Clinical trial results:
A Phase IV double blind multi-site, individually randomised parallel group controlled trial investigating the use of citalopram, sertraline, fluoxetine and mirtazapine in preventing relapse in patients in primary care who are taking long term maintenance antidepressants but now feel well enough to consider stopping medication.

Summary

EudraCT number	2015-004210-26
Trial protocol	GB
Global end of trial date	08 March 2020
Results information	
Result version number	v1 (current)
This version publication date	14 May 2022
First version publication date	14 May 2022
Summary attachment (see zip file)	ANTLER full report (nejmANTLER_trial.pdf) ANTLER supplementary (nejmANTLERsupplement.pdf)

Trial information

Trial identification	
Sponsor protocol code	14/0647
Additional study identifiers	
ISRCTN number	ISRCTN15969819
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	University College London
Sponsor organisation address	Tottenham Court Road, London, United Kingdom,
Public contact	Anne Marie Downey, PRIMENT Clinical Trials Unit, UCL , sponsor.priment@ucl.ac.uk
Scientific contact	Anne Marie Downey, PRIMENT Clinical Trials Unit, UCL , sponsor.priment@ucl.ac.uk

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the effectiveness and cost-effectiveness of antidepressant medication in preventing relapse in UK primary care in people who have had two or more episodes of depression (including the current episode) have taken antidepressants for at least 9 months and are now well enough to consider stopping the antidepressant.
We will carry out an individually randomised controlled trial that will compare (1) continuing with antidepressant medication (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) with (2) replacement of the medication with a placebo after a tapering period. We will follow up participants for 12 months.
Primary outcome will be time to depressive relapse.

Protection of trial subjects:

1. Risk of relapse
This risk was explained to participants and their GP. If the participant was concerned about the possibility of relapse they were told to immediately seek medical opinion from their GP or the PI. The PI could withdraw the participant from study medication and refer back to their GP for further treatment.
2. Risk of withdrawal symptoms
To reduce the risk, there was a 4 week period after randomisation when IMP dose (citalopram, sertraline and mirtazapine) was halved, then another 4 weeks when the dose was quartered before the placebo was introduced. Patients who were taking fluoxetine received 20 mg of IMP and placebo on alternate days in the first month. Since fluoxetine has a long half-life patients received placebo only from the second month. We also monitored withdrawal symptoms.
3. Risk of self-harm
People with depression have an increased risk of self-harm and suicide. We had a Suicidal Ideation SOP and staff were trained to follow this procedure.
4. Potential risk associated with other medical conditions
It was possible that some potential participants with other medical conditions would have been taking antidepressants even though they were subject to a caution. As the person had been taking antidepressants for at least 9 months the decision to prescribe antidepressants had already been taken by their GP. We did not exclude those people. However, the PI made the final decision about their enrolment person into the trial.
5. Risk of QT prolongation with citalopram
Citalopram can prolong the QT interval in higher doses. In ANTLER only people were taking 20mg citalopram so the risk was low. PI considered if there were any other medications that might also prolong the QT interval and took a decision whether participant should be randomised.
6. Risk associated with IMP distribution
IMP was dispensed from a central pharmacy via Royal Mail by recorded delivery to participant home addresses or GP practices.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 478
Worldwide total number of subjects	478
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	349
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We recruited patients from 150 general practices across four research sites in England (Bristol, London, Southampton, and York). Recruitment was done through database searches of electronic health records, after which potentially
eligible patients were sent an invitation letter, or via direct referral at primary care visits.

Pre-assignment

Screening details:

Eligible participants had at least two episodes of depression; were aged 18–74 years; were taking antidepressants for 9 months or more and were on citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30 mg; and were well enough to consider stopping their medication. Participants were excluded if they met ICD-10 criteria for depression

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Discontinuation arm

Arm description:

Placebo arm: 1 month of the current medication at half the dose, taken as 1 oral capsule per day of citalopram 10mg, sertraline 50mgor mirtazapine 15mg. This will be followed by one month of the medication at a quarter of the dose taken as 1 oral capsule per day alternating between a half dose capsule (citalopram 10mg, sertraline 50mg or mirtazapine 15mg) and a placebo capsule on odd and even days of the month. From the third month on participants will be taking placebo 1 capsule per day for the remainder of the study.
Placebo arm for fluoxetine: 1 month of the current medication at half the dose, taken as 1 oral capsule a day alternating between fluoxetine 20mg and a placebo capsule on odd and even days of the month. From the second month on participants will be taking placebo 1 capsule per day for the remainder of the study.

Arm type	Placebo
Investigational medicinal product name	Citalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Citalopram 20mg,

Arm title	Maintenance arm

Arm description:

The active medication arm will take 1 capsule per day orally (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) for 12 months.

Arm type	Active comparator
Investigational medicinal product name	Citalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: Citalopram 20mg,	
Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Sertraline 100mg	
Investigational medicinal product name	Fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Fluoxetine 20mg	
Investigational medicinal product name	Mirtazapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Mirtazapine 30mg	

Number of subjects in period 1	Discontinuation arm	Maintenance arm
Started	240	238
Completed	181	209
Not completed	59	29
Consent withdrawn by subject	38	18
Lost to follow-up	21	11

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	478	478	
Age categorical Units: Subjects			
Adults (18-64 years)	349	349	
From 65-84 years	129	129	
Gender categorical Units: Subjects			
Female	349	349	
Male	129	129	

End points

End points reporting groups

Reporting group title	Discontinuation arm

Reporting group description:

Placebo arm: 1 month of the current medication at half the dose, taken as 1 oral capsule per day of citalopram 10mg, sertraline 50mgor mirtazapine 15mg. This will be followed by one month of the medication at a quarter of the dose taken as 1 oral capsule per day alternating between a half dose capsule (citalopram 10mg, sertraline 50mg or mirtazapine 15mg) and a placebo capsule on odd and even days of the month. From the third month on participants will be taking placebo 1 capsule per day for the remainder of the study.
Placebo arm for fluoxetine: 1 month of the current medication at half the dose, taken as 1 oral capsule a day alternating between fluoxetine 20mg and a placebo capsule on odd and even days of the month. From the second month on participants will be taking placebo 1 capsule per day for the remainder of the study.

Reporting group title	Maintenance arm

Reporting group description:

The active medication arm will take 1 capsule per day orally (citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg) for 12 months.

Primary: Primary outcome

End point title	Primary outcome[1]

End point description:

The primary outcome was the first relapse of depression during the 52-week trial period, as evaluated in a time-to event analysis.

End point type	Primary

End point timeframe:

Primary outcome was assessed at 12 weeks follow-up

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Further details on statistical analyses included in the attached report.

End point values	Discontinuation arm	Maintenance arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	232		
Units: Relapse of depression no.	135	92		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Since this was a phase 4 trial of licensed medications within their licensed indications, we recorded adverse events of special interest only, using the Toronto and DESS scales at each follow-up.

Adverse event reporting additional description:

Serious adverse events were recorded by investigators using a recording-and-reporting form created by the trial sponsor. The principal investigator at each site rated each event according to seriousness, causal relationship to a trial medication, severity, and outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	3

Reporting groups

Reporting group title	Overall

Reporting group description:

As the data is blinded, the figures provided is a sum of the events reported in both the maintenance and discontinuation arm.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As this trial is a phase IV trial of licensed medications used within its licensed indication with a well-established safety profile, AEs were not recorded (apart from those AEs of special interest included in the follow up assessments).

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 478 (3.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer			
subjects affected / exposed	2 / 478 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			

subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Lumbar decompression			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgery			
subjects affected / exposed	2 / 478 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac problems			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticulitis			

subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prolapse			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cancer			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgery			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 478 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 478 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	1. Amendment includes an additional follow-up questionnaire 6 weeks after randomisation in order to capture information regarding withdrawal symptoms. The original follow-up was at 12 weeks but after discussion with PPI and others we decided it was important to include a further assessment towards the end of the tapering period to assess symptoms of depression, anxiety, physical symptoms and withdrawal symptoms. This questionnaire will be completed by participants either by post or over the telephone and will be accompanied by the cover letter. 2. The schedule of dispensing medication for participants was changed in order to reduce the cost and to make it more convenient for the participants. The scheduling has changed from dispensing one month's supply at months 0 and 2 and then bimonthly thereafter; to dispensing medication bimonthly for the duration of the 12 month follow-up period. The new schedule will be familiar to the trial participants because it is in lines with their GP repeat prescription system. The exclusion criteria for the PHQ9 score is a score of above 12. In some places in the protocol this was stated as 'above 10' or '12 and above' (pages 19 and 20), therefore the protocol has been updated to ensure the exclusion criteria for the PHQ9 score is consistent throughout. 3. The BDI-II is mentioned in the list of self-administered questionnaires on page 52. This is an error as we are not using the BDI-II in any of the assessments in the trial, so this has been removed from the protocol. 4. The protocol has been updated to include the 6-week follow-up wherever the schedule of follow-ups has been stated in the protocol, reflect the change in the schedule of dispensing study medication to participants, updated to explain the correct treatment procedures for the IMP. There will be no 'quarter dose' tablet for citalopram, sertraline and mirtazapine and no 'half dose' tablet for fluoxetine.
24 April 2017	Changes to the IMPD had to be made as it was necessary to change the supply of fluoxetine.
31 August 2017	The PHQ9 is a screening tool rather than a diagnostic measure so such discrepancies are to be expected. On reflection, we were using the PHQ9 score to improve the efficiency of the study and to prevent those likely to be excluded because they met the ICD10 depression criterion from having unnecessary further assessments. The important criterion is to ensure that those entering the study are no longer currently depressed according to the ICD10 criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported