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PrEgabalin for Treatment Resistant generalised Anxiety disorder (PETRA)

Submission date
05/08/2023

Recruitment status
No longer recruiting

Registration date
19/09/2023

Overall study status
Ongoing

Last Edited
25/03/2026

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
Background and study aims
Generalised anxiety disorder (GAD) is characterised by at least 6 months of symptoms including disproportionate worry, nervousness, poor concentration and sleep disturbance. GAD is a disabling condition that is highly comorbid with depression and other anxiety disorders. The prevalence of GAD is higher than depression in the UK yet is less often recognised in general practice. However, the rate of GAD recorded in primary care has increased dramatically, especially in young people. Pregabalin is an effective anti-anxiety drug when used on its own. We want to find out if a combination of an antidepressant and pregabalin is effective for anxiety where the antidepressant alone has not previously been very effective.

AIMS
1. To investigate whether pregabalin, in addition to an antidepressant, is an effective and cost-effective treatment for generalised anxiety disorder (GAD) in people who have not responded to antidepressant treatment
2. To investigate any adverse effects associated with the combined treatment of pregabalin and antidepressants
3. To investigate withdrawal symptoms from pregabalin when it is used in combination with antidepressants
4. To investigate the acceptability of prescribing pregabalin in addition to antidepressants for GAD from the perspectives of patients and general practitioners using qualitative methods

Who can participate?
Eligible participants will have an ICD11 diagnosis of GAD, be aged 18-74 years, be currently taking an antidepressant and meet a symptom severity criterion. They will not have responded to two or more antidepressants.

What does the study involve?
Participants are randomly allocated to pregabalin 50-200 mg or placebo using a flexible dosing strategy that will mimic usual care and enhance retention. All will receive usual care from their general practitioner who will continue to prescribe their existing antidepressant. Participants will be followed up for about 30 weeks.

What are the possible benefits and risks of participating?
GAD is highly comorbid with other anxiety disorders and depression. Anxiety is best described as a continuum between “normal” levels and more severe clinically important anxiety that affects function. Our approach is to include comorbidities of depression and other anxiety disorders if people meet the diagnostic criteria for GAD. This better reflects the decisions that general practitioners (GPs) have to make if someone presents with generalised anxiety. Further, someone with other diagnoses will still benefit from any reduction in anxiety even if their comorbid condition is not influenced. Finally, reducing GAD symptoms could also lead to benefits for other comorbid conditions. For example, generalised anxiety can increase later depressive symptoms so treatments that improve anxiety symptoms could also reduce depressive symptoms.
Psychological treatments (e.g. cognitive behavioural therapy) and antidepressants are the main options for GAD. The evidence so far is that psychological and pharmacological benefits are additive for most depressive and anxiety disorders so optimising pharmacological treatment will also be of benefit for those receiving psychological treatments. The COVID-19 pandemic may have led to increased anxiety. Access to psychological treatments is limited, with lengthening waiting lists, so research into improving the pharmacological treatment of anxiety is timely. There is evidence that selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and mirtazapine (a noradrenergic and specific serotonergic antidepressant) are effective in GAD. After antidepressant treatment, about 50% of people still have significant generalised anxiety, even if there has been some improvement. There is currently no consensus and much clinical uncertainty about what pharmacological treatments should be used after non-response or partial response to antidepressants.

Where is the study run from?
Comprehensive Clinical Trials Unit at UCL (UK)

When is the study starting and how long is it expected to run for?
August 2023 to September 2026

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
1. cctu.petra@ucl.ac.uk
2. Dr Glyn Lewis, glyn.lewis@ucl.ac.uk

Contact information

Type(s)
Scientific

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Type(s)
Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
1007569

Protocol serial number
143397

Study information

Scientific Title
PrEgabalin for Treatment Resistant generalised Anxiety disorder (PETRA) a double-blind randomised controlled clinical trial to evaluate the addition of pregabalin to primary care patients who have not responded or partially responded to treatment with antidepressants

Acronym
PETRA

Study objectives
Primary objective:
To investigate whether pregabalin, in addition to an antidepressant, is an effective and cost-effective treatment for generalised anxiety disorder (GAD) in people who have not responded to antidepressant treatment.

Secondary objectives:
To assess:
1. Changes in anxiety and depression
2. Changes in global improvement and quality of life
3. Adherence to study medication
4. Adverse events of pregabalin and antidepressants including withdrawal symptoms from pregabalin
5. Use of alternative anxiolytic methods (other anti-anxiety treatments including alcohol

consumption and benzodiazepine use)
6. Resource use including primary care resource use, antidepressant medication use, health resource use (including psychological therapies), social care resource use
7. Employment and time off work
8. Changes in cognitive assessments - tests of reinforcement learning , working memory and general cognitive function

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 15/09/2023, East Midlands - Leicester Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048227; leicestercentral.rec@hra.nhs.uk), ref: 23/EM/0192

Study design
Interventional double-blind randomized parallel-group placebo-controlled trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Generalised Anxiety Disorder (GAD)

Interventions
Participants will be randomised using Sealed Envelope https://www.sealedenvelope.com/ with a 1:1 ratio to pregabalin 50-300 mg or placebo using a flexible dosing strategy that will mimic usual care. Participants will initially start at one tablet (50 mg pregabalin) and may increase their dose up to a maximum of six tablets (300 mg) where appropriate.

Participants will be given clear instructions to titrate the dose starting:
Day 1-4 one tablet a day (50 mg)
Day 5-9 two tablets a day (100 mg)
Day 10-14 three tablets a day (150 mg)
Day 15 onwards four tablets a day (200 mg)

At the PI's discretion, study medication may be increased to five tablets a day (250 mg) or six tablets a day (300 mg).

Participants will be advised to stop increasing the medication dose at the point they find it is satisfactorily effective, or if they experience adverse effects which are not tolerable up to a maximum of four tablets. They will continue taking the study medication until the tapering period (see below) starts at the 26-week follow-up assessment.

After completion of the 26-week assessment, participants will reduce their study medication over the next 28 days. Participants will be given specific instructions for tapering depending on the number of tablets they are taking.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Pregabalin

Primary outcome(s)
Anxiety symptoms measured with GAD7 at 12 weeks as a continuous score

Key secondary outcome(s))
1. Anxiety and depression:
1.1. Anxiety scores (GAD7) at week 3, week 6, week 26 and week 30
1.2. Dichotomised anxiety scores (present or absent based on a cut-off of GAD7 ≥10) at week 3, week 6, week 12, week 26 and week 30
1.3. Depressive scores (PHQ9) at week 3, week 6, week 12, week 26 and week 30
1.4. Panic symptoms at all follow-up visits 3, 6, 12, 26, ~30 weeks
2. Global improvement and quality of life measured using EQ5D5L and SF-12 at week 3, week 6, week 12, week 26 and week 30
3. Adherence to study medication assessed using a single item asking if they are still taking study medication and a five-item scale used in the MIR and Cobalt studies repeated at all follow-up visits
4. Withdrawal and adverse events:
4.1. Adverse effects of pregabalin and antidepressants – based on the Toronto scales for antidepressants (as used in GENPOD study) with additional symptoms of pregabalin side effects and pregabalin withdrawal repeated at all follow-up visits
4.2. Withdrawal symptoms from pregabalin – these are included in the adverse effect scale above repeated at all follow-up visits
4.3. Stopping the study medication repeated at all follow-up visits
5. Use of alternative anxiolytic methods:
5.1. Alcohol consumption (AUDIT PC) measured at every visit
5.2. Benzodiazepine use measured at every visit
6. Resource use and employment:
6.1. Primary care resource use (6 months pre and post randomisation)
6.2. Antidepressant medication collected from primary care medical records (6 months pre and post randomisation)
6.3. Self-reported health resource use (baseline and 26 weeks asking about previous 6 months) including psychological therapies
6.4. Self-reported social care resource use (baseline and 26 weeks asking about previous 6 months)
6.5. Employment and time off work (baseline and 26 weeks asking about previous 6 months)
7. Cognitive assessments. Tests of reinforcement learning, working memory and general cognitive function (administered through a web browser using the Gorilla platform) at 3 and 12 weeks

Completion date
30/09/2026

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 26/11/2025:

1. Meeting ICD-11 criteria for generalised anxiety disorder using the revised clinical interview schedule (CIS-R)
2. Scoring ≥12 on the CIS-R total score
3. Age 18-74 years (upper age limit to ensure the validity of our measures)
4. Currently taking an SSRI, SNRI or mirtazapine (at specified doses; the full list is in the trial guidance document that all investigators at sites have to follow) for a minimum of 8 weeks prior to randomisation and with good adherence as agreed with PI
5. Treatment with at least one other antidepressant before their current antidepressant

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Previous key inclusion criteria:

1. Meeting ICD-11 criteria for generalised anxiety disorder using the revised clinical interview schedule (CIS-R)
2. Scoring ≥12 on the CIS-R total score
3. Age 18-74 years (upper age limit to ensure the validity of our measures)
4. Currently taking an SSRI, SNRI or mirtazapine in BNF recommended doses for a minimum of 8 weeks prior to randomisation
5. Treatment with at least one other antidepressant before their current antidepressant

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
74 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 26/11/2025:

1. Currently taking pregabalin or use within the previous 1 month (i.e. wash-out of 1 month required)

2. Taking regular antipsychotics
3. Have bipolar disorder, psychosis, or alcohol misuse
4. Current or recent opiate dependence where there is a risk of pregabalin abuse
5. Current use of opiates with a daily dose of >15 morphine milligram equivalents
6. Creatinine clearance (measured by eGFR is acceptable)
7. Requirement to use home oxygen machines daily for respiratory problems
8. Experience breathlessness and score ≥3 on the MRC Dyspnoea scale ('Stops for breath after walking about 100 metres or after a few minutes on the level' or 'Too breathless to leave the house or breathless when dressing or undressing')
9. Regular daily use of z drugs >3.75 mg zopiclone or >10mg zolpidem
10. Regular daily use of benzodiazepines or regular night-time use >10mg diazepam or equivalent
11. Currently receiving psychotherapy and within 6 months of starting therapy
12. Pregnancy, planned pregnancy and women who are breastfeeding
13. Unable to complete self-administered scales in English (some scales are not validated in other languages)
14. Taking part in another CTIMP

Previous key exclusion criteria:

1. Currently taking pregabalin or use within the previous 1 month (i.e. wash-out of 1 month required)
2. Taking regular antipsychotics
3. Have bipolar disorder, psychosis, or alcohol misuse
4. Current or recent opiate dependence where there is a risk of pregabalin abuse
5. Current use of opiates with a daily dose of >15 morphine milligram equivalents
6. Creatinine clearance <30 ml/min
7. Requirement to use home oxygen machines
8. Experience breathlessness and score ≥3 on the MRC Dyspnoea scale ('Stops for breath after walking about 100 metres or after a few minutes on the level' or 'Too breathless to leave the house or breathless when dressing or undressing')
9. Regular daily use of z drugs >3.75 mg zopiclone or >10mg zolpidem
10. Regular daily use of benzodiazepines or regular night-time use >10mg diazepam or equivalent.
11. Currently receiving or about to receive psychological treatment
12. Pregnancy, planned pregnancy and women who are breastfeeding
13. Unable to complete self-administered scales in English (some scales are not validated in other languages)
14. Taking part in another CTIMP

Date of first enrolment
31/08/2023

Date of final enrolment
31/03/2026

Locations

Countries of recruitment

United Kingdom

England

Study participating centre
University College London
Gower St
London
England
WC1E 6BT

Study participating centre
University of Keele
Keele
Newcastle Under Lyme
England
ST5 5BG

Study participating centre
University of Bristol
Beacon House
Queens Rd
Bristol
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BS8 1QU

Study participating centre
Vauxhall Primary Health Care
Vauxhall Health Centre
Limekiln Lane
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Sponsor information

Organisation
University College London

ROR

https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the PETRA study will be available to other researchers interested in collaboration with the PETRA team upon request from cctu.petra@ucl.ac.uk. Data will be available for sharing after the publication of the trial results. Researchers wishing to access PETRA data should contact the Trial Management Group in the first instance, clearly outlining the purposes. The researchers expect any researchers to collaborate with the PETRA research team and any requests will need to be approved by the TSC and Sponsor.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3.0	18/09/2023	27/01/2026	No	Yes
Protocol file	version 6.0	18/11/2024	27/01/2026	No	No