8] and is a critical component of the DPMS.[79] In humans, pain responses during experimentally induced central sensitisation[33] and multiple chronic pain conditions[53,60,61,80] are associated with increased rostral ACC activation. The ACC regions demonstrating a treatment-by-time interaction encompassed both the most rostral aspects of the anterior midcingulate cortex, and the pregenual subdivision. In healthy volunteers, these regions mediate placebo analgesia[81] in part via mu opioid receptors.[82] Interestingly, infusion of the rostral ACC with gabapentin in rats with spinal nerve ligation reduced the aversive aspects of pain and facilitated pain relief-motivated behaviours. This effect appeared to be dependent on endogenous opioid signalling, and was not associated with reduced tactile allodynia itself.[83] Others have proposed that pharmacological modulation of the ACC may allow for a reduction of the distress associated with chronic pain, without impairing the physiological function of acute pain.[84] This would be consistent with the regions known roles in processing negative emotions,[85] resolving conflict[86] and goal selection/maintenance.[87] It is proposed that the ACC integrates the aversiveness of pain to guide adaptive avoidant behaviours.[85] It is, therefore, significant that we observe gabapentin reducing ACC responses to pain in a way that correlates with improvements in pain-related interference in daily living.

We also demonstrated a significant treatment-by-time interaction in the cuneus, although it is less clear what role it may be playing. Its perfusion has been shown to be altered in migraine sufferers, in a manner inversely related to induced pain scores.[88] It also appears to relate to the affective appreciation of pain, with pain-induced responses correlating with affective ratings in healthy volunteers.[89] Here, we found no clinical correlations.

Here, we present evidence that gabapentin acts to alter function within the DPMS, the degree to which correlates with clinical improvement. However, we did not observe significant treatment-by-time interactions in other DPMS brainstem structures, such as the PAG or rostral ventromedial medulla. It may be that this study was underpowered to detect such changes, or that assessing simple differences in activation did not capture the relationship between these structures and other DPMS regions. Alternatively, it may be that the regions in the brainstem are too small to be detected with whole-brain/brainstem analyses.

The evoked data are the most meaningful with regard to understanding the mechanism of drug activity. The resting state data will be explored to understand this mechanism in more detail (informed by the results of the evoked analysis, i.e. specific ROIs to investigate) and to further understand a global impact of gabapentin, and how it potentially generates adverse effects.

Previous imaging studies of gabapentin in chronic pain have used a single pre-scan dose,[73,90] and, as far as we are aware, this study is the first to perform longitudinal neuroimaging pre treatment and post treatment in a cohort of women with established CPP. To date, most pharmacological functional imaging studies have involved male participants, in part because of concerns regarding controlling for hormonal variation and also to avoid exposure to potentially teratogenic effects of medication. Therefore, significant strengths of this study are that it involved a cohort of immediate relevance to CPP and that all women underwent their post-treatment scan at a similar point in their menstrual

cycle to the baseline scan. This study has also demonstrated the utility of incorporating pre-treatment and post-treatment neuroimaging into a clinical trial of pain medication; we can present evidence that gabapentin acts on chronic pain by modulating the DPMS system via ACC (in contrast to other mechanisms implicated in CPP).[63] We can also suggest that a subgroup of women, those demonstrating pronounced ACC responses to punctate stimulation, are more likely to benefit from taking gabapentin than others. The challenge remains to identify preclinical factors correlating with these enhanced ACC responses that would allow responders to be identified without the need for neuroimaging. The neuropathic PainDETECT score shows promise; however, no significant correlation with baseline ACC activation was identified.

Chapter 5 Discussion

Main findings

This multicentre, randomised, double-blind, placebo-controlled trial showed that in women with CPP and no obvious pelvic pathology gabapentin was no more effective than placebo in reducing pain. The incidence of side effects and SAEs was higher in the gabapentin group than in the placebo group. Gabapentin appears to exert an effect on the ACC in women with CPP. Those taking gabapentin show a significant reduction in ACC responses to punctate stimuli after treatment, which in turn was associated with improvements in pain interference scores.

Strengths

To the best of our knowledge, this study is the only randomised placebo-controlled clinical trial to report on the treatment of CPP with gabapentin. The robust study design, which included blinding to treatment allocation of both participants and investigators, ensured internal validity, enabling the results to be interpreted with confidence. Randomisation was concealed via a computer-generated allocation sequence and achieved balanced groups with respect to pain symptoms during menstruation, psychological functioning and concomitant hormone use, all potentially prognostic for reported pain.

Chronic pelvic pain can fluctuate or follow the menstrual cycle; therefore, eliciting a pain score at a single time point is unlikely to capture the effect of gabapentin or reflect the women's experience of pain. Instead, we sought a pain score weekly over a 4-week period, asking participants to rate both worst and average pain for the preceding week, and defined a minimum number of responses to create a valid outcome. Although it is preferable to have a single primary outcome, a survey of our patient involvement group found that worst pain and average pain were equally important to women. We, therefore, chose to use dual primary outcomes and considered both worst and average pain scores. These outcomes were considered separately and an improvement in one (or both) would conclude that gabapentin was efficacious. All of the outcome data in the GaPP2 study were subjective or participant-reported outcomes (rather than laboratory measurements), but the study was blinded, which reduced the risk of incurring assessor bias.

We calculated the sample size based on a recognised minimally important difference for chronic pain of 1 point on a 0–10 NRS, and used a SD from a comparable pilot study. We applied appropriate adjustments to account for the dual primary outcome in both the sample size calculation and the analysis. We recruited the target number of women and missing outcome data were as anticipated, with follow-up rate for the dual primary outcome of 80% of women.

A high proportion of women reported taking at least half of the study drug doses throughout the trial. The dose of gabapentin that participants received was based on individual adjustment of the dose by the participants themselves, which reflected their perception of pain relief and side effects. Adjustments were made in accordance with existing dosing recommendations, up to a dose of 2700 mg per day, and the final median doses ranged from 1200 mg per day to 1800 mg per day during the treatment phase. This is in line with the current NeuPSIG [neuropathic pain special interest group of IASP (International Association for the Study of Pain)] recommendations for the treatment of neuropathic pain,[91] where gabapentin at a dose of 1200–3600 mg in three divided doses is a first-line treatment.

The fact that a mechanistic substudy was included is a strength of this study as it allows us to begin to disentangle the treatment response from the placebo response, in addition to exploring the mechanism

by which gabapentin itself might work. fMRI provides a sensitive, objective outcome measure and, thus, allows a smaller sample size to be used than when patient-reported outcomes alone are used. All imaging was performed at the same site on the same MRI scanner and, thus, no additional variation with regard to data collection systems needs to be accounted for in the analysis. Furthermore, the evoked stimulus investigated was a punctate probe, which delivers a fixed force. This is less subject to variation than, for example, thermal stimuli, for which differences in methods of fixation to the skin or equipment calibration can produce variation in the actual stimulus delivered. It is relatively unusual for cohorts in such studies to be all women and, therefore, these findings may be of relevance to other chronic pain conditions (that are more prevalent in women), given how little is known about the mechanism of action and predictors of response to gabapentin.

Limitations

There are some limitations of our study that should be considered.

Twenty per cent of participants failed to provide pain scores at the end of treatment. Our analytical approach involved imputation of missing responses using a recognised method, but still makes an assumption about missing data being missing at random. Any deviation from this assumption could give rise to different results. The sensitivity analysis was almost identical to the observed data comparison and the CIs for both did not reach the minimally important clinical difference, so it is unlikely that a meaningful treatment effect was missed because of missing data.

There was a potential placebo response observed in the trial. Although we acknowledge that placebo responses are observed universally in almost all placebo-controlled randomised clinical trials,[92] the response observed in this trial is very relevant because of the side-effect profile of gabapentin and its potential addictive properties.[29] However, the trial was not designed to investigate this placebo response.

The rate of adherence to the trial regimen (women reported taking at least half of the study drug doses throughout the trial) was high; however, this was not validated against an objective method, such as pill counting.

The limitations of the mechanistic substudy were the small sample size, as not all women returned for their follow-up scan despite the best efforts of the research team. Moreover, by chance, the baseline data between the two groups were different for a number of variables. However, this has been accounted for as much as possible in the analysis strategies.

Despite recruitment from many hospitals across the UK, the study participants are overwhelmingly white women, which limited the generalisability of our study. CPP and dysmenorrhoea are commonly reported across the globe,[3] but barriers to seeking medically and culturally appropriate care may exist,[93] which is compounded by the well-documented under-representation in clinical trial research among black, Asian and minority ethic populations in the UK.[94]

Interpretation of findings

In conclusion, our results show that gabapentin did not relieve pain or improve physical and psychological function in women with CPP, as compared with placebo, over a course of 16 weeks. Gabapentin was associated with higher rates of side effects than placebo.

Data from a recent review[65] showed that the number needed to treat to be 6.6 (95% CI 5.0 to 10) to achieve at least 50% pain-intensity reduction in painful diabetic neuropathy (1331 patients), and 6.7 (95% CI 5.4 to 8.7) to achieve at least 50% pain-intensity reduction in postherpetic neuralgia (2260 patients).

The NeuPSIG review[91] suggests that across all neuropathic pain conditions the number needed to treat is 6.3 (95% CI 5.0 to 8.3), for a 50% reduction in pain intensity with an associated number needed to harm of 25.6 (95% CI 15.3 to 78.6). The lack of treatment effect of gabapentin in women with CPP may reflect differences in the aetiology of neuropathic pain, suggesting that recommendations from guidelines on neuropathic pain may not apply to women with CPP.[13,91] Alternatively, it may be that women gain less benefit but are more susceptible to harm from gabapentin. It is not possible to extract information on sexual dichotomies in responses from any of the existing systematic reviews.

Gabapentin was associated with higher rates of side effects than placebo in the trial (e.g. dizziness, drowsiness and visual disturbances), which is consistent with other published studies.[21,95] Another recent meta-analysis of all trials for postherpetic neuralgia and painful diabetic neuropathy[95] showed that, compared with placebo, gabapentin was associated with more drowsiness (14% for gabapentin vs. 5% for placebo; $p < 0.001$), dizziness (19% for gabapentin vs. 7% for placebo; $p < 0.001$), peripheral oedema (7% for gabapentin vs. 2% for placebo; $p < 0.001$) and gait disturbance or ataxia (14% for gabapentin vs. 3% for placebo; $p < 0.001$).

Although more women in the placebo group were able to correctly guess their allocation at the end of the treatment period (78/106 placebo, 54/111 gabapentin), their use of rescue medication was similar. It cannot be concluded that women who perceived that they were taking placebo compensated by increasing their analgesic use and, thus, negated any effect of gabapentin.

Public and patient involvement

We have been supported throughout the project by the charity Pelvic Pain Support Network (PPSN) and, in particular, its chief executive officer. Public and patient involvement was crucial in improving the acceptability of the GaPP2 trial and promoting engagement of gynaecologists. We engaged with PPSN throughout, improving our understanding of the opinions and uncertainty surrounding treatments for CPP, and the anecdotal evidence of the use of gabapentin that women have provided here. A survey disseminated by PPSN helped us to decide to include worst and average pain scores. We also discussed the other outcome questionnaires to be included in the trial. Members of the PPSN commented on patient-facing materials to ensure that they were clear and comprehensive. The PPSN promoted participating trial centres with their contact details on the website. We will engage with PPSN regarding the dissemination of our findings, providing a Plain English summary of the findings and the uncertainties around the evidence we have discussed here. This will be distributed via PPSN's website and on their social media channels. Any future research groups taking forward the research recommendations from this project would benefit from engaging with PPSN.

Chapter 6 Conclusions

Implications for practice

The key findings of the GaPP2 trial are clear and sufficiently generalisable to inform clinical practice. Women with CPP and no obvious pelvic pathology should be advised that gabapentin may not alleviate their pain and may give them unpleasant side effects.

Recommendations for future research

In our opinion, no further research is required to evaluate the role of gabapentin in the management of women with CPP and no obvious pelvic pathology. Questions that remain unaddressed relate to the use of other pharmacological interventions (monotherapy vs. combination therapy), physiotherapy and cognitive–behavioural therapy for treating women with CPP. These are outlined below.

Research question

What is the clinical effectiveness, cost-effectiveness and tolerability of pharmacological monotherapy compared with other pharmacological interventions (monotherapy vs. combination therapy), physiotherapy and cognitive–behavioural therapy for treating women with CPP?

Population

Women with a diagnosis of CPP with and without demonstrable pathology. Demonstrable pathology could include endometriosis, adenomyosis, adhesions, pelvic inflammatory disease, irritable bowel syndrome, bladder pain syndrome, nerve entrapment and musculoskeletal pain.

Intervention(s)

Any pharmacological agent as monotherapy or combination therapy, physiotherapy and cognitive–behavioural therapy. The pharmacological agents include:

- neuromodulators (e.g. amitriptyline, imipramine, nortriptyline, duloxetine, gabapentin and pregabalin)
- opiates (e.g. co-codamol, co-dydramol, dihydrocodeine, fentanyl, morphine, oxycodone, tapentadol and tramadol)
- ovarian suppressive drugs (e.g. combined oral contraceptive pill, progestogens and gonadotrophin-releasing hormone agonist)
- others (e.g. cannabis sativa extract).

Comparator(s)

Any of the pharmacological agents listed above as monotherapy compared with any combinations of the pharmacological agents listed above as combination therapy compared with physiotherapy and cognitive–behavioural therapy. Compare the treatment response across different groups of participants with different underlying aetiology.

Outcome(s)

- Patient-reported global improvement (on a 7-point scale).
- Patient-reported improvement in daily physical and emotional functioning, including sleep (on a 9-point scale).
- At least 30% and 50% pain reduction (on a 0–10-point NRS).
- Mean change from baseline pain scores (on a 11-point NRS).

- Withdrawal owing to adverse effects of the pharmacological agents.
- Adverse effects of the pharmacological agents.
- Health-related quality of life (e.g. EuroQol-5 Dimensions questionnaire).

Study design

- Randomised controlled trial.
- All participants should have a 'washout' period before assessment for inclusion in the study.
- Concomitant medications should not be allowed or should be restricted and maintained at a stable dose during the study. Differences in concomitant pain medication usage at baseline should be clearly described in each trial group, including details of the number of patients on different drugs.
- Rescue pain medications should either not be allowed or be accurately documented if they are used.

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Publications

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data are vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives. You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

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