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

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Scientific summary

The GaPP2 RCT

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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.

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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.

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Trial registration

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

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