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Health Technology Assessment

Volume 29 • Issue 57 • November 2025

ISSN 2046-4924

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DOI 10.3310/HFDO7575

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Extended Research Article

Effectiveness of Escitalopram and Nortriptyline on Depressive Symptoms in Parkinson's disease: the ADepT-PD RCT pilot

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Published November 2025
DOI: 10.3310/HFDO7575

This report should be referenced as follows:

Schrag A, Carroll C, Lewis G, Serfaty M, Duncan G, Molloy S, *et al*. Effectiveness of Escitalopram and Nortriptyline on Depressive Symptoms in Parkinson's disease: the ADepT-PD RCT pilot. *Health Technol Assess* 2025;**29**(57). https://doi.org/10.3310/HFDO7575

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 4

A list of Journals Library editors can be found on the NIHR Journals Library website

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This article

The research reported in this issue of the journal was funded by the HTA programme as award number 16/145/01. The contractual start date was in June 2018. The draft manuscript began editorial review in December 2024 and was accepted for publication in March 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

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Abstract

Background: There is insufficient evidence on the effectiveness of different antidepressants in Parkinson's disease. This trial was commissioned to provide robust evidence regarding the effectiveness of a tricyclic and a selective serotonin reuptake inhibitor on depression in people with Parkinson's disease.

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of the tricyclic nortriptyline and the selective serotonin reuptake inhibitor escitalopram in addition to standard psychological care in the National Health Service in the treatment of depression in Parkinson's disease.

Design: Forty-seven-month, multisite, three-arm, placebo-controlled, double-blind, randomised controlled trial, with an internal pilot phase. Four hundred and eight patients with a 1 : 1 : 1 randomisation between placebo, nortriptyline and escitalopram. The pilot study aimed to recruit 46 participants in the first 6 months from 10 sites to decide whether the trial is feasible.

Interventions: Participants were treated with nortriptyline (target dose 100 mg in patients 65 and under, or 50 mg in patients over 65 or those with hepatic impairment), escitalopram (target dose 20 mg in patients 65 and under, or 10 mg in patients over 65 or those with hepatic impairment) or placebo, in addition to available standard psychological care.

Outcomes: The primary outcome measure was the Beck Depression Inventory-II at 8 weeks. Secondary outcomes included clinician- and patient-reported outcomes, with safety summaries.

Results: Fifty-two patients were recruited and randomised to receive either nortriptyline, escitalopram, or a placebo-matched tablet. This was effectively the internal pilot period, with the trial being truncated at this point. There was a reduction in Beck Depression Inventory-II scores between baseline to week 8 in all arms. In the placebo arm, this was from a mean of 24.3 (SD 7.8) at baseline to 15.7 (SD 5.8) at week 8, in the nortriptyline arm from 20.5 (SD 3.8) to 12.6 (SD 8.1), and in the escitalopram arm from 23.3 (SD 8.0) to 14.6 (SD 8.4). The reduction in Beck Depression Inventory-II scores was not significantly different between either of the two active arms and the placebo arm, with a mean change of −3.1 (95% confidence interval −8.66 to 2.53, $p = 0.28$) in the nortriptyline versus placebo comparison, and a mean change of −0.7 (−6.11 to 4.70, $p = 0.80$) in the escitalopram versus placebo comparison. There was however a statistically significant difference in reduction of Patient Health Questionnaire-9 items scores between the nortriptyline and the placebo arm ($p = 0.01$) but not the escitalopram compared to the placebo arm ($p = 0.33$). There were no differences in adverse events, Movement Disorders Society Unified Parkinson's Disease Rating Scale scores or Montreal Cognitive Assessment scores. Descriptive analysis of health economic outcomes suggested no significant differences across time periods or groups.

Limitations: This trial was limited by low number of patients with depression in Parkinson's disease who could be recruited.

Future work: Future trials should concentrate on one rather than two medications to reduce the number of ineligible patients as well as the sample size. Alternatively, a three-arm comparison with a compound not currently available but with potential added benefit may also increase recruitment rate.

Conclusions: The ADepT-PD trial was terminated at the end of the pilot phase due to low recruitment. Only limited conclusions can be drawn as to the efficacy and safety of the active treatments.

Trial registration: This trial is registered as NCT03652870.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 16/145/01) and is published in full in *Health Technology Assessment*; Vol. 29, No. 57. See the NIHR Funding and Awards website for further award information.

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List of abbreviations

ADepT-PD	Antidepressants for depression in people with Parkinson's Disease
AE	adverse event
AR	adverse reaction
BDI-II	Beck Depression Inventory–II
BNF	*British National Formulary*
CALY	capability-adjusted life-year
CALW	capability-adjusted life-week
CONSORT	Consolidated Standards of Reporting Trials
CSRI	Client Service Receipt Inventory
dPD	depression in Parkinson's disease
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
HTA	Health Technology Assessment
ICECAP-O	ICEpop CAPability measure – Older people version
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
ITT	intention to treat
iVICQ	iMTA Valuation Of Informal Care Questionnaire
MAO-B	monoamine oxidase B
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
M-EDL	Motor Aspects of Experiences of Daily Living
MoCA	Montreal Cognitive Assessment
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
nM-EDL	Non-Motor Aspects of Experiences of Daily Living
PD	Parkinson's disease
PI	principal investigator
QALY	quality-adjusted life-year
QALW	quality-adjusted life-week
RCT	randomised controlled trial
SAE	serious adverse event
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TSC	Trial Steering Committee

Plain language summary

What was the question?

The ADepT-PD trial was designed to assess the effects of two different types of antidepressants for depressive symptoms in Parkinson's which work on different chemicals in the brain. They are commonly used in the National Health Service, but it is unclear how effective they are in people with Parkinson's.

What did we do?

This trial attempted to compare nortriptyline, a drug from the class of tricyclics, and escitalopram, a drug from the class of selective serotonin reuptake inhibitors, with identical-looking tablets that did not contain any of the drug (a placebo) to find out if they reduce these symptoms more than placebo and to compare their effects.

What did we find?

We were able to include only a small number of patients with depression in Parkinson's willing and able to participate in a randomised placebo-controlled trial with antidepressants. The main reason was that most people who have these symptoms are now already offered antidepressants already available in the National Health Service. This made it difficult to conduct a trial with these medications despite several strategies including the trial being run using video-assessments during the coronavirus disease pandemic. In this pilot study, we found that patients treated with either of the two medications or with placebo improved their scores. However, there was no difference between the groups in the main outcome measure. Nevertheless, the number of participants was not large enough to draw any conclusions from this, and the study did not progress to the full trial.

What does this mean?

Depression is a common feature of Parkinson's and once recognised it is now frequently recognised and commonly treated with antidepressants. Trials examining response to antidepressants for depression in Parkinson's compared to placebo and between different available antidepressants are therefore challenging. The information gathered on challenges in conducting large trials in Parkinson's in the United Kingdom, including those using remote assessments, is already helping design of other United Kingdom-wide trials in Parkinson's.

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Scientific summary

Background

The Antidepressants for depression in people with Parkinson's Disease (ADepT-PD) trial was a three-armed randomised placebo-controlled trial to test the effectiveness and cost-effectiveness of a tricyclic and a selective serotonin re-uptake inhibitor (SSRI) on depression in people with Parkinson's disease (PD) with an internal pilot study. The tricyclic nortriptyline (target dose 100 mg), and the SSRI escitalopram (target dose 20 mg) were compared to placebo, in addition to available standard psychological care.

Objectives

Primary objective

The aim of the ADepT-PD trial was to determine the clinical effectiveness and cost-effectiveness of an 8-week course of nortriptyline (target dose 100 mg), the SSRI escitalopram (target dose 20 mg) in the treatment of depression in PD. The primary outcome was the Beck Depression Inventory (BDI) II at 8 weeks of treatment.

Secondary objectives

The secondary objectives of the ADepT-PD trial were to assess efficacy on a number of secondary outcome measures including another depression measure, the Patient Health Questionnaire-9 items (PHQ-9); the Parkinson Anxiety Scale; the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS); levodopa-equivalence dose; EuroQol-5 Dimensions, five-level version (EQ-5D-5L); Shortened Client Service Receipt Inventory; ICEpop CAPability index measure; Carer EQ-5D-5L and Carers Quality of Life Questionnaire Parkinsonism; Patient-reported Global Clinical Impression scale; Montreal Cognitive Assessment (MoCA); Scales for Outcomes in Parkinson's disease-sleep; demographic data, comorbidities, medication modified; assessment of participant's awareness of allocated treatment arm; and repeat assessments at 26 and 52 weeks.

Methods

The ADepT-PD trial was funded to be a definitive, multisite, three-arm, placebo-controlled, double-blind, Phase IV randomised controlled trial in response to a commissioning brief set by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme. The trial had an internal pilot phase with prespecified go/no-go criteria.

The trial aimed to randomise participants (1 : 1 : 1) into either the nortriptyline group – 12-month course of up to 100 mg of nortriptyline per day; the escitalopram group – 12-month course of up to 20 mg of escitalopram per day; or the control group – 12-month course of matched placebo.

Results

Screening and recruitment

A total of 1396 patients were screened for entry onto the trial, but only 52 patients were recruited and randomised into the ADepT-PD trial. Seventeen participants were randomised to the escitalopram group, 16 to the nortriptyline and 19 participants were randomised to the control group.

Completion of primary end point and withdrawals

Five out of 52 (9.6%) withdrew before the primary end point, including one before administration of the investigational medicinal product. Of the participants randomised, 16 out of 17 in the escitalopram group, 14 out of 16 in the

nortriptyline group and 17 out of 19 in the placebo arm completed the 8-week assessment. Of the 52 participants randomised, 1 participant (in the escitalopram group) withdrew due to a serious adverse event.

Clinical outcomes

All allocated arms saw a reduction in their BDI-II total score from baseline to week 8, including the placebo. In the placebo arm, this was from a mean of 24.3 (standard deviation: 7.8) at baseline to 15.7 (5.8) at week 8, in the nortriptyline arm from 20.5 (3.8) to 12.6 (8.1), and in the escitalopram arm from 23.3 (8.0) to 14.6 (8.4). A generalised mixed-effects model was used to estimate the difference in BDI-II at 8 weeks post treatment between the treatment groups (separately). The model, separate for the two active treatments, included both a fixed and a random part, and included the treatment effect and baseline BDI-II measurement. When comparing each of the two active arms to the placebo, no statistically significant differences were observed with a mean change of −3.1 [95% confidence interval (CI) −8.66 to 2.53, $p = 0.28$)] for the nortriptyline versus placebo comparison, and a mean change of −0.7 (−6.11 to 4.70, $p = 0.80$) for the escitalopram versus placebo comparison. A reduction in the total score of the PHQ-9 was observed on all arms between baseline and 8 weeks. These reduced from 12.7 (3.4) to 9.6 (3.7) in the placebo arm, 9.1 (2.6) to 6.7 (3.5) in the nortriptyline arm, and 11.9 (5.2) to 7.3 (5.5) in the escitalopram arm. When these were formally compared using the same model described above, there was a statistically significant difference observed in favour of nortriptyline ($p = 0.01$) when compared to placebo (though not escitalopram vs. placebo, $p = 0.33$). No meaningful differences were observed in any other secondary outcome measures, such as the MDS-UPDRS scores (all parts), MoCA scores and adverse events.

Conclusions for practice and research

The ADepT-PD trial was terminated at the end of the pilot phase, because it did not meet its go/no-go criteria. The main issues were a low recruitment rate owing to high rate of screen failure and patient interest, difficulties in timely identifying the condition and more widespread use of the medications than expected.

Implications for future research

We would recommend that future studies in this field should concentrate on one rather than two medications, which reduces the number of ineligible patients as well as the sample size. Alternatively, a three-arm comparison with a compound not currently available but with potential added benefit may also increase recruitment rate.

Trial registration

This trial is registered as NCT03652870.

Funding

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Chapter 1 Background

Background and rationale

Parkinson's disease (PD) is a progressive neurological disorder that leads to increasing disability and functional decline. Currently, no medications have been shown to halt or delay disease progression. One of the most common complications in patients with this diagnosis is depression which affects approximately 40% of patients with PD. Depression is linked to functional impairment, cognitive decline and faster disease progression and are the main determinants of poor quality of life in PD. Psychological therapies are used via standard access to appropriate psychological services in the NHS, but often antidepressant medications are required. Despite the high incidence of depression in this population, no conclusive evidence on appropriate choice of antidepressants in PD exists in the NHS, and the risks of worsening of parkinsonism and aggravation of non-motor features of PD by antidepressants pose particular challenges in this population.

The most commonly used medications for the treatment of depressive disorders in the UK are selective serotonin reuptake inhibitors (SSRIs), with the National Institute for Health and Care Excellence (NICE) recommending that these are used in preference to other antidepressants. Tricyclic antidepressants (TCAs), which have mixed properties including serotonin reuptake inhibition and noradrenaline reuptake inhibition as well as anticholinergic and antihistamine actions, have similar efficacy to SSRIs. The TCA nortriptyline has also been suggested to have neuroprotective properties in preclinical studies. However, TCAs are currently only recommended as second-line treatments for depression in PD due to their increased risk of adverse reactions (ARs) including orthostatic hypotension, dry mouth, constipation, urinary retention, memory impairment, hallucinations and confusion. They are particularly poorly tolerated in patients with cognitive impairment.

Nevertheless, in depression in Parkinson's disease (dPD), TCAs have conventionally been used because their anticholinergic properties are considered beneficial for parkinsonian features, such as tremor, in early PD, and insomnia. Some trial evidence also supports efficacy of TCAs for depressive symptoms in PD. SSRIs on the other hand, while supported by some trial evidence, are sometimes used cautiously in dPD, as cases of new-onset parkinsonism or worsening of parkinsonism have been reported. The reported effects of SSRIs on PD motor symptoms have varied between different studies, with some animal models and case reports suggesting parkinsonism as a reversible adverse effect of SSRIs, and suggesting deterioration of parkinsonism in some but not others. Additionally, other side effects such as fatigue or postural hypotension can occur and may already be pre-existing in PD. Furthermore, there have been reports about an increase in falls in patients on SSRIs,[1] and very rarely serotonin syndrome has been reported. The *British National Formulary* (BNF) limits use of SSRIs and TCAs or advises caution in their use with the selective monoamine oxidase B (MAO-B) inhibitors rasagiline and selegiline that are used in PD due to increased central nervous system toxicity. Therefore, there remains concern that SSRIs worsen Parkinson's symptoms and that antidepressant treatment in dPD is not clinically effective.

Several systematic evidence reviews recommend the use of TCAs in dPD over SSRIs. There is a lack of large placebo-controlled trials, and overall surprisingly little evidence available on the effectiveness of antidepressants, either TCA or SSRI, in dPD, particularly in a real-life NHS setting rather than selected study populations of previous trials where age is typically relatively young and comorbidities low, and little evidence that SSRIs are effective and better tolerated than TCAs. Only two trials comparing both a SSRI and a TCA in dPD had been reported before this trial, both with small sample sizes. There was therefore insufficient evidence and consequent uncertainty in the role of SSRIs and TCAs in the treatment of dPD, and dPD was often undertreated.

Clinical data: previous trial evidence

Clinical effectiveness

Several meta-analyses on antidepressant medications for dPD have been published, most of which concluded that the small number of trials and methodological drawbacks preclude definitive conclusions about their efficacy and

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tolerability in dPD and further large trial evidence is needed. However, others concluded that there was evidence for benefit of SSRIs or TCAs, for dPD.

Among published trials, only two studies randomised patients to SSRI, TCA or placebo in a randomised controlled trial (RCT): the studies by Menza *et al.*[2] (nortriptyline and paroxetine) and Devos *et al.*[3] (desipramine and citalopram). Both studies reported improvement of depression with both the TCAs and SSRIs compared to placebo, including improved anxiety, dysphoria, and vegetative symptoms and tolerability of the active agents, but the numbers were small. Among the published trials, both SSRIs [effect size 0.49; 95% confidence interval (CI) 0.11 to 0.88] and TCAs (effect size 0.79; 95% CI 0.16 to 1.41) show improved symptoms of depression compared with placebo. Although TCAs show a numerically larger effect, there is no systematic difference between the two treatments (p-value for interaction = 0.44). The trials contributing are very small and are likely to be unreliable, with only 107 patients randomised in SSRI trials and 44 in TCA trials. A list of all identified RCTs using TCA or SSRI for dPD is in *Table 1*.

Cost-effectiveness

While evidence exists to suggest SSRIs are cost-effective compared with TCAs for major depression, no studies are available assessing the cost-effectiveness for a SSRI or TCA in dPD.

Rationale and risks/benefits: why is the research needed now?

As a result of the above-summarised levels of evidence, some international treatment recommendations advocate the use of both TCAs and SSRIs in PD, while others state a preference for TCAs or state there is insufficient evidence. There is therefore a need for conclusive trial evidence on the clinical effectiveness of SSRI and of TCA treatment in dPD in a real-life setting in the UK, and for the cost-effectiveness of a SSRI and a TCA in the NHS setting to guide evidence-based treatment in the NHS.

This was a randomised trial in an NHS setting, comparing the clinical effectiveness and cost-effectiveness of the SSRI escitalopram, and of the tricyclic nortriptyline, to placebo, undertaken in a real-life setting in addition to standard psychological care. Based on the previous evidence from small trials, the hypothesis was that both SSRIs and TCAs are effective compared to placebo and the difference in efficacy between TCAs and SSRIs was likely to be small, but that the tolerability of SSRIs is higher in this population than that of TCA due to the rate of adverse effects. The trial was designed to have statistical power to identify effects that were clinically important and slightly smaller than the pooled effects identified in the existing trials of SSRIs.

Results from an adequately powered, placebo-controlled trial in the NHS was planned to provide conclusive evidence on the effectiveness (using both efficacy and tolerability) of escitalopram, one of the newer, most effective and best tolerated SSRIs, in patients with PD, combined with a cost-effectiveness analysis; this was planned to allow for evidence-based treatment guidance of this common complication of PD in the NHS. In addition, it was planned to provide evidence on the real-life effectiveness of nortriptyline, a TCA which is currently the most widely recommended antidepressant in dPD.

This trial also had the potential to address the concern that worsening of Parkinson's symptoms is common with SSRIs and that antidepressant treatment in dPD is not effective or otherwise.

Conversely, this trial had the potential to support the notion that treatment with the TCA nortriptyline is associated with less severe parkinsonian features than placebo after 1 year. There is increasing preclinical evidence that nortriptyline has properties that reduce neurotoxicity and accumulation of alpha-synuclein, the pathological hallmark of PD, in the brain. This trial planned to provide the opportunity to study the effect of nortriptyline on slowing motor progression compared to placebo in this population.

Explanation for choice of comparators

Escitalopram is a SSRI similar to citalopram, the most widely used SSRI in the UK. Both citalopram and escitalopram, the S-enantiomer, are now off-patent with comparable costs and similar trial results. Until recently, escitalopram has been used less commonly in the NHS because it was more expensive. However comparative trial data in major depression (including non-industry-funded research) suggest that escitalopram is more effective than citalopram with similar or

TABLE 1 Randomised controlled trials with a SSRI or TCA in dPD

First author	Publication year	Study duration	Age range (years)	Diagnoses	Retention/sample size per group	Study outcome measure	Findings
Devos D	2008	4 weeks	57–65	PD with MDD, MARDS > 20	16/16 Placebo 13/15 Citaloprarn 16/17 Desiprarnine	MADRS	Improvement in all groups but both interventions better than placebo
Leentjens AFG	2003	10 weeks	67 ± 7.8	PD with MDD	6/6 Placebo 6/6 Sertraline	MADRS	50% reduction in both groups
Menza M	2009	8 weeks	62.2 ± 8.7	PD with MDD or dysthymia	11/17 Placebo 12/17 Nortriptyline 11/18 Paroxetine CR	HAM-D 17	Paroketine not superior and may be inferior to nortriptyline
Richard I	2012	12 weeks	63.5 ± 10.7	PD with any depressive disorder	33/39 Placebo 34/42 Paroxetine 30/34 Venlafaxine	MADRS HAM-017 GDS	Improvement in treatment groups compared to placebo
Rios Romenets	2013	6 weeks	64.5–69.5	PD with insomnia	6/6 Placebo 6/6 Doxepin 6/6 CBT	BDI	No change in all groups
Wermuth L	1998	6 weeks	64 (44–79)	PD with MDD HAM-D > 13	17/19 Placebo 13/18 Citalopram	HAM-D 17	Reduction in both groups
Antonini A	2005	12 weeks	68.5–71.8	PD with MDD	11/15 Amitriptyline 12/16 Sertraline	HAM-D 17 PDQ-39	Reduction in both groups
Avila A	2003	90 days	70.4 ± 6.4	PD with MDD or dysthymia	7/7 Fluoxetine 6/9 Nefazodone	BDI	Improvement in both groups

CBT, cognitive behaviour therapy; HAM-D, Hamilton Depression Rating Scale; MARDS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder.

Source
Adapted from Bomasang-Layno *et al.*[4]

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lower rates of side effects, and that it is associated with increased probability of response in trials of older patients with dementia and agitation. In addition, it has been reported that escitalopram has the highest probability of remission and is the most effective and cost-effective pharmacological treatment in a primary care setting.

Amitriptyline is the most widely used TCA in the UK but is used predominantly at low doses for pain and insomnia in PD. The side-effect profile of amitriptyline makes it poorly tolerated in patients with PD at higher, antidepressant doses. Nortriptyline is a metabolite of amitriptyline. However, unlike amitriptyline, nortriptyline has mainly noradrenergic effects, and weakly blocks dopaminergic reuptake. It also has fewer sedative, α1-blocking and anticholinergic effects than amitriptyline (by a factor of 8). It has been evaluated in multiple trials over several decades and its efficacy and adverse event (AE) profile in depressive disorders has been well studied. The trial evidence on TCA in dPD (see above) mainly reports on nortriptyline and desipramine (which is not available in the NHS). While nortriptyline has a slightly higher cost than amitriptyline in the NHS, nortriptyline is a more appropriate medication for treatment of depression in this population. In addition, there is accumulating evidence from preclinical studies that nortriptyline may delay disease progression in PD.

Objectives

Principal:

- Establish the clinical effectiveness and cost-effectiveness of *escitalopram* at 8 weeks compared to *placebo* in the treatment of dPD, in addition to standard psychological care in the NHS.
- Establish the clinical effectiveness and cost-effectiveness of *nortriptyline* at 8 weeks compared to *placebo* in the treatment of dPD, in addition to standard psychological care in the NHS.

Secondary:

- Establish whether after 1 year of treatment parkinsonism has deteriorated less in patients with PD with depression on nortriptyline than on placebo.
- Establish whether there is a difference in ARs between *escitalopram* and *nortriptyline*.
- Establish the long-term (after 1 year of treatment) clinical effectiveness and cost-effectiveness of *escitalopram* and *nortriptyline* compared to *placebo* in the treatment of dPD, in addition to standard psychological care.
- Establish the clinical effectiveness of escitalopram and of nortriptyline, compared to placebo on anxiety and other secondary outcome measures.
- Establish whether after 1 year of treatment parkinsonism has deteriorated more in patients with PD with depression on escitalopram than on placebo.

Trial truncation decision September 2022

The trial opened to recruitment on 30 November 2020, but due to issues with timely and feasible recruitment to the intended target sample size, on 22 September 2022 the funder NIHR informed the Trial Team that the trial would be truncated and asked the trial team to:

- Continue recruitment until 46 patients had been recruited OR the end of November 2022, whichever occurred soonest.
- Complete the primary outcome assessment at 8 weeks with no further follow-up.

For the purposes of the primary outcome measure in the trial, this decision severely hampered the opportunity to assess the impact of escitalopram or nortriptyline given the reduced sample size and shortened follow-up. In complying with these instructions, the strategy was to follow the original, agreed analysis plan as far as possible. Any analysis incorporating data beyond the primary window of baseline to week 8 will need to be interpreted with caution due to small patient numbers.

Chapter 2 Study methods

Trial design

Antidepressants for depression in people with Parkinson's Disease (ADepT-PD) was a multicentre, double-blind, parallel trial with an incorporated internal pilot study. Participants were randomly allocated 1 : 1 : 1 to receive escitalopram or nortriptyline or placebo (*Figure 1*).

Randomisation

Randomisation was performed using a minimisation algorithm provided by the randomisation service 'Sealed Envelope'. The minimisation factors were:[1]

- site
- depression severity [Beck Depression Inventory–II (BDI-II) 14–19/20–63]
- Hoehn and Yahr disease severity staging in the ON medication stage (≤ 2.0/≥ 2.5)
- amitriptyline usage (yes/no)

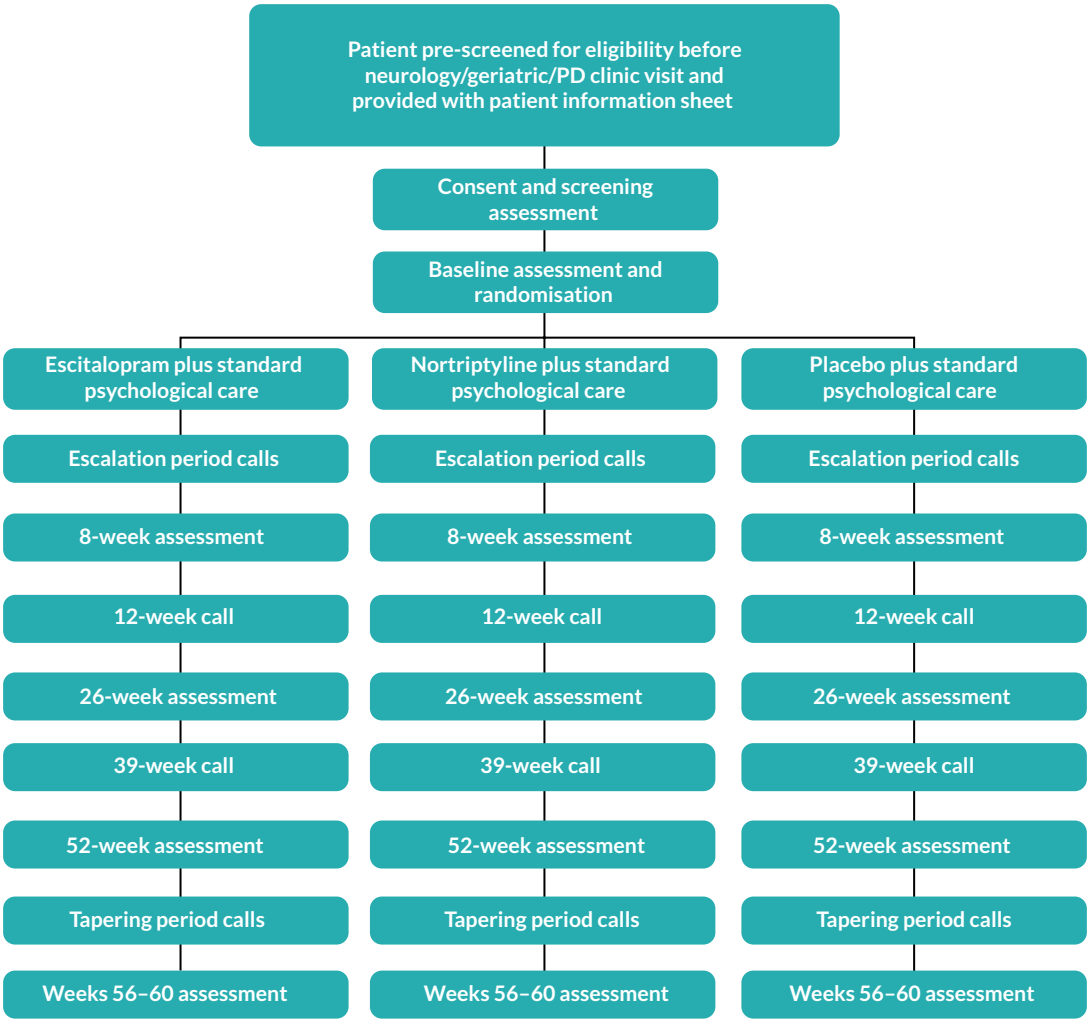

FIGURE 1 Study design.

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- clonazepam/benzodiazepine usage (yes/no)
- gabapentin/pregabalin usage (yes/no)
- pramipexole/dopamine antagonist usage (yes/no).

The trial statistician generated unique kit codes for every active/placebo trial medication bottle which were entered into the web-based, password-protected, secure randomisation service provided by the independent data management company ('Sealed Envelope') which was commissioned by the Priment Clinical Trials Unit to support randomisation and data management for the trial. Priment staff members followed Priment Standard Operating Procedures when developing the randomisation system in the Sealed Envelope database.

Sample size

The primary outcome was the change in depressive symptoms measured using the BDI-II after 8 weeks of trial treatment.[1] In order to have 90% power and a significance level of 0.025 (for each comparison to preserve study-wise alpha), 113 participants were needed per group to detect a three-point BDI-II difference [standard deviation (SD) for change 6.35][5,6] for the escitalopram–placebo and the nortriptyline–placebo comparisons at 8 weeks. Allowing for 20% attrition, 136 participants were required per randomised group (408 overall).[7]

If, following the pilot study (described in a standalone section), 1 randomised group was dropped and the trial was to continue with 2 arms comparing either escitalopram or nortriptyline with placebo, then 230 participants would have been required in total (115 per arm including 20% allowance for attrition or other challenges to the study assumptions) at 90% power with significance of 0.05.

With this sample size, the study had 90% power (1-beta) to find a mean difference of change of three points on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (part 3), with a nominal alpha of 0.025 for each active comparison, taking the effective SD from Athauda *et al.*[8]

For the estimation of ARs we used the Modified Toronto Side Effects Scale which elicits rates of side effects.[9] We used estimation and provide 95% CIs around the difference in percentage side effects for each item; however, the width of these CIs will depend upon their position on the binomial distribution. Thus, a trial with 136 subjects in each experimental condition will provide 95% CIs on the comparison between active agents ± 12% when the rate of events is around 50%, and ± 7% when the rate of events is around 10%.

Pilot phase

The internal pilot phase aimed to recruit 46 participants in 6 months. The progression criteria relating to recruitment were as follows:

1. If recruitment was 70% (n = 32) of the target in the first 6 months, the trial was to be continued in its entirety.
2. If recruitment in the pilot study was 50–70% (n = 23–31) at month 6, the Trial Steering Committee (TSC) was to review the recruitment data to determine if recruitment could be enhanced for the full trial.
3. If recruitment was < 50% ($n \leq 22$) at month 6, the nortriptyline treatment arm was to be dropped in the full trial.

In addition, the following trial conduct characteristics were to contribute to the decision-making:

1. Rate of clinically significant ARs: If the rate of ARs necessitating withdrawal exceeded 30% in one of the active arms of the pilot study, the independent Data Monitoring Committee (iDMC) were to review the AEs to consider if that active arm should be dropped in the full trial.
2. Loss to follow-up before primary outcome: If > 20% of participants did not complete the week 8 visit assessment (primary end point), the TSC were to consider stopping the trial.

3. Adherence to trial medication through pill count: If there was < 60% adherence to trial medication, the TSC were to consider stopping the trial.

If needed, according to the progression criteria listed above, iDMC and TSC meetings could be convened to provide advice on whether the results of the pilot study allowed for the trial to either continue as planned, be modified to drop one of the treatment arms or to stop the trial completely. However, the Health Technology Assessment (HTA) Programme would make the final decision on continuation. This decision-making was not to be an automatic process, and recruitment was to continue after the first 6 months until a final decision on the continuation of the trial was reached by the HTA Programme.

At the TSC meeting on 29 October 2021, and in the context of the disruption to the trial as a result of the COVID-19 pandemic, the Chair agreed to the suggestion of 'resetting' the internal pilot phase. This meant that 6 months were given from October 2021 to March 2022. This approach was also agreed by Nick Eaton on behalf of the NIHR on 9 November 2021.

Statistical interim analyses and stopping guidance

There were no formal interim analyses, although there was an incorporated pilot phase. Monitoring of the safety of the trial was undertaken by an iDMC which had unrestricted access to the trial data, and whose work was governed by a separate charter.

The iDMC reviewed unblinded data and made recommendations to the TSC. Further details of the roles and responsibilities of the iDMC, including membership, relationships with other committees, decision-making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable), are described in detail in the ADepT-PD iDMC terms of reference.

Timing of primary analysis

The primary analysis was started when all available data for the primary end point at 8 weeks of treatment, and other key outcome measures, were entered into the database and all corresponding queries resolved. Data query and cleaning were ongoing during the course of the trial, but final cleaning commenced once the last relevant case report form was entered into the database.

The primary outcome was assessed at 8 weeks, as this provided sufficient time for the titration of the antidepressant with a potential 2-week period on the maximum dose, while at the same time minimising the risk of drop-outs due to lack of response in the placebo group. However, the trial continued to overall duration of 52 weeks on their maximum dose before the participant was tapered off the trial medication (ending at 56–60 weeks) in order to determine long-term effectiveness.

Timing of outcome assessments

The timing of outcome assessments is provided in *Table 2*.

Statistical principles

Confidence intervals and p-values

All applicable statistical tests were two-sided. *p*-values from hypothesis testing for the main treatment effects were tested at the 1.25% level in line with the sample size calculation. All CIs presented are 95% and two-sided.

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TABLE 2 Participant timeline

Flexibility of schedule ± days	Screening/baseline visit (week 0)[a]		IMP dispensing receipt call (week 1)[b]	Escalation period calls (week 2, 4, 6)[c]	8-week visit[d]	IMP dispensing receipt call (week 12)	26-week visit[d]	IMP dispensing receipt call (week 26)	IMP dispensing receipt call (week 39)	52-week visit[d]	Tapering period calls (week 54, 56, 58)[e]	End-of-study visit (week 56–60)[f]
	0				± 1 week		± 2 week			−1 week		+ 4 weeks
	1											
Visit number	Screening	Baseline			2		3			4		5
Informed consent	●											
Eligibility screen	●											
Depressive Symptoms Evaluation	●											
BDI-II	●				●		●			●		●
MoCA	●				●		●			●		●
Demographics	●											
Medical history	●											
Concomitant medications (levodopa-equivalence dose)	●				●		●			●		●
Concomitant psychological therapies	●				●		●			●		
Vital signs[g]	●				●		●			●		●
Pregnancy testing (if applicable)	●				●		●			●		
Inflammatory blood sampling (optional)[h]	●				●		●			●		●
Genetic blood sampling (optional)[h]	●											
Randomisation		●										

TABLE 2 Participant timeline (*continued*)

Flexibility of schedule ± days	Screening/baseline visit (week 0)[a]		IMP dispensing receipt call (week 1)[b]	Escalation period calls (week 2, 4, 6)[c]	8-week visit[d]	IMP dispensing receipt call (week 12)	26-week visit[d]	IMP dispensing receipt call (week 26)	IMP dispensing receipt call (week 39)	52-week visit[d]	Tapering period calls (week 54, 56, 58)[e]	End-of-study visit (week 56–60)[f]
	0				± 1 week		± 2 week			−1 week		+ 4 weeks
	1											
Visit number	Screening	Baseline			2		3			4		5
Trial medication/ dosing diary discussion[i]		•			•		•			•		
Check receipt of trial medication			•			•		•	•			
AEs				•	•		•			•		•
MDS-UPDRS[j]		•			•		•			•		•
Timed Sit-Stand-Walk Assessment		•			•		•			•		•
PHQ-9		•			•		•			•		
ICECAP-O		•			•		•			•		
Parkinson's anxiety scale		•			•		•			•		
CGI (change in health)					•		•			•		
EQ-5D-5L		•			•		•			•		
Modified Toronto Side Effects Scale		•			•		•			•		
Modified CSRI (incorporating modified iVICQ)		•			•		•			•		
QoL-carer[k]		•			•		•			•		
EQ-5D-5L carer[k]		•			•		•			•		

continued

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TABLE 2 Participant timeline (*continued*)

Flexibility of schedule ± days	Screening/baseline visit (week 0)[a]		IMP dispensing receipt call (week 1)[b]	Escalation period calls (week 2, 4, 6)[c]	8-week visit[d]	IMP dispensing receipt call (week 12)	26-week visit[d]	IMP dispensing receipt call (week 26)	IMP dispensing receipt call (week 39)	52-week visit[d]	Tapering period calls (week 54, 56, 58)[e]	End-of-study visit (week 56–60)[f]
	0				± 1 week		± 2 week			−1 week		+ 4 weeks
	1											
Visit number	Screening	Baseline			2		3			4		5
Pill count (IMP Review and Compliance)					•		•			•		•
Dose escalation/ reduction reminders[l]				•							•	
Movement Sensor (optional)[m]		•					•					•

CGI, global clinical impression; CSRI, Client Services Receipt Inventory; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; ICECAP-O, ICEpop CAPability measure – Older people version; IMP, investigational medicinal product; iVICQ, iMTA Valuation Of Informal Care Questionnaire; MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire-9 items; QoL, quality of life.

a The Screening and Baseline assessments can occur on the same day or be completed within 14 days.

b Week 1 will commence when the participant takes their first dose of IMP.

c The Escalation period calls will occur at the end of week 2, week 4 and week 6 for participants aged 65 and under, and at the end of week 2 for participants aged over 65 (or with hepatic impairment).

d Where attendance at the trial site is not possible, efforts will be made to collect the information remotely (e.g. via telephone).

e The Tapering period calls will occur at the end week 54, week 56 and week 58 for participants aged 65 and under, and at the end week 54 for participants aged over 65 (or with hepatic impairment).

f The End-of-Study visit will take place at week 60 for participants aged 65 and under and at week 56 for participants aged over 65 (or with hepatic impairment).

g If the patient is seen remotely, the vital signs do not need to be performed.

h Optional genetic substudy blood sampling (*refer to genetic substudy guidance document*) will be taken at the screening/baseline visit (*but can be taken at a later visit if necessary*). *Optional blood samples for analysis of inflammatory markers will be taken at every visit (but consent can be obtained anytime during the trial).* If the participant is unable to attend clinic, cytokine blood samples can be collected using blood spot tests that will be sent to the participant using a provided stamped addressed envelope. After completion, the participant will then send the blood spot test to the Department of Clinical and Movement Neurosciences, UCL Royal Free Campus using a provided stamped addressed envelope.

i A member of the site trial team will provide the participant with copies of the Dosing Diaries which confirms how much trial medication the participant has to take daily and is also used for the participant to record the actual number of tablets they take each day.

j If the participant has Off-periods, at baseline and 1-year follow-up, it should be attempted to also assess the participants during a practically defined Off-period, for example before the first dose of antiparkinsonian medication, with an additional assessment of the MDS-UPDRS motor assessments. This Off-period assessment could be done during an assessment of the participant at home.

k Only if participant has a carer.

l A member of the local site research team will contact the participant at the relevant times during the relevant escalation/tapering periods (i.e. every 2 weeks when the dose is being escalated at the start of the participant's trial treatment and every 2 weeks when the dose is being reduced at the end of the participant's trial treatment) to remind the participant when the dosage needs to be changed.

m Worn for 7 days, before being returned in the post in a provided stamped addressed envelope.

Analysis population

The primary outcome analysis was conducted following the intention-to-treat (ITT) principle where all randomised patients were analysed in their allocated group whether or not they went on to receive this randomised treatment.

An ITT analysis has been performed for all secondary outcomes.

Imputation of missing data for any of the study outcomes has only been considered in scenarios where large amounts of, or informative, missingness has been observed.

Trial population

Screening, recruitment, withdrawal/follow-up

Patients screened but not enrolled in the trial and reasons for exclusions have been reported, and recruitment has been presented by centre and month. The full eligibility criteria for enrolment into ADepT-PD are listed in this report.

The number of patients who withdrew or were unwilling to continue in follow-up were reported by the last follow-up visit attended and treatment arm. Reasons for patient withdrawals have been tabulated by treatment arm. The throughput of patients from those screened, enrolled, assessed for trial end points, and included in the analysis, have been summarised in a Consolidated Standards of Reporting Trials (CONSORT) flow chart.[10]

The number of patients who have been withdrawn or were unwilling to continue trial follow-up once having joined the trial will be reported by treatment arm.

Eligibility

Participants were considered eligible for enrolment in this trial if they fulfilled all the inclusion criteria and none of the exclusion criteria as defined below.

Participant inclusion criteria

1. Patients with a diagnosis of idiopathic PD, based on a history and neurological exam performed by the enrolling investigator with presence of at least two of the three cardinal signs of PD: rigidity, bradykinesia, and rest tremor with no evidence of diagnostic alternatives.
2. Aged 18 years old or above.
3. Fulfilling operationally defined subsyndromal depression {presence of two or more depressive symptoms at threshold or subthreshold levels, at least one of which had to include depressed mood or anhedonia or diagnostic [*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-V*)] criteria for a depressive disorder [i.e. major depressive disorder or persistent depressive disorder]}.
4. BDI-II score ≥ 14.
5. Written informed consent provided.
6. Treatment with antiparkinsonian medication is optimised or stable for at least 4 weeks before date of randomisation and there are no plans to change up to primary end point (8 weeks).

Participant exclusion criteria

No patients were excluded based on PD motor severity, but the following were excluded:

1. Women who are pregnant, breastfeeding or of childbearing potential without effective contraception (hormonal or barrier method of birth control; or abstinence). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Patients who do not have sufficient understanding of the English language to be or are not able to understand the patient information sheet or the self-completed questionnaires or patients who are unable to communicate answers to the self-rating questionnaires.

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3. Patients with Montreal Cognitive Assessment (MoCA) score < 16 or without capacity to consent.
4. Treatment with an antidepressant within 4 weeks of enrolment (except for a small dose of amitriptyline up to 30 mg for indications other than depression).
5. Patients with known severe liver failure.
6. Absolute contraindications to escitalopram or nortriptyline. These include:
    a. Patients with known QT-interval prolongation or congenital long QT syndrome.
    b. Recent myocardial infarction (< 3 months), any degree of heart block or other cardiac arrhythmias precluding treatment with nortriptyline or escitalopram according to clinical judgement.
7. Medications contraindicated on nortriptyline or escitalopram. These include:
    a. Non-selective and selective irreversible monoamine oxidase inhibitors within 14 days. However, the antiparkinsonian selective reversible MAO-B inhibitors rasagiline, selegiline and safinamide are not contraindicated.
    b. Concomitant QT prolonging drugs, including domperidone, apomorphine at high doses (single dose or hourly rate of > 6 mg), certain neuroleptics (not quetiapine or clozapine), quinine, class IA and III antiarrhythmics (amiodarone, dronedarone and disopryamide), the antihistamines astemizole, mizolastine, the antimicrobial agents sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment, and some antiretrovirals.
8. Patients indicating active suicidal ideation or intent on the BDI-II item 9 and who, after clinical review of risk using the standardised Suicide Risk Management Protocol, need to be referred for immediate treatment.
9. Participation in another clinical trial of an investigational medicinal product (IMP) or device within the last 30 days of randomisation.
10. Any clinical condition which in the opinion/clinical judgement of the investigator would make the patient unsuitable for the trial due to safety concerns.

Baseline patient characteristics

Baseline characteristics have been summarised for all patients in the study. Summary measures for the baseline characteristics have been presented as mean and SD for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed continuous variables, and frequencies and percentages for categorical variables.

Baseline characteristics include the percentage of patients within each of the categories defined by the minimisation factors: site, depression severity, Hoehn and Yahr disease severity staging in the ON medication stage, amitriptyline usage, clonazepam/benzodiazepine usage, gabapentin/pregabalin usage and pramipexole/dopamine antagonist usage.

Analysis

Primary objective

To determine the effects of escitalopram and nortriptyline (separately), in addition to standard psychological care in the NHS, on depressive symptoms measured using the BDI-II. This was chosen as it is a well-validated instrument for the assessment of depressive symptoms, has been recommended for use in patients with PD, and is patient-reported.[11]

Treatment

Escitalopram (target dose 20 mg in patients aged 65 and under, or 10 mg in patients aged over 65 or those with hepatic impairment) OR nortriptyline (target dose 100 mg in patients aged 65 and under, or 50 mg in patients aged over 65 or those with hepatic impairment). These doses were in keeping with those in the BNF.

Outcome definitions

Primary outcome

- Establish the clinical effectiveness and cost-effectiveness of *escitalopram* at 8 weeks compared to *placebo* in the treatment of dPD, in addition to standard psychological care in the NHS.
- Establish the clinical effectiveness and cost-effectiveness of *nortriptyline* at 8 weeks compared to *placebo* in the treatment of dPD, in addition to standard psychological care in the NHS.

Secondary outcomes

- Establish whether after 1 year of treatment parkinsonism has deteriorated less in patients with PD with depression on nortriptyline than on placebo.
- Establish whether there is a difference in ARs between *escitalopram* and *nortriptyline*.
- Establish the long-term (after 1 year of treatment) clinical effectiveness and cost-effectiveness of *escitalopram* and *nortriptyline* compared to *placebo* in the treatment of dPD, in addition to standard psychological care.
- Establish the clinical effectiveness of escitalopram and of nortriptyline, compared to placebo on anxiety and other secondary outcome measures.
- Establish whether after 1 year of treatment parkinsonism has deteriorated more in patients with PD with depression on escitalopram than on placebo.

Analysis methods

The results of the analyses have been reported following the principle of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines on the Structure and Content of Clinical Study Reports.[12] Generally, the reporting of the trial has adhered to the multiarm specific extension of the CONSORT statement, as an arm was not dropped.[13] The pilot/feasibility stage took guidance from the dedicated CONSORT extension for trials of that type.[14]

A CONSORT diagram has been used to describe the course of patients through the trial. Baseline characteristics have been summarised by randomised group. Continuous variables have been summarised using summary statistics (mean, SD, median, minimum, and maximum) by treatment group, and categorical variables have been presented using frequency distributions by treatment group.

Graphical representations of both the events of interest and the harm profile have been guided by the Phillips *et al.* publication.[15]

Adjustment factors

Sites were to be included as random intercept terms, as were participants.

Primary outcome analysis

A generalised mixed-effects model has been used to estimate the difference in BDI-II at 8 weeks post treatment between the treatment groups (separately).

The model, separate for the two active treatments, included both a fixed and a random part, and included the treatment effect and baseline BDI-II measurement. The model for score at week 8, where *yi,j,k* is the BDI-II score of patient *i* at time *j* (weeks) from site *k*, is:

$$y_{i,8,k} = \beta_0 + \beta_1 (Z_{1i}) + \beta_2 (y_{i,0,k}) + u_k + e_{ijk}$$

where Z_1 = dummy variable for active treatment [0 = placebo, 1 = (escitalopram or nortriptyline)]

and

$$u_k \sim N\left(0,\ \sigma^2{}_u\right)$$

$$e_{ij} \sim N\left(0,\ \sigma^2{}_e\right)$$

The primary outcome was estimated by β_1 as the difference in BDI-II score among patients randomised to the relevant active treatment compared to the placebo group at 8 weeks.

The model assumes linear relationship between outcome and factors and of normality, homogeneity and independence of errors which will be investigated using plots of residuals.

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Baseline characteristics
Descriptive analyses were used to examine the baseline characteristics of the treatment groups.

Sensitivity analysis of primary outcome
The only sensitivity analysis used is the replication of the primary analysis model adjusted for the minimisation factors described in *Randomisation*.

Secondary outcome analysis
Efficacy
As part of the secondary analyses,[1] generalised mixed models with repeated measurements were planned to be used to examine the treatment responses over time though this is now less likely valuable as we are focusing on the time on trial up to 8 weeks.

Secondary analyses of outcomes were performed at 8 weeks primarily, using the same model as for the primary outcome measure, and where feasible on those who have completed the 26- and 52-week assessments (blinded long-term follow-up with placebo group).

An additional secondary analysis has compared effect of *any* active treatment versus placebo on BDI-II score at 8 weeks.

A comparison between the escitalopram and nortriptyline arms for the following secondary outcomes has also been described: motor examination (part III; with additional analysis during Off-periods), the combined part I and part II (motor and non-motor experiences), and the motor complications part of the MDS-UPDRS scores and their changes from baseline; of the global clinical impression change in health score, the number of AEs and of drop-outs; and all other secondary outcome measures.

Safety
Secondary analysis describing the number of participants experiencing AEs on the Modified Toronto Side Effects Scale.

Sensitivity analyses
If there are obvious differences in the baseline characteristics in the trial, this could potentially introduce confounding. In those circumstances, we will therefore conduct sensitivity analyses that will include any variables that show imbalance between randomised arms as participant level covariates.

A model adjusting for all minimisation factors will also be considered.

Multivariate joint models were used to explore the relationship between stopping treatment and the BDI-II should the recruitment be sufficient to make it justified.

Exploratory outcome analysis
As an exploratory analysis, we provided an estimate of the difference in mean BDI-II score and 95% CIs between the two active treatments.

Statistical software
Most analyses were performed in Stata version 17 (StataCorp LP, College Station, TX, USA), although other suitable and stable software packages were used according to the Trial Statistician's judgement.

Health economics analysis

Overview
We had aimed to calculate the net monetary benefit (NMB) of (1) escitalopram plus standard psychological care, (2) nortriptyline plus standard psychological care and (3) standard psychological care alone over the 52 weeks of the

study, to evaluate which of the three treatment options was the most cost-effective treatment of dPD. NMB was to be calculated as the cost per quality-adjusted life-year (QALY) gained of each treatment option multiplied by a willingness to pay for a QALY gained. We considered truncating this analysis to cover only an 8-week time horizon, but the small sample size and structure of the cost information make this analysis insufficiently meaningful, so instead we have calculated descriptive statistics only.

The primary analysis was from a health and social care cost perspective and included participant data only, with secondary analyses including carer data. The analysis used trial data. Descriptive statistics for costs and outcomes at baseline and 8 weeks are reported in line with the trial's primary outcome measure, and those at 26 and 52 weeks are also reported as far as possible within the truncated analysis time frame, but a comparative analysis across the randomised arms will not be performed due to the truncation of the trial.

Data to be used for economic analysis

No directly identifiable participant information was used for this analysis. The analysis used trial data on resource use and quality of life collected from participants and carers during the ADepT-PD RCT as described above, supplemented with published unit costs and other information as required. The descriptive statistics are reported according to randomised groups, that is according to ITT.

Results to be reported (8-week data)

Mean adjusted bootstrapped costs and QALYs are reported for patient participants as part of the descriptive analysis. A secondary analysis had aimed to report the NMB per capability-adjusted life-year (CALY) gained calculated using the ICEpop CAPability measure – Older people version (ICECAP-O) and associated algorithm and again we are instead reporting only descriptive statistics for capabilities and CALYs.[16] Mean per-patient costs and QALYs/CALYs have been calculated using non-parametric bootstrapping and controlling only for baseline values (cost, utility or capability). We have not controlled for site as the distribution of patients across sites was uneven, with some sites only enrolling 1 or 2 patients and 1 site enrolling 17.

We have focused on the baseline and 8-week data for resource use and costs, but provide descriptive statistics for the utilities, QALYs, capabilities and CALYs where available.

Outputs for costs and outcomes descriptive statistics: participants only

Mean (SD) cost per participant of escitalopram in escitalopram arm; mean (SD) cost per participant of nortriptyline in nortriptyline arm; mean (SD) cost per participant of other medications and therapies, including standard psychological care and excluding concomitant medications, in each of the three arms; mean (SD) total healthcare cost per participant in each arm, excluding concomitant medications; descriptive statistics of utility scores calculated from EuroQol-5 Dimensions, five-level version (EQ-5D-5L) responses as completed by participants; mean (SD) total participant-level QALYs for each arm; descriptive statistics for the ICECAP-O and the associated valuation algorithm; mean (SD) total participant-level CALYs calculated using the algorithm; descriptive statistics for the above items at baseline, 8, 26 and 52 weeks wherever possible. The intervention medications were provided at 1, 12, 24 and 36 weeks, so those descriptive statistics are given according to those time points.

Resource use and cost data

Participant resource use was assessed using a shortened version of the Client Services Receipt Inventory (CSRI) and using the Concomitant Medications and Concomitant Psychological Therapies Logs and iMTA Valuation Of Informal Care Questionnaire (iVICQ) for carer input. Please note that in the trial documentation the CSRI questionnaire incorporated the modified iVICQ. These questionnaires were modified according to the needs and activities of people with PD and a depressive disorder and were administered at baseline (asking about the previous 3 months), 8, 26 and 52 weeks (each time collecting information on resources used since the last visit). These questionnaires asked participants for details of primary, community, secondary and social care resource use related to their Parkinson's or symptoms of depression, and were asked not to include visits that took place specifically for the ADepT-PD study. Dispensing of trial medications took place at weeks 1, 12, 24 and 36, providing 12 weeks of medications at each time point. Drug unit costs, including the cost of escitalopram and nortriptyline, were taken from the online BNF. Other unit costs were taken from nationally published sources and the literature and publicly available sources and applied to data collected in the trial.

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Unit costs for community and social care services were taken from the Unit Costs of Health and Social Care 2022 Manual. Unit costs for healthcare services provided by the NHS were taken from the National Schedule of NHS Costs 2020–1 and uprated to 2021–2 values using the NHS Cost Inflation Index (NHSCII). The inflation rate for NHSCII pay was applied to unit costs for hospital outpatient and specialist appointments, whereas the NHSCII pay and prices inflation rate was applied to unit costs for hospital admissions, accident and emergency visits, and day patient procedures. Annual salaries for roles such as prison nurse and NHS 111 Health Line advisor were taken from NHS Agenda for Change to estimate a cost per working hour as this information was not available in the Unit Costs of Health and Social Care 2022 Manual or National Schedule of NHS Costs 2020–1.

Total cost for a particular service used by each patient was calculated as the frequency of using the service multiplied by the unit cost. For services where only a cost per working hour was available, we assumed the length of visit to be 15 minutes if it occurred in the community or via telephone. For home visits, we assumed the travel time to be 1 hour for round trip and the amount of time spent at the patient's home to be 30 minutes. The cost per working hour taken from nationally published sources was multiplied by the total length of visit to derive the cost per visit. The unit costs were per visit or finished consultant episode. Unless specified to be consultant-led, we assumed the hospital outpatient appointments were led by a mix of consultants and non-consultants and applied the weighted unit costs for Total Outpatient Activities. For services where there were multiple applicable currency or service codes, we calculated the mean unit cost weighted by the volume of activity of all applicable codes unless the participants specified otherwise in the free text.

The total healthcare service costs incurred by a patient was the sum of the total costs for all the services reported by the patient on CSRI. Mean and median unadjusted costs were calculated for baseline and 8 weeks. Patients who did not complete any items on the CSRI were excluded from the total sample size in the cost calculations but included as missing in the resource use table.

Utility, capability and health-related quality-of-life data

Quality-adjusted life-years were calculated as the area under the curve using the van Hout *et al.* mapping algorithm from the EQ-5D-5L to 3L utility scores (the method currently preferred by NICE), bootstrapped and adjusting for baseline values, using responses to the EQ-5D-5L provided by participants at baseline, 8 weeks (and 26 and 52 weeks where possible).[17] A similar method has been used to calculate CALYs using the ICECAP-O.

Impact on informal/unpaid carers

A secondary analysis was planned to include impact on informal/unpaid carers but cannot be completed due to low numbers of carers. We had aimed to capture the impact of the three treatments on the time spent by informal/unpaid carers on caring tasks, and on carers' health-related quality of life. At baseline, 8, 26 and 52 weeks, we administered a questionnaire to participants asking about time spent being assisted with a range of carer tasks (informal/unpaid and paid carers including both state and out-of-pocket funded) using a modified version of the iVICQ developed as part of the HomeHealth trial. Unpaid/informal carer time was to be costed using the Proxy Good Method, where time spent on specific tasks is valued at the hourly wage for if it was provided by paid carers.[18] Carers (if the participant has a main carer) were asked to complete the EQ-5D-5L at baseline, 8, 26, and 52 weeks so that it could be directly translated into QALYs using the area under the curve, and added to the cost–utility index, as recommended by Koopmanschap *et al.*[19] Descriptive statistics only for carer EQ-5D-5L utility scores are reported here.

Chapter 3 Identified challenges and mitigation strategies

Delayed set-up

The set-up of the ADepT-PD trial was significantly delayed. The reasons for this were the following.

Availability of investigational medicinal product

There were shortages in the availability of escitalopram which necessitated an interruption of the study of 12 months.

Staff shortage and turnover

The sponsor's office experienced a high turnover and staff shortage at the initial stages. Despite the initial protocol having been written before start of the project, and ethics approval having been obtained at the appropriate time, there were longer review times by the sponsor and a delay in contracting with the pharmacy and the HTA. Following the study pause, there was a further delay due to staff shortages of 4 months.

Together, these delays resulted in an interruption of the trial for 10 months as well as a delay in start of recruitment by 6 months.

Site set-up

The trial was anticipated to require recruitment from up to 30 sites of whom many were recruiting to other studies in PD. However, the trial started at a time when there were a considerable number of other studies recruiting patients with PD, introducing competition for resources, particularly staff, as well as patients. These delays were compounded by the COVID-19 pandemic during which site set-up was severely affected, but which also led to considerable delays in sites restarting trials like ADepT-PD that were not the highest priority. While the NIHR Clinical Research Network (CRN) restart programme did prioritise the study, this did not lead to an increase in recruitment.

Capacity issues

Many sites reported capacity issues in both research and development and nursing capacity and were reluctant to commence with start-up activities until permitted by their Trust. In addition, where sites actively expressed interest, staff members at all levels appeared to be overstretched due to multiple ongoing studies which has led to delays at every phase during set-up.

We undertook multiple activities, working with patient organisations (Parkinson's UK and Cure Parkinson's Trust), the Clinical Research Network and professional organisations, and continued to identify and recruit new sites.

There were also issues regarding set-up in relation to other factors. Three sites have had substantial delays in the sign off of the data-sharing agreement due to General Data Protection Regulation. The Welsh and Scottish sites had delays as they no longer use encrypted e-mail accounts. A way of sending encrypted documents is required as patient information is being sent from site to the central pharmacy. Microsoft SharePoint (Microsoft Corporation, Redmond, WA, USA) was then set up by these sites to transfer sensitive documents.

Eligibility criteria

We had anticipated a prevalence of depression of 30% in the PD population of whom we anticipated, based on the literature, that the majority would be untreated. However, the majority of those who were found to have depression by the recruiting sites were already taking antidepressants, making them ineligible for the study. While it was possible to withdraw antidepressants that were not effective on clinical grounds before rescreening, it was not considered ethical to withdraw antidepressants for the purpose of the trial alone. Other exclusion criteria listed in the Summary of Product Characteristics of both trial medications included medications causing QTc prolongation for escitalopram and conduction defects including atrial fibrillation as well as cognitive impairment for nortriptyline, the combined list

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of which excluded a number of patients in this mainly older population. We undertook a number of steps to widen the population eligible for the study, including eliminating the upper age limit, but this did not lead to a substantial increase in recruitment.

Under-recognition of depression

There are recognised barriers to diagnosis of depression in patients with PD. In particular, there is considerable overlap in symptoms of PD and depression, such as reduced facial expression, slowness of movement and apathy. Together with reluctance to start antidepressants as below, this leads to a delayed diagnosis in many. Sites were encouraged to use a range of screening instruments and strategies to identify those with unrecognised depression.

Availability of both trial medications for the indication tested in this trial

While there is insufficient evidence to judge the effectiveness of either trial medication for dPD or for their comparison, both trial medications are currently available in the NHS for prescription to this population within their licensed indication. This reduced the incentive for trial participation, particularly as there was a placebo arm included which disincentivised those wishing to start an antidepressant.

Attitudes towards antidepressants

In addition to generally lower recruitment rates to antidepressant trials in this population, patients with PD are frequently on a number of different medications, taken several times a day, for their PD symptoms, including motor and non-motor symptoms. This, in addition to other medications taken by this age group, contributed to the reluctance to add another medication both by patients and by some clinicians.

Strategies to boost recruitment

Over the length of the trial, the trial team have adopted numerous strategies to improve recruitment. These are as follows:

- Creation of a Screening Support Document to inform sites of the best ways to identify patients in addition when approaching and presenting the trial to potential participants, suggestions on the most appropriate wording that should be adopted regarding depressive disorders and its treatment. This addition aimed to help minimise the stigma attached to this depression.
- Updated Site Initiation Visit slides to emphasise that it is a diagnosis of subsyndromal depression that is required for the patient to be eligible, and not only a diagnosis of major depressive disorder based on DSM-V.
- Internal advertising using the updated version 3.0 of the ADepT-PD poster at participating Trusts.
- Creation of patient recruitment letters that could be sent to patients who were potentially suffering from low mood. A quiz was included so a patient could gauge if they potentially suffer from low mood.
- Engagement in outreach to increase awareness of the trial such as the involvement of both The Cure Parkinson's Trust and Parkinson's UK through their websites and presentations by the chief investigator, as well as social media outlets.
- A number of presentations and talks by the chief investigator to patient groups and potential principal investigators (PIs) in the PD field.
- Adding 'Top tips' for recruitment in the ADepT PD Newsletter that is sent to sites.
- Screening logs were requested twice a month to ensure sites are engaged with identifying patients.
- Engagement with other Trials (e.g. TOPHAT) to identify highly recruiting centres to be approached by the ADepT-PD team.
- Frequent and responsive contact with sites to increase staff engagement with the trial.
- Engagement with the community-based Parkinson nurses to identify potential patients not being seen in clinics.
- Further engagement/training with sites on a one-to-one basis, for example, to explain the Screening Support Document.
- Amendment of the inclusion criteria to emphasise that a diagnosis of subsyndromal depression is sufficient for the patient to be eligible, not only a diagnosis of major depressive disorder based on DSM-V criteria.
- Emphasis to sites that have access to patient-specific databases to ensure they screen these databases.

- A circular e-mail to members of the British Association of Neurologists Movement Disorders group.
- The addition of Patient Identification Centre (PIC) sites to identify potential patients and refer them to recruiting centres.
- The sites were instructed to emphasise the substudy to potential patients, which is to examine the potential effects of nortriptyline on slowing motor progression in PD.
- Protocol amendment to change the inclusion criteria to emphasise that a diagnosis of subsyndromal depression is sufficient for the patient to be eligible, not only a diagnosis of major depressive disorder based on DSM-V criteria.
- Protocol amendment to add the addition of PIC sites to identify potential patients and refer them to recruiting centres.
- Protocol amendment to remove the maximum age of exclusion.
- Creation of an official Twitter account which has been used to increase engagement with the trial.
- The trial became part of the NIHR CRN Associate PI Scheme, and it was hoped that the enthusiasm brought with Junior PIs joining the trial would help increase recruitment.
- PI meetings to discuss recruitment issues in the trial. The two main takeaways were that when discussing this trial with patients to use wording such as 'low mood' instead of 'depression' or 'depressive symptoms'.
- Network Support was provided as ADepT PD was a Managed Recovery Study, and it was prioritised by the CRN.
- A request for 'One patient in March' was tweeted and was e-mailed in March 2022 to sites that had not recruited.
- Recruitment Drive requests were tweeted as well as being e-mailed to all sites.

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Chapter 4 Results

Explanatory statement

At the TSC meeting held on 29 October 2021, the Chair recommended that the internal pilot phase is 'reset' with an end date in March 2022 to account for the delays during the COVID-19 pandemic (*Table 3*). This was agreed with the HTA (Nick Eaton) on 9 November 2021. In total, 15 participants were recruited during this period.

Following consultation and advice by the HTA on 22 September 2022, it was decided that the ADepT-PD trial should be closed with immediate effect except for those who had already been approached about the study.

We present a brief final report. Only limited formal statistical tests were performed due to the small number of participants recruited to the trial.

Sites open to recruitment

The trial aimed to open at 30 sites. By September 2022, when the trial was shut prematurely, 16 sites had opened to recruitment.

Figure 2 shows the target number of sites compared with the actual number of sites open to recruitment. Of the 16 open sites, 13 recruited at least one participant before the trial was closed to recruitment.

TABLE 3 Recruitment by month, highlighting the 'restarted' pilot phase

Month	Frequency	%
March 2021	1	2
April 2021	2	4
May 2021	4	8
June 2021	5	10
July 2021	2	4
August 2021	1	2
September 2021	2	4
October 2021	**1**	**2**
November 2021	**2**	**4**
December 2021	**3**	**6**
January 2022	**1**	**2**
February 2022	**2**	**4**
March 2022	**6**	**12**
April 2022	1	2
May 2022	5	10
June 2022	3	6
July 2022	6	12
August 2022	2	4
September 2022	3	6

Study participants

The number of participants per site is shown in *Table 4*. The flow of participants through the trial from screening through randomisation to follow-up is presented in a CONSORT flow diagram (*Figure 3*). Twenty-three randomised participants had reached the primary outcome time point at 8 weeks when the trial was stopped – 17 in the 26-week and 11 in the 52-week time point.

Recruitment breakdown

Randomisation data are summarised by recruitment site in *Table 4*. In total, 1396 were screened for entry onto the trial, with 1187 not meeting the inclusion criteria, 150 refusing and 7 other reasons.

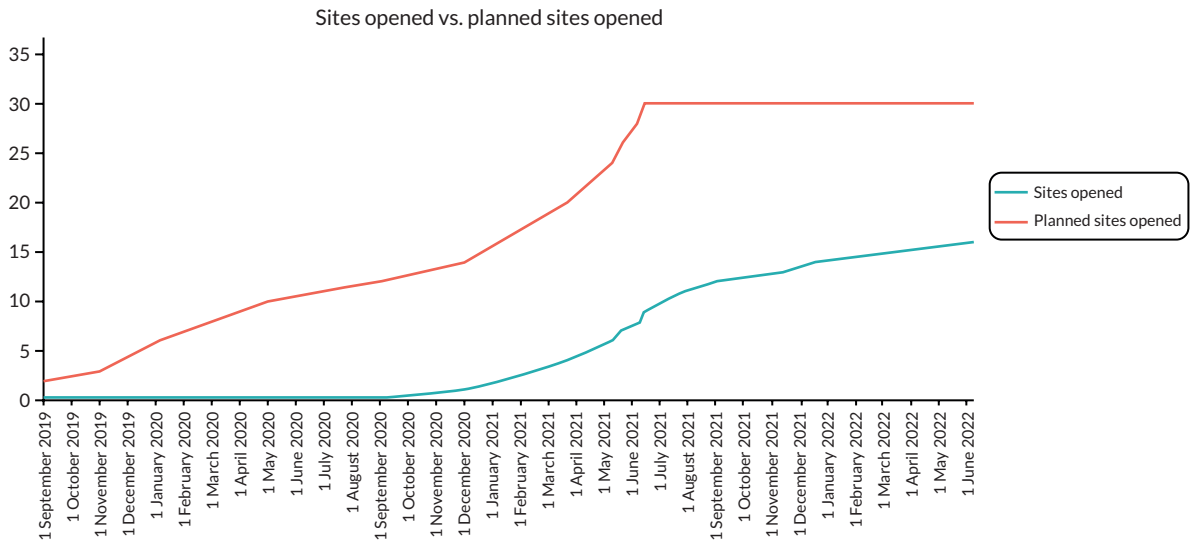

FIGURE 2 Sites open vs. those planned to be opened.

TABLE 4 Recruitment by site

Site	Count	%
National Hospital for Neurology and Neurosurgery	17	32.7
Royal Free London NHS Foundation Trust	9	17.3
Campus for Ageing and Vitality	6	11.5
Lewisham and Greenwich NHS Trust	4	7.7
Luton and Dunstable University Hospital	3	5.8
Royal Cornwall Hospitals NHS Trust	3	5.8
North Tyneside General Hospital	2	3.9
John Radcliffe Hospital	2	3.9
Charing Cross Hospital	2	3.9
Christchurch Hospital	1	1.9
St Peter's Hospital, Chertsey	1	1.9
Yeovil District Hospital	1	1.9
Livewell Southwest	1	1.9

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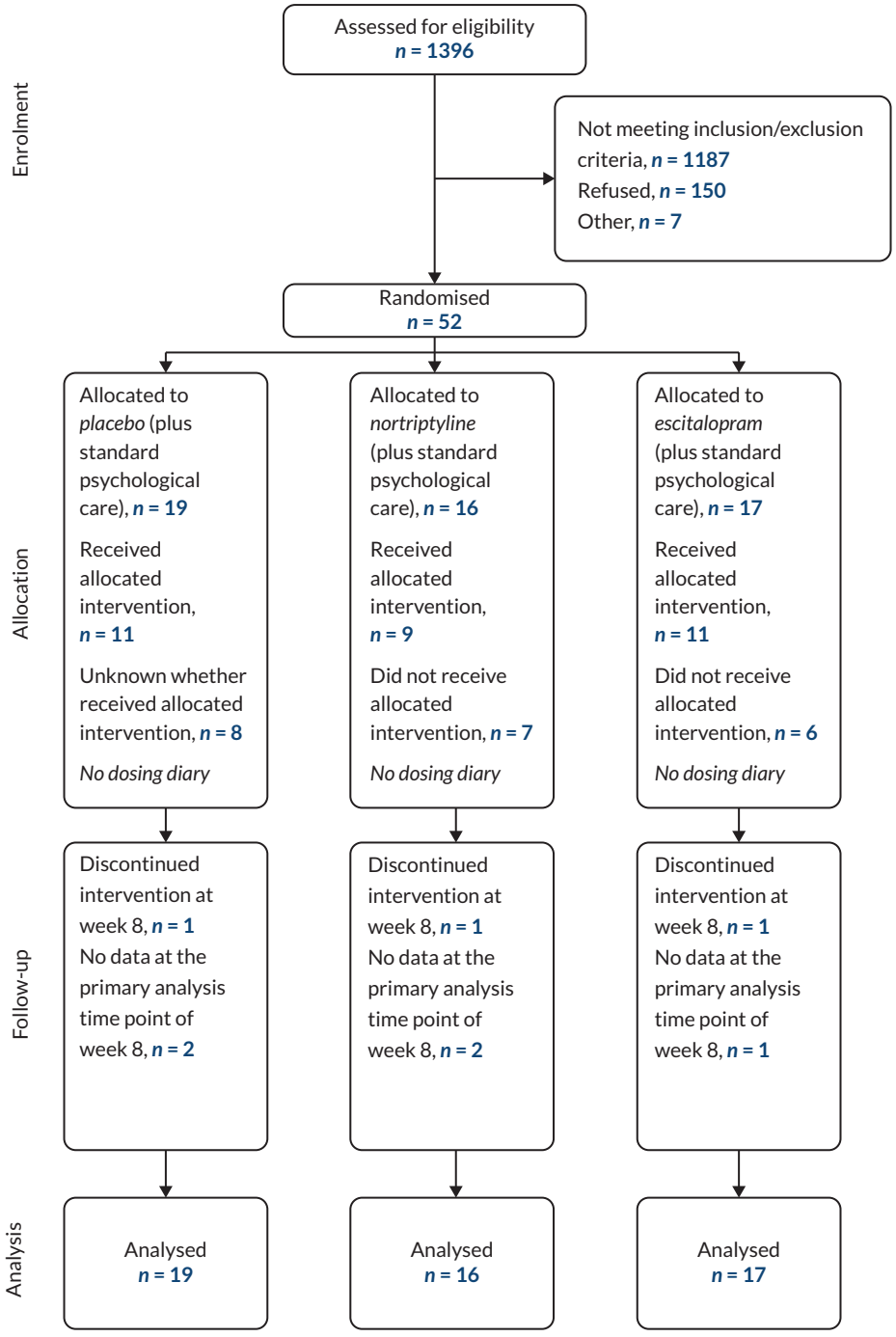

FIGURE 3 Recruitment over time compared to the overall proposed total.

Figure 4 shows the recruitment over time compared to the overall proposed total and *Figure 5* shows recruitment over time restricted to the total actually recruited.

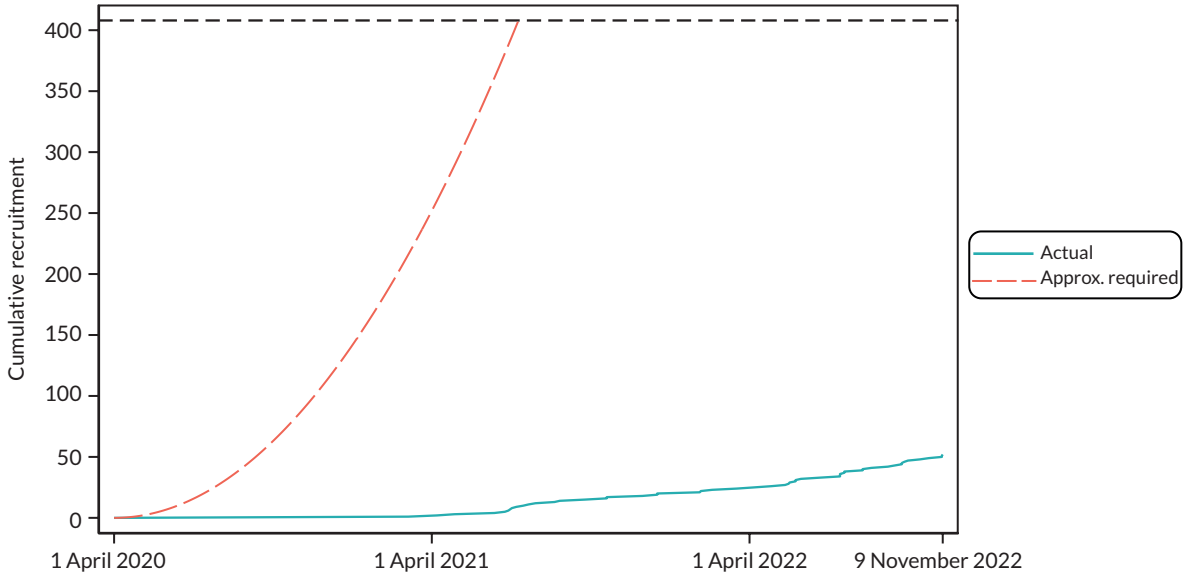

FIGURE 4 Recruitment over time restricted to the total actually recruited.

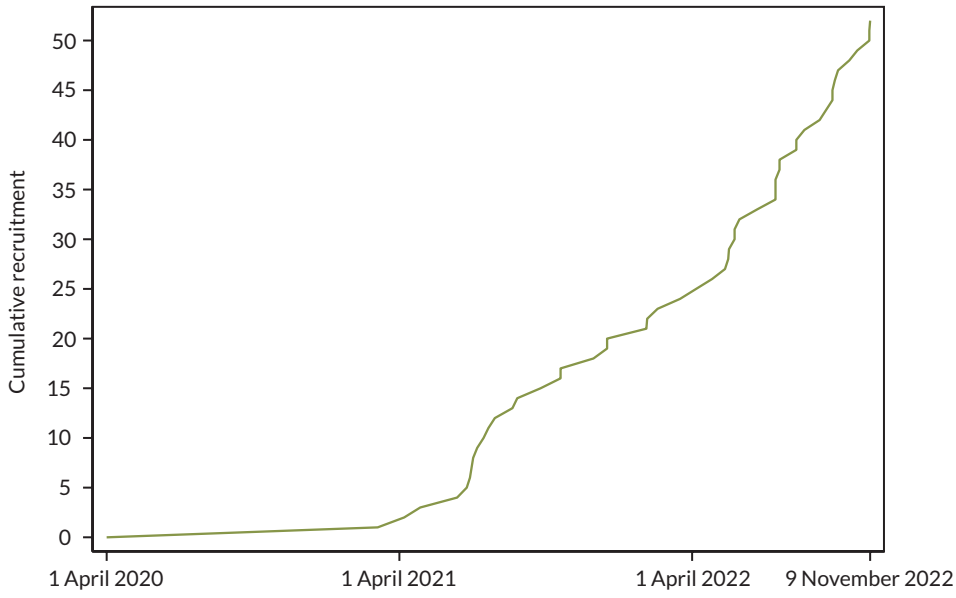

FIGURE 5 Consolidated Standards of Reporting Trials diagram showing the flow of participants through the trial.

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Participant characteristics

Tables 5 and *6* show information on the baseline characteristic comparability by allocated treatment arm. Bearing in mind the fairly low numbers within each arm, we are content with the balance across allocated arms and did not feel any small imbalances would affect the conclusions. Approximately two-thirds of participants were male, heights were almost identical and higher weights were observed in the placebo arm. Most (92%) of participants were right-handed with one ambidextrous in the placebo arm. A greater proportion (82% vs. 63% and 69%) of those allocated escitalopram identified as 'White British', with some all four participants of 'Indian' ethnicity being in the placebo group. Only two participants were women of child-bearing age, one each in the placebo and escitalopram arms, with reasons for not being so (male or post-menopausal) being even split by arm. No patient had hepatic impairment. The percentage of participants in the 65 and above age group was 58% in the placebo group, 50% in the nortriptyline and 35% in the escitalopram group.

Study entry

Required information at study entry

We specifically recorded information on whether participants had hepatic impairment at study entry – which none did (*Table 7*).

We also recorded vital sign information including their systolic (mmHg); mean (SD) and diastolic (mmHg); mean (SD) (*Table 8*).

Randomisation stratification factors

As was expected, the factors used in the stratification element of the randomisation were balanced across the allocated arms as shown in *Table 9*. There was a minor imbalance with both participants using clonazepam/benzodiazepine being allocated escitalopram though this was to be expected with the low numbers.

Baseline

Optional blood samples were taken on approximately two-thirds of participants – though this did vary with treatment arm, as shown in *Table 10*.

Clinical outcomes

Primary outcome measure: Beck Depression Inventory–II total score change between baseline and 8 weeks

The BDI-II total score ranges from 0 to 63 in response to 21 questions. Both active treatment arms saw small, but not statistically significant, decreases in the total BDI-II score at 8 weeks in comparison to placebo. While cut-offs for categorisation of scores should be adjusted based on the characteristics of the population, a broad guide to give context to the change is that a total score of 0–13 is considered minimal range, 14–19 is mild, 20–28 is moderate and 29–63 is severe. Two groups of 14–19 and 20–63 were used as a randomisation factor, with the balance shown in *Table 9*. All allocated arms saw a reduction in their BDI-II total score from baseline to week 8, including the placebo, as shown in *Figure 6*. Five participants were missing the primary outcome measure, two each on placebo and nortriptyline and one on the escitalopram arm.

Nortriptyline versus placebo

The larger decrease of the two comparisons was observed in the nortriptyline arm in comparison to placebo, with just over a three-point decrease in the total score. This drop, as anticipated given it was underpowered given the trial truncation, was not statistically significant ($p = 0.28$). It is difficult to tell, but this may have been considered clinically meaningful, albeit a small difference, with more data and consequently narrower CIs – the observed 95% interval was −8.66 to 2.53. This is shown in *Table 11*.

TABLE 5 Participant characteristics at study entry

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Gender				
Female; *N* (%)	5 (26.3)	5 (31.3)	6 (35.3)	16 (30.8)
Male; *N* (%)	14 (73.7)	11 (68.8)	11 (64.7)	36 (69.2)
Age (years); mean (SD)	63 (11.7)	63 (11.3)	61 (9.4)	62 (10.7)
Age category				
Under 65; *N* (%)	8 (42%)	8 (50%)	11 (65%)	27 (52%)
65 and over; *N* (%)	11 (58%)	8 (50%)	6 (35%)	25 (48%)
Height (cm); mean (SD)	170.6 (11.7)	168.6 (9.7)	172.6 (8.8)	170.7 (10.1)
Weight (kg); mean (SD)	82.7 (15.6)	76.9 (11.3)	77.4 (14.4)	79.2 (14.0)
Hand preference				
Left; *N* (%)	0 (0.0)	2 (12.5)	1 (5.9)	3 (5.8)
Right; *N* (%)	18 (94.7)	14 (87.5)	16 (94.1)	48 (92.3)
Ambidextrous; *N* (%)	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)
Which ethnic group does patient belong to? (ONE option)				
White British; *N* (%)	12 (63.2)	11 (68.8)	14 (82.4)	37 (71.2)
White Irish; *N* (%)	0 (0.0)	0 (0.0)	3 (17.6)	3 (5.8)
White (other background); *N* (%)	2 (10.5)	2 (12.5)	0 (0.0)	4 (7.7)
Indian; *N* (%)	4 (21.1)	0 (0.0)	0 (0.0)	4 (7.7)
Bangladeshi; *N* (%)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.9)
Caribbean; *N* (%)	0 (0.0)	2 (12.5)	0 (0.0)	2 (3.8)
Other ethnicity (please specify); *N* (%)	1 (5.3) *'British White Turkish'*	0 (0.0)	0 (0.0)	1 (1.9)

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TABLE 6 Pregnancy by allocated arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Is the participant a woman of childbearing potential?				
Yes; *N* (%)	1 (5.3)	0 (0.0)	1 (5.9)	2 (3.8)
No; *N* (%)	18 (94.7)	16 (100.0)	16 (94.1)	50 (96.2)
If no, please specify				
Male; *N* (%)	14 (73.7)	11 (68.8)	11 (64.7)	36 (69.2)
Post-menopausal; *N* (%)	4 (21.1)	5 (31.3)	5 (29.4)	14 (26.9)

TABLE 7 Hepatic impairment by allocated arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Does the participant have hepatic impairment?				
No; *N* (%)	19 (100.0)	16 (100.0)	17 (100.0)	52 (100.0)

Escitalopram versus placebo

The difference in score between escitalopram and placebo arms is extremely small and is unlikely to be meaningful (*Table 12*). Overall score mean at all time points on trial and treatment arm is given in *Table 13* and shown graphically in *Figure 7*.

Sensitivity analysis of primary outcome

The sensitivity analysis replicating the primary analysis model adjusted for the minimisation factors showed very little difference to the primary model albeit with a minor reduced treatment effect for nortriptyline (*Table 14*) and an insignificant increased effect of escitalopram (*Table 15*).

Secondary outcome measures

A sizable number of secondary outcome measures were planned for the ADepT-PD trial as defined in *Secondary outcomes*. As outlined in *Trial truncation decision September 2022*, the lack of recruited participants will make interpretation of these outcome measures very challenging, with the temptation to take the lack of an effect as definitive, when in reality the likelihood of seeing an effect should it exist with the sample size recruited is improbable.

Any active treatment versus placebo on Beck Depression Inventory–II score at 8 weeks

There was no evidence of a difference in the total BDI-II score at 8 weeks using all time points in the generalised mixed-effects model when combining the two active treatment arms ($p = 0.46$).

TABLE 8 Vital signs by allocated arms

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Is the participant able to complete the vital signs assessment?				
Yes; *N* (%)	12 (63.2)	8 (50.0)	8 (47.1)	28 (53.8)
No; *N* (%)	5 (26.3)	5 (31.3)	8 (47.1)	18 (34.6)
Systolic (mmHg); mean (SD)	130.5 (21.6)	130.8 (22.3)	127.5 (19.6)	129.7 (20.5)
Diastolic (mmHg); mean (SD)	76.4 (9.2)	78.5 (12.2)	71.0 (9.2)	75.5 (10.2)

TABLE 9 Randomisation stratification factors by allocated arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
BDI-II score				
14–19; *N* (%)	6 (31.6)	7 (43.8)	6 (35.3)	19 (36.5)
20–63; *N* (%)	13 (68.4)	9 (56.3)	11 (64.7)	33 (63.5)
Hoehn and Yahr staging				
≤ 2.0; *N* (%)	13 (68.4)	12 (75.0)	13 (76.5)	38 (73.1)
≥ 2.5; *N* (%)	6 (31.6)	4 (25.0)	4 (23.5)	14 (26.9)
Amitriptyline usage				
Yes; *N* (%)	1 (5.3)	1 (6.3)	1 (5.9)	3 (5.8)
No; *N* (%)	18 (94.7)	15 (93.8)	16 (94.1)	49 (94.2)
Clonazepam/benzodiazepine usage				
Yes; *N* (%)	0 (0.0)	0 (0.0)	2 (11.8)	2 (3.8)
No; *N* (%)	19 (100.0)	16 (100.0)	15 (88.2)	50 (96.2)
Gabapentin/pregabalin usage				
Yes; *N* (%)	3 (15.8)	1 (6.3)	2 (11.8)	6 (11.5)
No; *N* (%)	16 (84.2)	15 (93.8)	15 (88.2)	46 (88.5)
Pramipexole/dopamine antagonist usage				
Yes; *N* (%)	3 (15.8)	2 (12.5)	2 (11.8)	7 (13.5)
No; *N* (%)	16 (84.2)	14 (87.5)	15 (88.2)	45 (86.5)

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TABLE 10 Optional blood samples

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Has the participant provided written informed consent to have optional blood samples taken for inflammatory markers analysis?				
Yes; *N* (%)	11 (57.9)	10 (62.5)	12 (70.6)	33 (63.5)
No; *N* (%)	8 (42.1)	6 (37.5)	5 (29.4)	19 (36.5)

Montreal Cognitive Assessment

In the formal comparison of the MoCA, using the same model as for the primary outcome measure, there was no evidence of a difference at 8 weeks for either nortriptyline (p = 0.23) or escitalopram (p = 0.78); see for mean and SD at each visit. The MoCA over time by allocated arm is shown in *Table 16*.

Movement Disorders Society-Unified Parkinson's Disease Rating Scale

Extensive summaries of the MDS-UPDRS have been produced for both the 'On' and 'Off' periods as shown in *Tables 17–20*. These consisted of four parts each:

1. Part I: Non-motor aspects of experiences of daily living (nM-EDL)
2. Part II: Motor aspects of experiences of daily living (M-EDL)
3. Part III: Motor examination
4. Part IV: Motor complications.

Forty-three participants were assessed in an 'On' period, and nine in an 'Off' period. Scores are comparable across treatment arms at screening, with the exception of 'On' period – Part III: Motor Examination and most of the 'Off' period scores due to low numbers. Improvements in participant's responses were observed on trial between baseline and week 8 in all arms, although with no differences between treatment arms. Using the same mixed model as in the primary outcome measure. For nortriptyline versus placebo comparison, we observed p-values of p = 0.57 for part I,

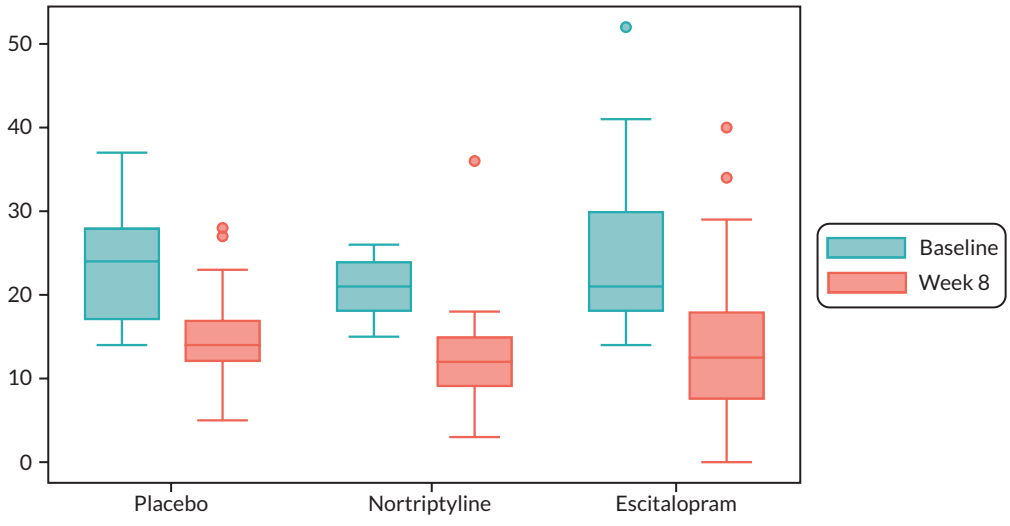

FIGURE 6 Beck Depression Inventory–II total score at baseline and week 8, by allocated arm.

TABLE 11 Beck Depression Inventory–II total score change between baseline and 8 weeks – nortriptyline vs. placebo

Difference between arms	Standard error	UL 95% CI	LL 95% CI	*z*	*p*-value
−3.1	2.86	−8.66	2.53	−1.07	0.28

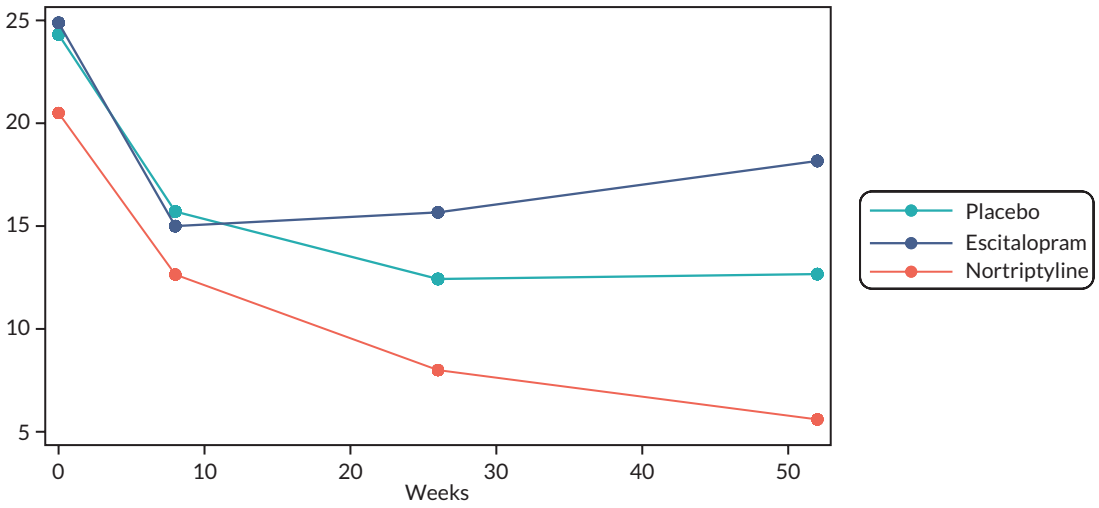

FIGURE 7 Beck Depression Inventory-II total score over time, by allocated arm.

p = 0.41 for part II, p = 0.09 for part III, and p = 0.91 for part IV. Then for the escitalopram versus placebo comparison, we observed p = 0.86 for part I, p = 0.45 for part II, p = 0.15 for part III, and p = 0.46 for part IV.

A secondary outcome measure was a direct comparison between the two active arms escitalopram and nortriptyline arms for the: motor examination (part III; with additional analysis during Off-periods), the combined part I and part II (motor and non-motor experiences), and the motor complications part of the MDS-UPDRS scores and their changes from baseline. However, given the early truncation of the trial, these comparisons will be underpowered and so we have pooled both the 'On' and 'Off' period data to represent data collected primarily 'over the last week'. Comparisons were done by each of the four parts separately, using the same mixed model as in the primary outcome. No significant differences were observed: for part I p = 0.57, part II p = 0.41, part III p = 0.09 and part IV p = 0.91.

Combined 'On' and 'Off' periods

Timed Sit-Stand-Walk Assessment

As shown in *Table 21*, only a subset of participants completed the Timed Sit-Stand-Walk Assessment, and only one experienced freezing at a scheduled trial visit, at week 8 on the placebo arm. The low number of participants contributing data at any scheduled visit make the time taken to do the task (*Table 22*) and the steps taken (*Table 23*) of limited utility.

Patient Health Questionnaire-9 items

While we urge cautious interpretation, there is a statistically significant decrease in the Patient Health Questionnaire-9 items total score at 8 weeks using all time points in the generalised mixed-effects model. The fall in the score was greater on the nortriptyline arm (p = 0.01) in comparison to placebo. There was no evidence of a difference in the escitalopram versus placebo comparison (p = 0.33). The mean score by time point and treatment arm is shown in *Table 24*.

Parkinson Anxiety Scale

This scale was chosen as specifically developed for use in PD, as the validity of other scales has been criticised.[20] The total number of items in the Parkinson Anxiety Scale is 12. Items are scored on a five-point Likert scale, with '0' meaning 'not or never' and '4' meaning 'severe or almost always' implying a maximum total score of 48. Mean responses by time point for the subscales are described in *Tables 25–27*, with the total scores in *Table 28*. There is no evidence of a

TABLE 12 Beck Depression Inventory-II total score change between baseline and 8 weeks – escitalopram vs. placebo

Difference between arms	Standard error	UL 95% CI	LL 95% CI	*z*	*p*-value
−0.7	2.76	−6.11	4.70	−0.26	0.80

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TABLE 13 Beck Depression Inventory-II over time by allocated arm

Total score: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	24.3 (7.8) (19)	20.5 (3.8) (16)	24.9 (10.4) (17)	23.3 (8.0) (52)
8 weeks	15.7 (5.8) (17)	12.6 (8.1) (14)	15.0 (11.0) (16)	14.6 (8.4) (47)
26 weeks	12.4 (8.7) (7)	8.0 (5.9) (10)	15.7 (11.9) (9)	11.8 (9.3) (26)
52 weeks	12.7 (9.5) (6)	5.6 (5.1) (5)	18.2 (16.9) (6)	12.5 (12.3) (17)
End of study	10.6 (6.7) (13)	10.0 (5.2) (10)	13.3 (12.8) (12)	11.4 (8.9) (35)
Withdrawal visit	24.0 (5.7) (2)	24.5 (0.7) (2)	14.0 (.) (1)	22.2 (5.4) (5)

TABLE 14 Beck Depression Inventory-II total score change between baseline and 8 weeks, adjusted for minimisation factors – nortriptyline vs. placebo

Difference between arms	Standard error	UL 95% CI	LL 95% CI	*z*	*p*-value
−1.9	2.22	−6.27	2.45	−0.86	0.39

TABLE 15 Beck Depression Inventory-II total score change between baseline and 8 weeks, adjusted for minimisation factors – escitalopram vs. placebo

Difference between arms	Standard error	UL 95% CI	LL 95% CI	*z*	*p*-value
−1.9	2.17	−6.16	2.35	−0.88	0.38

TABLE 16 Montreal Cognitive Assessment over time by allocated arm

Mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	27.3 (2.6) (19)	28.2 (1.7) (16)	28.4 (2.1) (17)	27.9 (2.2) (52)
8 weeks	27.6 (2.2) (17)	28.9 (1.5) (14)	28.2 (1.6) (16)	28.2 (1.9) (47)
26 weeks	28.4 (1.3) (7)	28.9 (1.3) (10)	25.5 (9.3) (10)	27.5 (5.8) (27)
52 weeks	27.3 (2.9) (6)	28.8 (1.8) (5)	21.6 (12.3) (5)	26.0 (7.3) (16)
End of study	27.8 (2.0) (13)	29.7 (0.7) (10)	27.8 (3.6) (12)	28.4 (2.6) (35)

TABLE 17 Movement Disorders Society Unified Parkinson's Disease Rating Scale – Part I: Non-motor aspects of experiences of daily living

nM-EDL: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	27.3 (5.2) (19)	27.1 (3.8) (16)	28.5 (5.3) (17)	27.6 (4.8) (52)
8 weeks	26.2 (5.5) (17)	24.1 (6.0) (14)	24.2 (8.4) (16)	24.9 (6.7) (47)
26 weeks	21.4 (5.1) (7)	21.5 (5.3) (10)	26.0 (12.1) (8)	22.9 (8.0) (25)
52 weeks	24.2 (7.5) (6)	20.2 (4.5) (5)	26.2 (7.4) (4)	23.4 (6.6) (15)
End of study	22.2 (6.1) (13)	22.3 (5.9) (10)	24.7 (9.5) (12)	23.1 (7.3) [35)

TABLE 18 Movement Disorders Society Unified Parkinson's Disease Rating Scale – Part II: Motor aspects of experiences of daily living

M-EDL: Mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	28.2 (7.7) (19)	26.8 (7.8) (16)	26.1 (6.4) (17)	27.1 (7.2) (52)
8 weeks	25.5 (9.3) (17)	23.6 (6.7) (14)	24.1 (6.8) (16)	24.5 (7.7) (47)
26 weeks	26.0 (7.3) (7)	21.7 (6.3) (10)	25.6 (8.1) (8)	24.2 (7.2) (25)
52 weeks	26.5 (8.0) (6)	19.4 (8.0) (5)	22.2 (3.8) (4)	23.0 (7.4) (15)
End of study	24.2 (6.8) (13)	23.0 (6.5) (10)	23.9 (7.4) (12)	23.7 (6.8) (35)

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TABLE 19 Movement Disorders Society Unified Parkinson's Disease Rating Scale – Part III: Motor examination

Motor examination: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	56.2 (15.9) (19)	48.2 (17.8) (16)	46.0 (10.5) (17)	50.4 (15.4) (52)
8 weeks	53.4 (18.7) (17)	41.0 (15.8) (14)	47.7 (10.4) (16)	47.8 (15.9) (47)
26 weeks	43.0 (14.7) (7)	42.6 (15.0) (10)	49.2 (17.0) (8)	44.8 (15.2) (25)
52 weeks	55.0 (18.3) (6)	45.2 (16.6) (5)	54.0 (19.6) (4)	51.5 (17.4) (15)
End of study	51.5 (15.4) (13)	40.8 (12.0) (10)	43.2 (20.1) (12)	45.6 (16.6) (35)

difference in either the nortriptyline versus placebo comparison ($p = 0.06$) nor the escitalopram comparison ($p = 0.15$) in the total score at 8 weeks using all time points in the generalised mixed-effects model.

Modified Toronto Side Effects Scale

The Modified Toronto Side Effects Scale asks participants to assess their symptoms experienced using the following phrasing:

> *To begin, I am going to ask you some questions about symptoms you may have experienced since I saw you. When I read out each question, please tell me if you have or have not experienced the symptom during the last 2 weeks. If you have, I'd like to know on how many days you have experienced that symptom in the past 7 days.*

Participants rate their responses to 14 questions on the scale of No = 1 then for Yes: None = 2, 1–3 days = 3, 4–7 days = 4. A total score will therefore be between 14 and 56 for these 14 items. The mean scores at each time point have been provided in *Table 29*. The scores vary only very little over time on trial; consequently, it is not surprising there is no evidence of a difference in either the nortriptyline versus placebo comparison ($p = 0.96$) nor the escitalopram comparison ($p > 0.99$) in the total score at 8 weeks using all time points in the generalised mixed-effects model.

Safety reporting

Adverse events

Just under half of participants (48.1%, *Table 30*) experienced no AEs on trial. Two nortriptyline participants reported a large volume of events, with one reporting 11 separate events and one 14. Using the Pearson chi-squared test ($p = 0.75$), there is no evidence of a difference by treatment allocation; this is the same for the maximum grade experienced on trial ($p = 0.37$, *Table 31*) where most experienced none or mild and only nine in total experienced a moderate graded event. When broken down by System Organ Class (*Table 32*), there is some evidence ($p = 0.03$) of a difference between the treatment arms, though this is primarily driven by one participant on each active arm that experienced six (nortriptyline) and four (escitalopram) 'Gastrointestinal disorders' events. *Table 33* illustrates that these were primarily minor events such as 'dry mouth'. A complete listing of all AEs reported on trial is given in *Table 34*.

TABLE 20 Movement Disorders Society Unified Parkinson's Disease Rating Scale – Part IV: Motor complications

Motor complications: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	10.8 (5.5) (19)	10.9 (4.6) (15)	12.4 (6.0) (17)	11.4 (5.4) (51)
8 weeks	9.8 (4.5) (17)	9.9 (4.7) (14)	11.1 (4.6) (16)	10.2 (4.5) (47)
26 weeks	10.4 (3.8) (7)	10.0 (3.7) (10)	10.5 (4.3) (8)	10.3 (3.8) (25)
52 weeks	11.3 (5.2) (6)	9.8 (2.9) (5)	12.2 (2.9) (4)	11.1 (3.8) (15)
End of study	10.2 (3.7) (13)	9.4 (3.9) (10)	10.1 (4.7) (12)	9.9 (4.0) (35)

TABLE 21 Timed Sit-Stand-Walk Assessment responses by allocated arm

Is the participant able to perform the Timed Sit-Stand-Walk assessment?	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening				
No; *N* (%)	8 (42.1)	10 (62.5)	9 (52.9)	27 (51.9)
Yes; *N* (%)	7 (36.8)	6 (37.5)	7 (41.2)	20 (38.5)
Did freezing occur?				
No; *N* (%)	7 (36.8)	6 (37.5)	7 (41.2)	20 (38.5)
8 weeks				
No; *N* (%)	10 (52.6)	10 (62.5)	10 (58.8)	30 (57.7)
Yes; *N* (%)	7 (36.8)	4 (25.0)	5 (29.4)	16 (30.8)
Did freezing occur?				
Yes; *N* (%)	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)
No; *N* (%)	6 (31.6)	4 (25.0)	5 (29.4)	15 (28.8)
26 weeks				
No; *N* (%)	5 (26.3)	6 (37.5)	8 (47.1)	19 (36.5)
Yes; *N* (%)	2 (10.5)	4 (25.0)	1 (5.9)	7 (13.5)
Did freezing occur?				
No; *N* (%)	2 (10.5)	4 (25.0)	1 (5.9)	7 (13.5)
52 weeks				
No; *N* (%)	4 (21.1)	2 (12.5)	3 (17.6)	9 (17.3)
Yes; *N* (%)	2 (10.5)	2 (12.5)	2 (11.8)	6 (11.5)
Did freezing occur?				
No; *N* (%)	2 (10.5)	2 (12.5)	2 (11.8)	6 (11.5)
End of study				
No; *N* (%)	9 (47.4)	7 (43.8)	9 (52.9)	25 (48.1)
Yes; *N* (%)	4 (21.1)	3 (18.8)	3 (17.6)	10 (19.2)
Did freezing occur?				
No; *N* (%)	4 (21.1)	3 (18.8)	3 (17.6)	10 (19.2)

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TABLE 22 Timed Sit-Stand-Walk Assessment – time taken by allocated arm

Seconds: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	25.4 (9.3) (7)	16.2 (3.2) (6)	42.6 (53.8) (7)	28.6 (32.7) (20)
8 weeks	23.0 (12.2) (7)	19.3 (1.0) (4)	47.6 (58.3) (5)	29.8 (33.5) (16)
26 weeks	36.5 (10.6) (2)	16.8 (2.4) (4)	15.0 (.) (1)	22.1 (10.9) (7)
52 weeks	20.0 (2.8) (2)	15.0 (7.1) (2)	15.0 (1.4) (2)	16.7 (4.3) (6)
End of study	23.0 (5.1) (4)	18.0 (4.6) (3)	11.3 (3.8) (3)	18.0 (6.5) (10)

TABLE 23 Timed Sit-Stand-Walk Assessment – steps taken by allocated arm

Seconds: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	25.3 (10.1) (7)	27.3 (5.0) (6)	24.7 (9.7) (7)	25.7 (8.3) (20)
8 weeks	31.4 (8.8) (7)	28.0 (7.0) (4)	29.8 (5.7) (5)	30.1 (7.2) (16)
26 weeks	37.5 (12.0) (2)	28.0 (11.0) (4)	25.0 (.) (1)	30.3 (10.5) (7)
52 weeks	34.5 (7.8) (2)	31.0 (8.5) (2)	29.5 (0.7) (2)	31.7 (5.6) (6)
End of study	34.0 (6.7) (4)	30.0 (4.6) (3)	24.7 (8.1) (3)	30.0 (7.1) (10)

TABLE 24 Patient Health Questionnaire-9 items – total score

Total; mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	12.7 (3.4) (19)	9.1 (2.6) (16)	11.9 (5.2) (17)	11.3 (4.1) (52)
8 weeks	9.6 (3.7) (17)	6.7 (3.5) (14)	7.3 (5.5) (16)	8.0 (4.4) (47)
26 weeks	8.4 (5.1) (7)	5.4 (3.5) (10)	8.4 (6.5) (7)	7.2 (5.0) (24)
52 weeks	6.5 (4.1) (6)	3.0 (2.0) (3)	9.0 (8.5) (5)	6.6 (5.9) (14)

TABLE 25 Parkinson Anxiety Scale – A. Persistent anxiety

A: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	11.5 (4.2) (19)	9.2 (3.8) (16)	9.6 (5.2) (17)	10.2 (4.5) (52)
8 weeks	8.5 (3.9) (17)	5.1 (4.4) (14)	6.3 (4.5) (16)	6.7 (4.4) (47)
26 weeks	7.9 (4.7) (7)	3.4 (2.5) (10)	6.1 (6.8) (7)	5.5 (4.9) (24)
52 weeks	6.2 (4.2) (6)	3.7 (3.2) (3)	8.0 (6.7) (5)	6.3 (5.0) (14)

TABLE 26 Parkinson Anxiety Scale – B. Episodic anxiety

B: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	4.4 (3.3) (19)	2.7 (2.9) (16)	3.5 (3.2) (17)	3.6 (3.2) (52)
8 weeks	2.2 (2.3) (17)	1.6 (2.5) (14)	1.8 (2.8) (16)	1.9 (2.5) (47)
26 weeks	1.1 (2.0) (7)	0.6 (0.8) (10)	1.3 (1.5) (7)	1.0 (1.4) (24)
52 weeks	1.5 (2.0) (6)	0.3 (0.6) (3)	3.6 (2.7) (5)	2.0 (2.4) (14)

TABLE 27 Parkinson Anxiety Scale – C. Avoidance behaviour

C: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	4.4 (3.3) (19)	2.7 (2.9) (16)	3.5 (3.2) (17)	3.6 (3.2) (52)
8 weeks	2.2 (2.3) (17)	1.6 (2.5) (14)	1.8 (2.8) (16)	1.9 (2.5) (47)
26 weeks	1.1 (2.0) (7)	0.6 (0.8) (10)	1.3 (1.5) (7)	1.0 (1.4) (24)
52 weeks	1.5 (2.0) (6)	0.3 (0.6) (3)	3.6 (2.7) (5)	2.0 (2.4) (14)

TABLE 28 Parkinson Anxiety Scale – total

Total: mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	19.8 (7.7) (19)	15.3 (7.0) (16)	15.9 (8.4) (17)	17.2 (7.8) (52)
8 weeks	13.2 (5.7) (17)	8.9 (8.4) (14)	10.1 (9.3) (16)	10.9 (7.9) (47)
26 weeks	10.6 (4.9) (7)	5.1 (3.8) (10)	9.1 (9.9) (7)	7.9 (6.6) (24)
52 weeks	8.3 (6.9) (6)	6.0 (6.0) (3)	15.8 (13.0) (5)	10.5 (9.7) (14)

TABLE 29 Modified Toronto Side Effects Scale – total score

Mean (SD) (*n*)	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Screening	21.6 (4.2) (18)	20.9 (4.1) (15)	22.1 (3.3) (17)	21.5 (3.8) (50)
8 weeks	20.3 (3.4) (15)	22.5 (3.8) (14)	20.2 (4.4) (15)	21.0 (3.9) (44)
26 weeks	20.6 (3.1) (7)	19.7 (2.9) (10)	22.0 (5.4) (5)	20.5 (3.6) (22)
52 weeks	20.8 (4.8) (5)	19.3 (3.2) (3)	21.3 (3.9) (4)	20.6 (3.8) (12)

TABLE 30 Total number of AEs experienced by participant by randomised arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
0; *N* (%)	11 (57.9)	8 (50.0)	6 (35.3)	25 (48.1)
1; *N* (%)	3 (15.8)	2 (12.5)	2 (11.8)	7 (13.5)
2; *N* (%)	1 (5.3)	2 (12.5)	4 (23.5)	7 (13.5)
3; *N* (%)	2 (10.5)	1 (6.3)	2 (11.8)	5 (9.6)
4; *N* (%)	1 (5.3)	0 (0.0)	2 (11.8)	3 (5.8)
5; *N* (%)	1 (5.3)	1 (6.3)	1 (5.9)	3 (5.8)
…				
11; *N* (%)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.9)
…				
14; *N* (%)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.9)

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TABLE 31 Maximum-grade AE experienced on trial, by allocated arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
(0) None; *N* (%)	11 (57.9)	8 (50.0)	6 (35.3)	25 (48.1)
(1) Mild; *N* (%)	5 (26.3)	4 (25.0)	9 (52.9)	18 (34.6)
(2) Moderate; *N* (%)	3 (15.8)	4 (25.0)	2 (11.8)	9 (17.3)

Serious adverse events

Only two serious adverse events (SAEs) occurred on trial, with both being in the same participant – participant ADP-16-003 who was allocated the escitalopram arm. The first event had an onset date of 7 June 2022 with a Common Terminology Criteria for Adverse Event grade 3 'Severe' urinary tract infection which was resolved 9 days later on 16 June 2022. Following this, they had a further grade 3 hospitalisation SAE for a spinal infection. This occurred on 30 August 2022 and was resolved by 24 November 2022. These are summarised in *Table 35*.

Adherence

Escalation

The escalation period calls occurred at the end of week 2, week 4 and week 6 for participants aged 65 and under, and at the end of week 2 for participants aged over 65 (or with hepatic impairment) and are summarised in *Table 36*. Three

TABLE 32 Total number of AEs experienced by AE category by randomised arm

System organ class	Placebo (*N* = 20)	Nortriptyline (*N* = 39)	Escitalopram (*N* = 29)	Total (*N* = 88)
Cardiac disorders; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Ear and labyrinth disorders; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Eye disorders; *N* (%)	0 (0.0)	3 (6.4)	0 (0.0)	3 (2.7)
Gastrointestinal disorders; *N* (%)	2 (6.5)	14 (29.8)	9 (25.7)	25 (22.1)
General disorders and administration site conditions; *N* (%)	2 (6.5)	1 (2.1)	2 (5.7)	5 (4.4)
Infections and infestations; *N* (%)	5 (16.1)	2 (4.3)	1 (2.9)	8 (7.1)
Injury, poisoning and procedural complications; *N* (%)	0 (0.0)	3 (6.4)	3 (8.6)	6 (5.3)
Investigations; *N* (%)	0 (0.0)	2 (4.3)	0 (0.0)	2 (1.8)
Musculoskeletal and connective tissue disorders; *N* (%)	2 (6.5)	0 (0.0)	1 (2.9)	3 (2.7)
Nervous system disorders; *N* (%)	3 (9.7)	6 (12.8)	5 (14.3)	14 (12.4)
Psychiatric disorders; *N* (%)	3 (9.7)	3 (6.4)	1 (2.9)	7 (6.2)
Reproductive system and breast disorders; *N* (%)	0 (0.0)	0 (0.0)	3 (8.6)	3 (2.7)
Respiratory, thoracic and mediastinal disorders; *N* (%)	2 (6.5)	0 (0.0)	1 (2.9)	3 (2.7)
Skin and subcutaneous tissue disorders; *N* (%)	0 (0.0)	3 (6.4)	1 (2.9)	4 (3.5)
Vascular disorders; *N* (%)	0 (0.0)	1 (2.1)	2 (5.7)	3 (2.7)

TABLE 33 Total number of AEs experienced by both System Organ Class and Common Terminology Criteria for Adverse Events term, by randomised arm

System organ class CTCAE term	Placebo (*N* = 20)	Nortriptyline (*N* = 39)	Escitalopram (*N* = 29)	Total (*N* = 88)
Cardiac disorders				
Other, 'tightness upper abdomen'; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Ear and labyrinth disorders				
Vertigo; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Eye disorders				
Blurred vision; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Cataract; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Dry eye; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Gastrointestinal disorders				
Abdominal pain; *N* (%)	0 (0.0)	0 (0.0)	2 (5.7)	2 (1.8)
Constipation; *N* (%)	0 (0.0)	2 (4.3)	2 (5.7)	4 (3.5)
Diarrhoea; *N* (%)	1 (3.2)	0 (0.0)	2 (5.7)	3 (2.7)
Dry mouth; *N* (%)	0 (0.0)	6 (12.8)	1 (2.9)	7 (6.2)
Dyspepsia; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Flatulence; *N* (%)	0 (0.0)	1 (2.1)	1 (2.9)	2 (1.8)
Nausea; *N* (%)	0 (0.0)	1 (2.1)	1 (2.9)	2 (1.8)
Vomiting; *N* (%)	1 (3.2)	3 (6.4)	0 (0.0)	4 (3.5)
General disorders and administration site conditions				
Fatigue; *N* (%)	1 (3.2)	1 (2.1)	2 (5.7)	4 (3.5)
Flu-like symptoms; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Infections and infestations				
Lung infection; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Rash pustular; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Tooth infection; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Urinary tract infection; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)

continued

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TABLE 33 Total number of AEs experienced by both System Organ Class and Common Terminology Criteria for Adverse Events term, by randomised arm (*continued*)

System organ class CTCAE term	Placebo (*N* = 20)	Nortriptyline (*N* = 39)	Escitalopram (*N* = 29)	Total (*N* = 88)
Other, COVID-19; *N* (%)	2 (6.5)	1 (2.1)	1 (2.9)	4 (3.5)
Injury, poisoning and procedural complications				
Fall; *N* (%)	0 (0.0)	3 (6.4)	2 (5.7)	5 (4.4)
Infusion-related reaction; *N* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)
Investigations				
Lipase increased; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Serum amylase increased; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Musculoskeletal and connective tissue disorders				
Back pain; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Muscle cramp; *N* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)
Neck pain; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Nervous system disorders				
Dizziness; *N* (%)	0 (0.0)	3 (6.4)	0 (0.0)	3 (2.7)
Headache; *N* (%)	1 (3.2)	1 (2.1)	2 (5.7)	4 (3.5)
Movements involuntary; *N* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)
Somnolence; *N* (%)	1 (3.2)	2 (4.3)	0 (0.0)	3 (2.7)
Tremor; *N* (%)	1 (3.2)	0 (0.0)	1 (2.9)	2 (1.8)
Other, 'Increased "OFF" time'; *N* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)
Psychiatric disorders				
Confusion; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Delusions; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Depression; *N* (%)	1 (3.2)	0 (0.0)	1 (2.9)	2 (1.8)
Hallucinations; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Insomnia; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Other, 'low mood following bereavement'; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)

TABLE 33 Total number of AEs experienced by both System Organ Class and Common Terminology Criteria for Adverse Events term, by randomised arm (*continued*)

System organ class CTCAE term	Placebo (*N* = 20)	Nortriptyline (*N* = 39)	Escitalopram (*N* = 29)	Total (*N* = 88)
Reproductive system and breast disorders				
Ejaculation disorder; *N* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)
Erectile dysfunction; *N* (%)	0 (0.0)	0 (0.0)	2 (5.7)	2 (1.8)
Respiratory, thoracic and mediastinal disorders				
Cough; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Epistaxis; *N* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)
Sore throat; *N* (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (0.9)
Skin and subcutaneous tissue disorders				
Hyperhidrosis; *N* (%)	0 (0.0)	1 (2.1)	1 (2.9)	2 (1.8)
Rash acneiform; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Rash maculo-papular; *N* (%)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.9)
Vascular disorders				
Hot flashes; *N* (%)	0 (0.0)	1 (2.1)	2 (5.7)	3 (2.7)

CTCAE, Common Terminology Criteria for Adverse Events.

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TABLE 34 Adverse event listing of all patients and all events

Patient	AE	Causality	Grade	Arm
ADP-01-001	Nervous system disorders: somnolence	(2) Possibly	(1) Mild	Placebo
ADP-01-003	Gastrointestinal disorders: flatulence	(0) Not related	(1) Mild	Nortriptyline
ADP-01-006	Reproductive system and breast disorders: ejaculation disorder	(2) Possibly	(1) Mild	Escitalopram
ADP-01-006	Reproductive system and breast disorders: erectile dysfunction	(2) Possibly	(1) Mild	Escitalopram
ADP-01-007	Investigations: lipase increased	(2) Possibly	(2) Moderate	Nortriptyline
ADP-01-007	Nervous system disorders: somnolence	(2) Possibly	(1) Mild	Nortriptyline
ADP-01-007	Eye disorders: dry eye	(2) Possibly	(1) Mild	Nortriptyline
ADP-01-007	Gastrointestinal disorders: dry mouth	(2) Possibly	(1) Mild	Nortriptyline
ADP-01-007	Investigations: serum amylase increased	(2) Possibly	(2) Moderate	Nortriptyline
ADP-01-008	Nervous system disorders: headache	(2) Possibly	(1) Mild	Escitalopram
ADP-01-008	Gastrointestinal disorders: constipation	(2) Possibly	(1) Mild	Escitalopram
ADP-01-008	Respiratory, thoracic and mediastinal disorders: epistaxis	(3) Probably	(2) Moderate	Escitalopram
ADP-01-009	Musculoskeletal and connective tissue disorders: muscle cramp	(0) Not related	(1) Mild	Escitalopram
ADP-01-009	Nervous system disorders: headache	(2) Possibly	(1) Mild	Escitalopram
ADP-01-009	Gastrointestinal disorders: diarrhoea	(2) Possibly	(1) Mild	Escitalopram
ADP-03-003	General disorders and administration site conditions: fatigue	(2) Possibly	(1) Mild	Escitalopram
ADP-03-003	Nervous system disorders: tremor	(2) Possibly	(1) Mild	Escitalopram
ADP-04-001	Musculoskeletal and connective tissue disorders: neck pain	(1) Unlikely	(1) Mild	Placebo
ADP-04-001	Nervous system disorders: headache	(1) Unlikely	(1) Mild	Placebo
ADP-05-002	Respiratory, thoracic and mediastinal disorders: sore throat	(0) Not related	(1) Mild	Placebo
ADP-05-002	General disorders and administration site conditions: flu-like symptoms	(0) Not related	(1) Mild	Placebo
ADP-05-002	Musculoskeletal and connective tissue disorders: back pain	(0) Not related	(1) Mild	Placebo
ADP-05-002	Respiratory, thoracic and mediastinal disorders: cough	(0) Not related	(1) Mild	Placebo
ADP-09-002	Gastrointestinal disorders: nausea	(0) Not related	(1) Mild	Escitalopram
ADP-09-002	Vascular disorders: hot flashes	(2) Possibly	(1) Mild	Escitalopram
ADP-09-003	Gastrointestinal disorders: dry mouth	(2) Possibly	(1) Mild	Nortriptyline
ADP-09-003	Gastrointestinal disorders: constipation	(2) Possibly	(2) Moderate	Nortriptyline

TABLE 34 Adverse event listing of all patients and all events (*continued*)

Patient	AE	Causality	Grade	Arm
ADP-09-003	General disorders and administration site conditions: fatigue	(2) Possibly	(1) Mild	Nortriptyline
ADP-10-001	Gastrointestinal disorders: abdominal pain	(2) Possibly	(1) Mild	Escitalopram
ADP-10-001	Gastrointestinal disorders: abdominal pain	(2) Possibly	(1) Mild	Escitalopram
ADP-10-001	Gastrointestinal disorders: flatulence	(2) Possibly	(1) Mild	Escitalopram
ADP-10-001	Gastrointestinal disorders: diarrhoea	(2) Possibly	(1) Mild	Escitalopram
ADP-10-004	Infections and infestations: tooth infection	(0) Not related	(2) Moderate	Placebo
ADP-10-011	Skin and subcutaneous tissue disorders: hyperhidrosis	(0) Not related	(1) Mild	Escitalopram
ADP-10-011	Gastrointestinal disorders: dry mouth	(2) Possibly	(2) Moderate	Escitalopram
ADP-10-012	Nervous system disorders: headache	(0) Not related	(1) Mild	Nortriptyline
ADP-10-012	Gastrointestinal disorders: dry mouth	(3) Probably	(1) Mild	Nortriptyline
ADP-11-001	Gastrointestinal disorders: dry mouth	(3) Probably	(2) Moderate	Nortriptyline
ADP-11-001	Psychiatric disorders: psychiatric disorders – other, specify: 'Low mood following bereavement'	(0) Not related	(2) Moderate	Nortriptyline
ADP-11-001	Eye disorders: cataract	(0) Not related	(1) Mild	Nortriptyline
ADP-11-001	Ear and labyrinth disorders: vertigo	(1) Unlikely	(2) Moderate	Nortriptyline
ADP-11-001	Infections and infestations: infections and infestations – other, specify: 'COVID-19'	(0) Not related	(2) Moderate	Nortriptyline
ADP-11-001	Infections and infestations: rash pustular	(0) Not related	(2) Moderate	Nortriptyline
ADP-11-001	Injury, poisoning and procedural complications: fall	(1) Unlikely	(1) Mild	Nortriptyline
ADP-11-001	Nervous system disorders: dizziness	(2) Possibly	(2) Moderate	Nortriptyline
ADP-11-001	Nervous system disorders: dizziness	(0) Not related	(1) Mild	Nortriptyline
ADP-11-001	Injury, poisoning and procedural complications: fall	(0) Not related	(1) Mild	Nortriptyline
ADP-11-001	Eye disorders: blurred vision	(2) Possibly	(2) Moderate	Nortriptyline
ADP-11-002	Injury, poisoning and procedural complications: fall	(0) Not related	(1) Mild	Escitalopram
ADP-11-002	Injury, poisoning and procedural complications: infusion-related reaction	(0) Not related	(1) Mild	Escitalopram
ADP-11-002	Psychiatric disorders: depression	(0) Not related	(1) Mild	Escitalopram
ADP-11-002	Injury, poisoning and procedural complications: fall	(0) Not related	(1) Mild	Escitalopram
ADP-13-001	Infections and infestations: infections and infestations – other, specify: 'COVID-19'	(0) Not related	(1) Mild	Escitalopram
ADP-16-001	Gastrointestinal disorders: diarrhoea	(0) Not related	(1) Mild	Placebo

continued

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Patient	AE	Causality	Grade	Arm
ADP-16-001	General disorders and administration site conditions: fatigue	(1) Unlikely	(1) Mild	Placebo
ADP-16-001	Gastrointestinal disorders: vomiting	(0) Not related	(1) Mild	Placebo
ADP-16-002	Psychiatric disorders: confusion	(0) Not related	(2) Moderate	Placebo
ADP-16-002	Cardiac disorders: cardiac disorders – other, specify: 'tightness upper abdomen'	(0) Not related	(2) Moderate	Placebo
ADP-16-002	Infections and infestations: urinary tract infection	(0) Not related	(2) Moderate	Placebo
ADP-16-002	Infections and infestations: lung infection	(0) Not related	(2) Moderate	Placebo
ADP-16-002	Infections and infestations: infections and infestations – other, specify: 'COVID-19 Confirmed'	(0) Not related	(2) Moderate	Placebo
ADP-16-004	Skin and subcutaneous tissue disorders: rash acneiform	(1) Unlikely	(1) Mild	Nortriptyline
ADP-16-005	Infections and infestations: infections and infestations – other, specify: 'COVID-19'	(0) Not related	(1) Mild	Placebo
ADP-16-006	Nervous system disorders: movements involuntary	(0) Not related	(1) Mild	Escitalopram
ADP-16-006	Gastrointestinal disorders: constipation	(0) Not related	(1) Mild	Escitalopram
ADP-16-006	General disorders and administration site conditions: fatigue	(0) Not related	(1) Mild	Escitalopram
ADP-16-006	Nervous system disorders: nervous system disorders – other, specify: 'Increased "OFF" time'	(0) Not related	(1) Mild	Escitalopram
ADP-16-006	Vascular disorders: hot flashes	(0) Not related	(1) Mild	Escitalopram
ADP-17-001	Gastrointestinal disorders: vomiting	(2) Possibly	(1) Mild	Nortriptyline
ADP-17-001	Gastrointestinal disorders: dry mouth	(2) Possibly	(1) Mild	Nortriptyline
ADP-18-001	Nervous system disorders: dizziness	(2) Possibly	(1) Mild	Nortriptyline
ADP-18-001	Psychiatric disorders: delusions	(2) Possibly	(1) Mild	Nortriptyline
ADP-18-001	Injury, poisoning and procedural complications: fall	(2) Possibly	(1) Mild	Nortriptyline
ADP-18-001	Gastrointestinal disorders: dry mouth	(4) Definitely	(1) Mild	Nortriptyline
ADP-18-001	Gastrointestinal disorders: vomiting	(3) Probably	(1) Mild	Nortriptyline
ADP-18-001	Vascular disorders: hot flashes	(0) Not related	(1) Mild	Nortriptyline
ADP-18-001	Skin and subcutaneous tissue disorders: rash maculo-papular	(3) Probably	(1) Mild	Nortriptyline
ADP-18-001	Psychiatric disorders: hallucinations	(2) Possibly	(1) Mild	Nortriptyline
ADP-18-001	Skin and subcutaneous tissue disorders: hyperhidrosis	(3) Probably	(1) Mild	Nortriptyline

TABLE 34 Adverse event listing of all patients and all events (*continued*)

Patient	AE	Causality	Grade	Arm
ADP-18-001	Gastrointestinal disorders: constipation	(4) Definitely	(1) Mild	Nortriptyline
ADP-18-001	Gastrointestinal disorders: vomiting	(0) Not related	(2) Moderate	Nortriptyline
ADP-18-001	Gastrointestinal disorders: nausea	(3) Probably	(1) Mild	Nortriptyline
ADP-18-001	Gastrointestinal disorders: dyspepsia	(2) Possibly	(1) Mild	Nortriptyline
ADP-18-001	Nervous system disorders: somnolence	(4) Definitely	(1) Mild	Nortriptyline
ADP-18-002	Psychiatric disorders: depression	(2) Possibly	(2) Moderate	Placebo
ADP-18-002	Psychiatric disorders: insomnia	(2) Possibly	(2) Moderate	Placebo
ADP-18-002	Nervous system disorders: tremor	(2) Possibly	(2) Moderate	Placebo
ADP-18-003	Reproductive system and breast disorders: erectile dysfunction	(4) Definitely	(1) Mild	Escitalopram

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TABLE 35 Serious adverse events by allocated treatment

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Summary				
Number of patients reporting at least 1 SAE; *N* (%)	0	0	1 (5.9)	1 (1.9)
Number of SAEs; *N*	0	0	2	2
SAE term				
Urinary tract infection	0	0	1	1
Spinal infection	0	0	1	1

participants missed their week 2 dose escalation period call – all three on nortriptyline. Three further participants on escitalopram did not escalate at this point, with two due to safety concerns and one discontinuing completely. At weeks 4 and 6 it was primarily the placebo arm participants that did not escalate and continued at their previous dose level. At week 6 two participants de-escalated, one on each of the two active arms, and a placebo arm participant discontinuing treatment completely.

Compliance

Compliance data, and consequently conclusions, are rather limited as only 31 of 52 in total provided their dosing diaries at the key visit of week 8 (*Table 37*). The majority of those reporting their dosing did not miss any IMP, though we cannot be sure as to whether the remaining 40% also adhered at the same rate. Of the three that did miss days, the participant on placebo missed 15 days as 'participant developed a rash around his neck area', the nortriptyline participant forgot for 2 days, and the escitalopram forgot for one. Going forwards from this visit, the decision for most participants was to continue at the same dose. The data available are even lower at week 26, but there does seem to be a suggestion of an increase in missing doses, though the window of time is now 18 weeks over 8 (*Table 38*). Similar difficulties exist at week 52 (*Table 39*).

Withdrawals

In total, there were 22 withdrawals from the trial (*Table 40*), with the majority of these (21 of the 22, *Table 41*) providing a reason. Only one of these was at or prior to the week 8 time point critical for the outcome measure. One allocated nortriptyline withdrew prior to IMP administration. Most withdrew consent for both IMP administration and follow-up on the trial. One participant allocated escitalopram withdrew due to a SAE. Seven of these withdrawals were due to the closedown of the trial and the enforced unblinding of participants who had not completed the trial yet (*Table 42*). Three participants had withdrawn prior to the primary outcome measure; these were two on placebo and one in the nortriptyline arm.

Health economics analysis

Results for quality of life and capability measures: EuroQol-5 Dimensions, five-level version and ICEpop CAPability measure – Older people version

The results are presented here according to randomised groups, and for all arms combined. We present the mean unadjusted utility scores at each time point, and the mean 8-week QALYs (or CALYs) as well as quality-adjusted life-weeks [QALWs or capability-adjusted life-week (CALWs)], as these numbers are more accessible given the very short time horizon of the analysis. The QALYs/CALYs and QALWs/CALWs are presented both as the unadjusted raw values and calculated using non-parametric bootstrapping while adjusting for baseline utility (or capability) scores, in *Appendix 6* (*Tables 43–47*), *Appendix 7* (*Table 48*) and *Appendix 8* (*Table 49*) for patient participants.

TABLE 36 Dose escalation at weeks 2, 4 and 6 by allocated arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
Week 2 – Please confirm dose-level decision made for participant from this call onwards				
Escalate to next dose level; *N* (%)	19 (100.0)	13 (81.3)	14 (82.4)	46 (88.5)
Continue on current dose level due to safety concerns; *N* (%)	0 (0.0)	0 (0.0)	2 (11.8)	2 (3.8)
Discontinue trial medication; *N* (%)	0 (0.0)	0 (0.0)	1 (5.9)	1 (1.9)
Week 4 – Please confirm dose-level decision made for participant from this call onwards				
Escalate to next dose level; *N* (%)	10 (52.6)	9 (56.3)	12 (70.6)	31 (59.6)
Continue on current dose level as per protocol; *N* (%)	8 (42.1)	3 (18.8)	3 (17.6)	14 (26.9)
Continue on current dose level due to safety concerns; *N* (%)	0 (0.0)	0 (0.0)	1 (5.9)	1 (1.9)
Week 6 – Please confirm dose-level decision made for participant from this call onwards				
Escalate to next dose level; *N* (%)	9 (47.4)	8 (50.0)	10 (58.8)	27 (51.9)
Decrease to previous dose level; *N* (%)	0 (0.0)	1 (6.3)	1 (5.9)	2 (3.8)
Continue on current dose level as per protocol; *N* (%)	8 (42.1)	3 (18.8)	5 (29.4)	16 (30.8)
Discontinue trial medication; *N* (%)	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)

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TABLE 37 Week 8 IMP review and compliance

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
On review of Dosing Diary, were any trial days missed since the previous visit?				
Yes; *N* (%)	1 (5.3)	1 (6.3)	1 (5.9)	3 (5.8)
No; *N* (%)	10 (52.6)	8 (50.0)	10 (58.8)	28 (53.8)
Please confirm dose-level decision made for participant from this visit onwards				
Continue on current dose level; *N* (%)	13 (68.4)	13 (81.3)	10 (58.8)	36 (69.2)
Escalate dose level; *N* (%)	0 (0.0)	0 (0.0)	2 (11.8)	2 (3.8)
Taper dose level; *N* (%)	3 (15.8)	0 (0.0)	2 (11.8)	5 (9.6)
Discontinue trial medication; *N* (%)	1 (5.3)	0 (0.0)	2 (11.8)	3 (5.8)
If decision concludes participant should taper down/discontinue trial medication, reason				
AE; *N* (%)	1 (5.3)	0 (0.0)	3 (17.6)	4 (7.7)
Lack of efficacy; *N* (%)	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)
Other; *N* (%)	2 (10.5)	0 (0.0)	1 (5.9)	3 (5.8)

TABLE 38 Week 26 IMP review and compliance

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
On review of Dosing Diary, were any trial days missed since the previous visit?				
Yes; *N* (%)	2 (10.5)	3 (18.8)	2 (11.8)	7 (13.5)
No; *N* (%)	3 (15.8)	4 (25.0)	3 (17.6)	10 (19.2)
Please confirm dose-level decision made for participant from this visit onwards				
Continue on current dose level; *N* (%)	7 (36.8)	6 (37.5)	8 (47.1)	21 (40.4)
Taper dose level; *N* (%)	0 (0.0)	3 (18.8)	1 (5.9)	4 (7.7)
If decision concludes participant should taper down/discontinue trial medication, reason				
AE; *N* (%)	0 (0.0)	2 (12.5)	0 (0.0)	2 (3.8)
Other; *N* (%)	0 (0.0)	1 (6.3)	1 (5.9)	2 (3.8)

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TABLE 39 Week 52 IMP review and compliance

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
On review of Dosing Diary, were any trial days missed since the previous visit?				
Yes; *N* (%)	0 (0.0)	3 (18.8)	3 (17.6)	6 (11.5)
No; *N* (%)	2 (10.5)	0 (0.0)	0 (0.0)	2 (3.8)
Please confirm dose-level decision made for participant from this visit onwards				
Taper dose level; *N* (%)	4 (21.1)	3 (18.8)	6 (35.3)	13 (25.0)
Discontinue trial medication; *N* (%)	2 (10.5)	1 (6.3)	0 (0.0)	3 (5.8)
If decision concludes participant should taper down/discontinue trial medication, reason				
Week 52 (visit 4); *N* (%)	5 (26.3)	4 (25.0)	6 (35.3)	15 (28.8)
Other; *N* (%)	1 (5.3)	2 (12.5)	0 (0.0)	3 (5.8)

TABLE 40 Total withdrawals from the trial, by allocated arm

	Placebo (*N* = 19)	Nortriptyline (*N* = 16)	Escitalopram (*N* = 17)	Total (*N* = 52)
No; *N* (%)	11 (57.9)	7 (43.8)	12 (70.6)	30 (57.7)
Yes; *N* (%)	8 (42.1)	9 (56.3)	5 (29.4)	22 (42.3)

Plots showing the utility (or capability) scores by time point, both split by arm and for all arms combined, and in overlaid plots, are given in *Appendix 1* (*Figures 8–12*), *Appendix 2* (*Figures 13–17*), and *Appendix 3* (*Figures 18–22*). Sample sizes by time point are given in the numbers along the bottom of each plot).

Appendix 4 (*Figures 23–27*) shows the mean unadjusted utility scores by time point for carers, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis). *Appendix 5* (*Figures 28–32*) shows the mean unadjusted utility scores by time point for carers, from the responses to the EQ-5D-5L, and valued using the Devlin Value Set for England tariff (secondary analysis).

The results show that there is no statistically significant difference by time point or by group for any of the measures, which is perhaps unsurprising given the small patient and carer numbers. There is a slight suggestion that patients have a small increase in utility from baseline to the 8-week time point, and a similarly small and statistically insignificant decrease in capability from baseline to 8 weeks. By 26 and 52 weeks, any possible effect is no longer visible. No further conclusions can be drawn from these immature results, and NMB analysis has therefore not been performed.

Results for resource use and costs

Intervention medications

The numbers of bottles dispensed by arm and time point are given in *Appendix 7*, *Table 48*, and the costs calculated for the nortriptyline and escitalopram arms are given in *Appendix 8*, *Table 49*. Unit costs were taken from the online BNF, accessed June 2023, using the cheapest Drug Tariff Price for suitably sized packs, that is 100 tablets of 25 mg nortriptyline (£2.53 per pack) and 28 tablets of 5 mg escitalopram (£1.15 per pack). As the bottles used in the trial were bespoke sizes of 185 tablets per bottle, the assumed price of the bottle for each medication was calculated pro rata.

It is unlikely that all medications dispensed were used, as most of the participants were titrated up to the full dose more slowly than planned in the protocol; therefore, the costs calculated in *Appendix 8*, *Table 49* here are likely to be an overestimate. Also, the results here are subject to the same caveats as elsewhere, regarding small patient numbers. Note that in some cases the interquartile range is zero, and this is because the 25th and 75th (and 50th, i.e. the median) percentiles are all the same number, therefore the difference between them is zero.

Only two participants reported use of psychological therapies during the truncated study, both in the nortriptyline arm: one at baseline (five counselling sessions, total cost £330) and one at 8 weeks (two counselling sessions, total cost £132).

Client Service Receipt Inventory

The activity and corresponding costs were calculated for health and social care resource use as captured in the CSRI, for baseline and 8 weeks, split by treatment group, but as numbers were small no formal comparisons were made, and the tables are not presented here.

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TABLE 41 Withdrawal reasons, by allocated arm

	Placebo (*N* = 8)	Nortriptyline (*N* = 9)	Escitalopram (*N* = 5)	Total (*N* = 22)
Withdrawal initiated by				
Participant; *N* (%)	4 (50.0)	4 (44.4)	3 (60.0)	11 (50.0)
Clinician; *N* (%)	4 (50.0)	5 (55.6)	2 (40.0)	11 (50.0)
Is the participant withdrawing prior to IMP administration?				
Yes; *N* (%)	0 (0.0)	1 (11.1)	0 (0.0)	1 (4.5)
No; *N* (%)	8 (100.0)	8 (88.9)	5 (100.0)	21 (95.5)
Has the participant withdrawn consent from further study intervention?				
Yes; *N* (%)	4 (50.0)	5 (55.6)	5 (100.0)	14 (63.6)
No; *N* (%)	4 (50.0)	4 (44.4)	0 (0.0)	8 (36.4)
Has the participant withdrawn consent from study intervention AND follow-up?				
Yes; *N* (%)	5 (62.5)	5 (55.6)	5 (100.0)	15 (68.2)
No; *N* (%)	3 (37.5)	4 (44.4)	0 (0.0)	7 (31.8)
Reason given?				
Yes; *N* (%)	7 (87.5)	9 (100.0)	5 (100.0)	21 (95.5)
No; *N* (%)	1 (12.5)	0 (0.0)	0 (0.0)	1 (4.5)
Participant experienced unacceptable treatment toxicity or AE				
Yes; *N* (%)	0 (0.0)	0 (0.0)	4 (80.0)	4 (18.2)
No; *N* (%)	7 (87.5)	9 (100.0)	1 (20.0)	17 (77.3)
Participant experienced SAE				
Yes; *N* (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (4.5)
No; *N* (%)	7 (87.5)	9 (100.0)	4 (80.0)	20 (90.9)
Pregnancy				
No; *N* (%)	7 (87.5)	9 (100.0)	5 (100.0)	21 (95.5)
A change in the participant's condition that, in the clinician's opinion, justifies the discontinuation of treatment				
Yes; *N* (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (4.5)
No; *N* (%)	7 (87.5)	9 (100.0)	4 (80.0)	20 (90.9)

TABLE 41 Withdrawal reasons, by allocated arm (*continued*)

	Placebo (*N* = 8)	Nortriptyline (*N* = 9)	Escitalopram (*N* = 5)	Total (*N* = 22)
Intercurrent illness or requirement for medication that prevents further treatment with trial medication				
Yes; *N* (%)	1 (12.5)	1 (11.1)	0 (0.0)	2 (9.1)
No; *N* (%)	6 (75.0)	8 (88.9)	5 (100.0)	19 (86.4)
Unable/unwilling to adhere to trial medication dosing schedule				
Yes; *N* (%)	1 (12.5)	3 (33.3)	1 (20.0)	5 (22.7)
No; *N* (%)	6 (75.0)	6 (66.7)	4 (80.0)	16 (72.7)
Unable to commit to follow-up visit schedule				
Yes; *N* (%)	1 (12.5)	2 (22.2)	2 (40.0)	5 (22.7)
No; *N* (%)	6 (75.0)	7 (77.8)	3 (60.0)	16 (72.7)
Unwilling to complete follow-up questionnaires				
Yes; *N* (%)	1 (12.5)	1 (11.1)	0 (0.0)	2 (9.1)
No; *N* (%)	6 (75.0)	8 (88.9)	5 (100.0)	19 (86.4)
Other				
Yes; *N* (%)	7 (87.5)	7 (77.8)	1 (20.0)	15 (68.2)
No; *N* (%)	0 (0.0)	2 (22.2)	4 (80.0)	6 (27.3)

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TABLE 42 Withdrawal reasons, classified as 'other'

Identifier	Treatment	Withdrawal 'other' reason
ADP-03-002	Placebo	Lack of efficacy
ADP-03-003	Escitalopram	Patient experienced intolerable side effects
ADP-05-001	Placebo	Lack of efficacy and possible worsening
ADP-05-002	Placebo	*Patient has been unblinded and stopped taking IMP following end-of-study visit due to process of early trial closedown*
ADP-07-001	Placebo	As per participant, there is no change or improvement in her condition
ADP-10-003	Nortriptyline	Participant's Parkinson's condition is deteriorating, and his wife has a cancer diagnosis
ADP-10-004	Placebo	Patient has sudden plans to travel to Brazil and thinks the trial medication has not helped him
ADP-10-012	Nortriptyline	*Patient has been unblinded and stopped taking IMP after end-of-study visit due to early trial closedown*
ADP-10-013	Nortriptyline	*Patient has been unblinded following end-of-study visit and stopped taking IMP once unblinded as per early trial closedown*
ADP-10-016	Nortriptyline	*Patient has been unblinded following end-of-study visit and stopped taking IMP once unblinded as per early trial closedown*
ADP-15-021	Placebo	*Patient has been unblinded and stopped taking IMP after end-of-study visit due to early trial closedown*
ADP-16-004	Nortriptyline	*Patient has been unblinded and stopped taking IMP following end-of-study visit due to process of early trial closedown*
ADP-16-005	Placebo	*Patient has been unblinded and stopped taking IMP following end-of-study visit due to process of early trial closedown*
ADP-17-001	Nortriptyline	Participant's personal circumstances have changed due to his partner being seriously ill in a nursing home; participant stated that his sole concern and his time must be for the partner, unable to give more time to this study
ADP-18-005	Nortriptyline	Participant started taking sertraline and feels better on it and is not keen in re-starting the trial medication

Chapter 5 Discussion

The ADepT-PD trial was a trial in response to a commissioned call to investigate the clinical and cost-effectiveness of a TCA and a SSRI for dPD. The tricyclic tested was nortriptyline and the SSRI was escitalopram.

The trial had an in-built phase with defined progression criteria to the full trial, which had a sample size target of 408. There were delays in the initial set-up of the study which required recruitment from ~30 recruiting sites including due to a shortage of one of the compounds in manufacturing and due to staff shortages in the clinical trials unit, which necessitated a pause. After recruitment had started, the COVID-19 pandemic brought recruitment to a halt and site capacity issues further slowed down recruitment after restarting. The pilot phase was extended and multiple avenues were explored in increasing recruitment, including modification of exclusion criteria, a publicity campaign through the major charities in the field, and the possibility to run the trial completely remotely at each site, which was taken up by two sites which were then the main recruiters. Nevertheless, it became clear that the target of 408 could not be achieved, and it was decided that the trial would close after all patients already approached were included, with all enrolled participants completing after the primary end point at 8 weeks. This allowed the pilot phase to reach its target of 46 participants, with overall inclusion of 52 participants at recruitment closure.

Overall, 19 patients were randomised to placebo, 16 to nortriptyline and 17 to escitalopram. There were no significant differences in the primary outcome, the BDI-II, between the groups, and the change from baseline did not reach significance in either arm. However, only a small proportion reached the target dose at 8 weeks, with slower increase and lower maximum dose due to experience of AEs. It is therefore not possible to draw any conclusions on the effectiveness of either antidepressant for dPD. AEs were compatible with the known AE profile of these medications.

Patient and public involvement

Patients contributed to the design of the study and supported the conduct of the study. Early in the project, the patient and public involvement group helped ensure that patient information sheets and report forms were accessible and user-friendly. A patient representative was a very active member of the TSC and, as part of this role, contributed to the monitoring and supervision of the trial progress.

Equality, diversity and inclusion

The trial was designed to be as inclusive and representative of clinical care as possible. The inclusion criteria were broad and all patients who meet the selection criteria at participating sites were candidates. As the trial started during the COVID pandemic, we converted all assessment to remote assessments to allow for a wider ability to participate.

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Chapter 6 Lessons learnt

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This trial was unable to recruit sufficient numbers to answer the study question. While dPD was under-recognised and undertreated until quite recently, this has now changed due to advances and publications in the field, including our own. As a result, most patients with PD, who were potentially eligible, were already taking antidepressants. Others however, who were not currently diagnosed, were difficult to identify in secondary care or were not eligible due to comorbidities or were unwilling to take antidepressants. Furthermore, while previously there was a greater stigma attached to antidepressants, those who were depressed and had been diagnosed with depression were sometimes not willing to participate in a trial with a 30% chance of being prescribed placebo, particularly as both of the intervention medications are available and can be prescribed in the NHS for depression, including in PD.

Furthermore, the call was a for a three-arm trial with a SSRI and TCA and placebo. However, as the population of patients with PD include a generally older and frail population, the side-effect profiles of these medications excluded a relatively large number of patients, particularly with cardiovascular conditions. Future trials that consider eligibility for one active agent in comparison to placebo, thus reducing the number of potential participants who fulfil exclusion criteria, may exclude fewer patients. This would also reduce the overall sample size considerably. This and the above considerations have already informed the design of another large initiative, the design of the Edmond J. Safra Accelerating Clinical Trials (EJS-ACT) in Parkinson's PD multiarm, multistage trial, where eligibility will be assessed separately for each arm and patients will be randomised only to arms they are eligible for. This has been discussed with and is supported by the patient and public involvement and engagement collaborators in the EJS-ACT-PD planning group, and is anticipated to have an important impact on recruitment rates for this groundbreaking study in PD, thanks to the lessons learnt during ADepT-PD.

Furthermore, while the question of superiority of one antidepressant class over another is of importance, as is the superiority over placebo, as both are currently available for prescription for this indication, there was a low incentive for patients to participate in this trial, particularly as those willing to take an antidepressant sometimes did not wish to be potentially be randomised to the placebo arm.

Finally, the trial was judged as low priority by many sites during the recovery from COVID-19, particularly as the medications are otherwise available. This led to a delay in sites re-opening.

We undertook a range of study and recruitment modifications and initiatives in order to recruit as widely as possible. While particularly the publicity through Parkinson's UK increased recruitment, this was not sufficient to justify continuation of the trial.

Lessons learnt include not only the above considerations in trial design in a vulnerable population with medications already available for prescription for the same indication, but also the benefit of positive actions that can be taken through involvement and publicity of the charity sector, and the possibility and practicality of recruitment and running of a Clinical Trial of an Investigational Medicinal Product trial in the UK using remote access.

Additional information

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Andrew Embleton-Thirsk (https://orcid.org/0000-0001-9402-8132): Formal analysis, Methodology, Writing – original draft.

Acknowledgements

Participants

We would like to thank all participants and their families for their participation and acknowledge the role of Clinical Research Network sites to the recruitment of participants.

Trial Management Group

The trial was managed through the Comprehensive Clinical Trials Unit (CCTU) and the PRIMENT Clinical Trials Unit at UCL. The TMG was responsible for the day-to-day management of the trial and included the chief investigator, lead collaborative investigators and trial staff.

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Professor Per Odin, Dr David McNulty, Dr Parmina Mitter, Dr David Nicholl, Dr Smitaa Patel.

Trial Steering Committee members

Professor Andrea Cipriani, Professor Emma McIntosh, Professor David Okai, Mr Alan Leibert, Mr Bryar Kadir.

Data-sharing statement

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

Ethics statement

London Bloomsbury Research Ethics Committee (REC) reviewed and approved (14/LO/0807) the trial protocol and all material given to prospective participants, including the informed consent forms (ICFs). Subsequent amendments to these documents were submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents were reviewed and approved by local research and development. The date of approval was 15 March 2019.

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/HFDO7575.

Primary conflicts of interest: Camille Carroll has a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid by the NIHR of direct payment for national lead role. Glyn Lewis has grants or contracts from NIHR 17/42/02, 202201, 19/160, 131647, 15313, 134074, Welcome Trust, UKRI which was paid to UCL. He was also the TSC chair for NIHR study STOP-D: A multi-centre randomised controlled trial of the clinical and cost-effectiveness of sertraline in preventing depression in adults following a traumatic brain injury: Sertraline TO prevent Post-TBI Depression/STOP-D (TBI Study) ISRCTN17518945 NIHR131125. This duty was unpaid. Nicholas Freemantle has grants or contracts from the MRC, the Cure Parkinson's Trust, and the European Union.

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Appendix 1 Mean unadjusted utility scores by time point from the responses to the EuroQol-5 Dimensions, five-level version, and valued by mapping to the EuroQol-5 Dimensions, three-level version tariff, as currently preferred by the National Institute for Health and Care Excellence (base-case analysis)

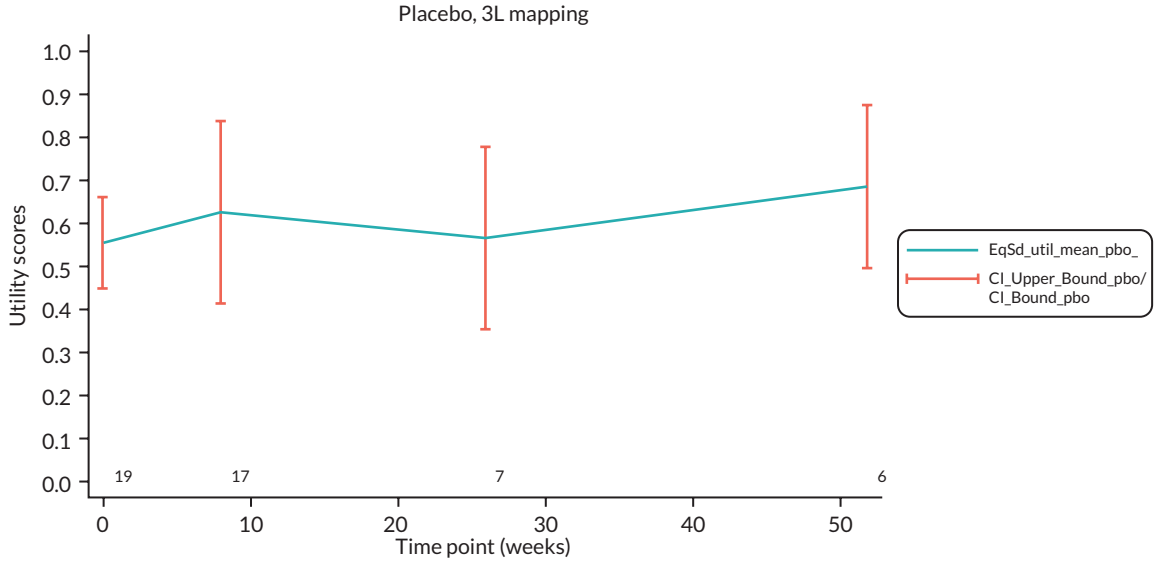

FIGURE 8 Mean unadjusted utility scores by time point for participants on placebo, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

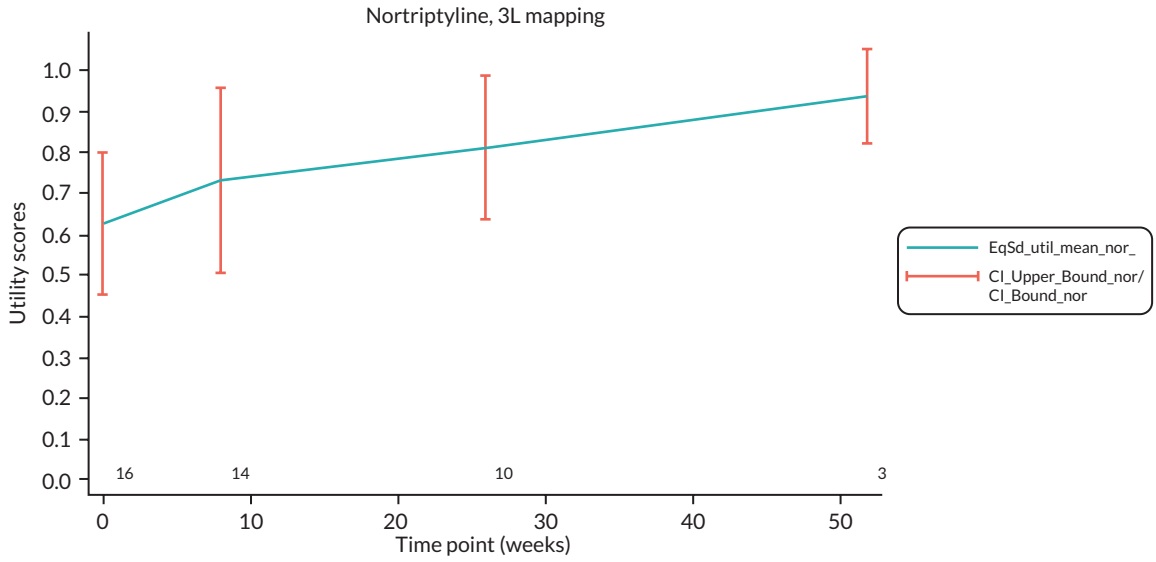

FIGURE 9 Mean unadjusted utility scores by time point for participants on nortriptyline, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

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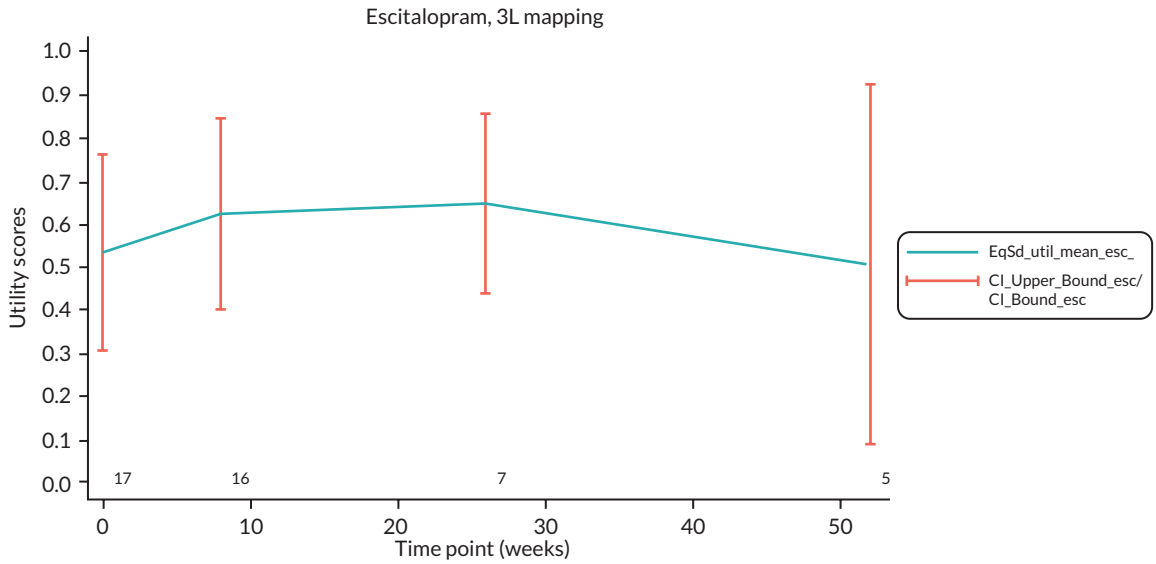

FIGURE 10 Mean unadjusted utility scores by time point for participants on escitalopram, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

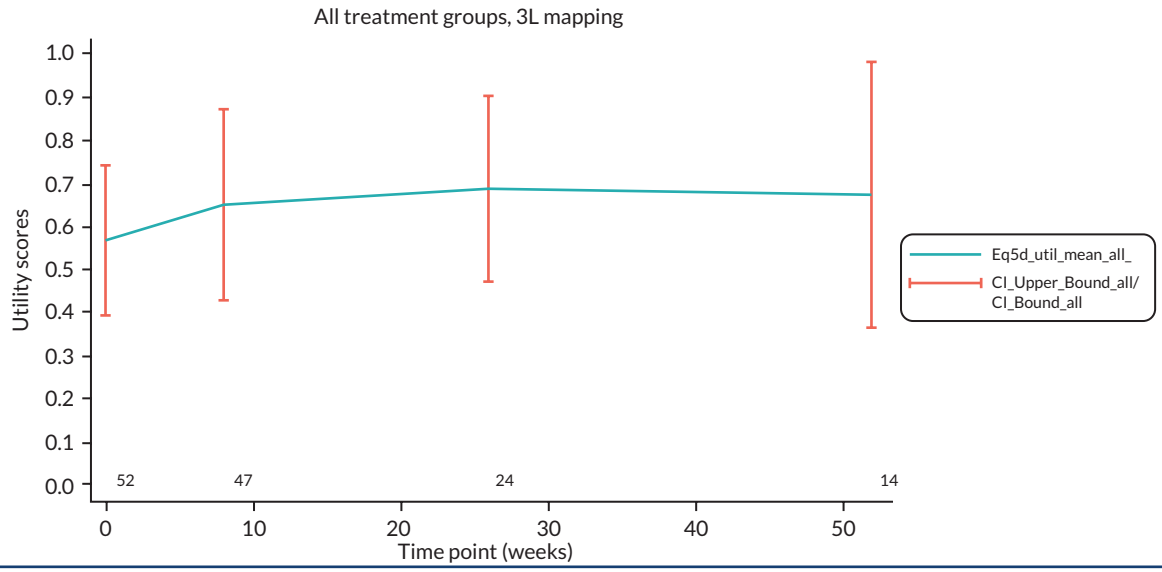

FIGURE 11 Mean unadjusted utility scores by time point for all treatment groups, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

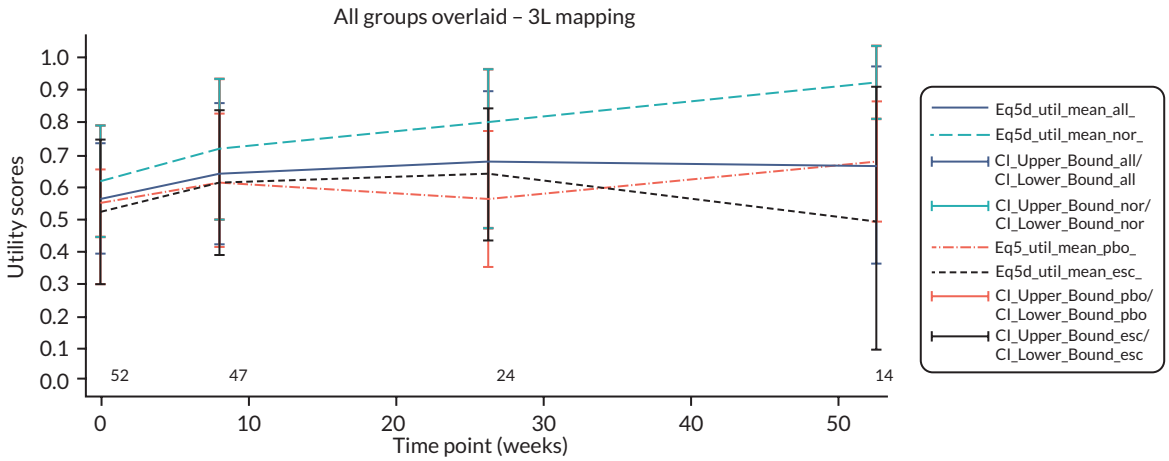

FIGURE 12 Mean unadjusted utility scores by time point for participants, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

Appendix 2 Mean unadjusted utility scores by time point, from the responses to the EuroQol-5 Dimensions, five-level version, valued using the Devlin Value Set for England tariff (secondary analysis)

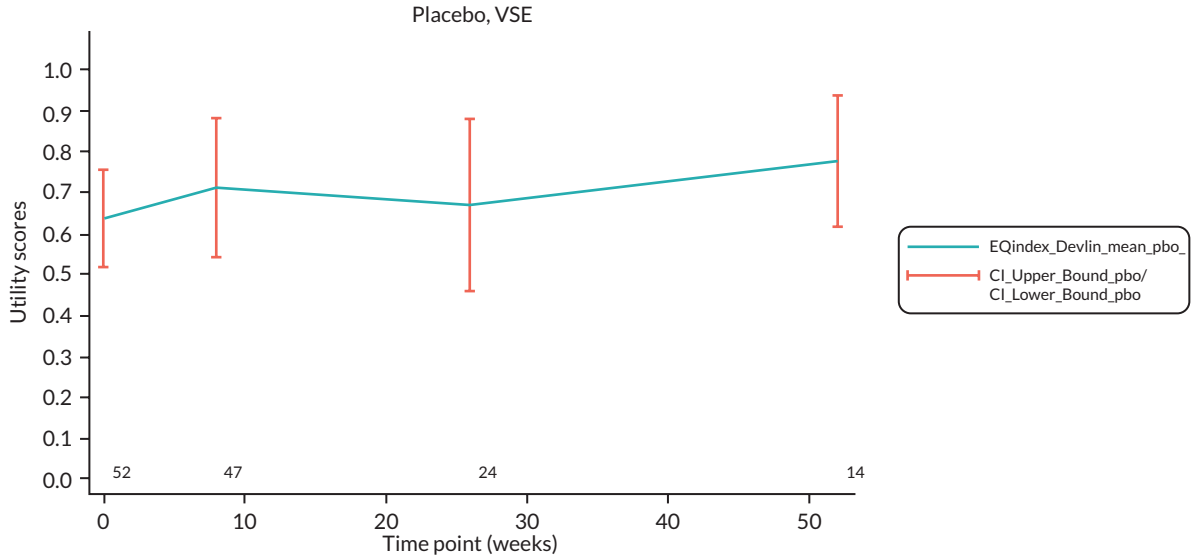

FIGURE 13 Mean unadjusted utility scores by time point for participants on placebo, from the responses to the EQ-5D-5L, valued using the Devlin Value Set for England tariff (secondary analysis).

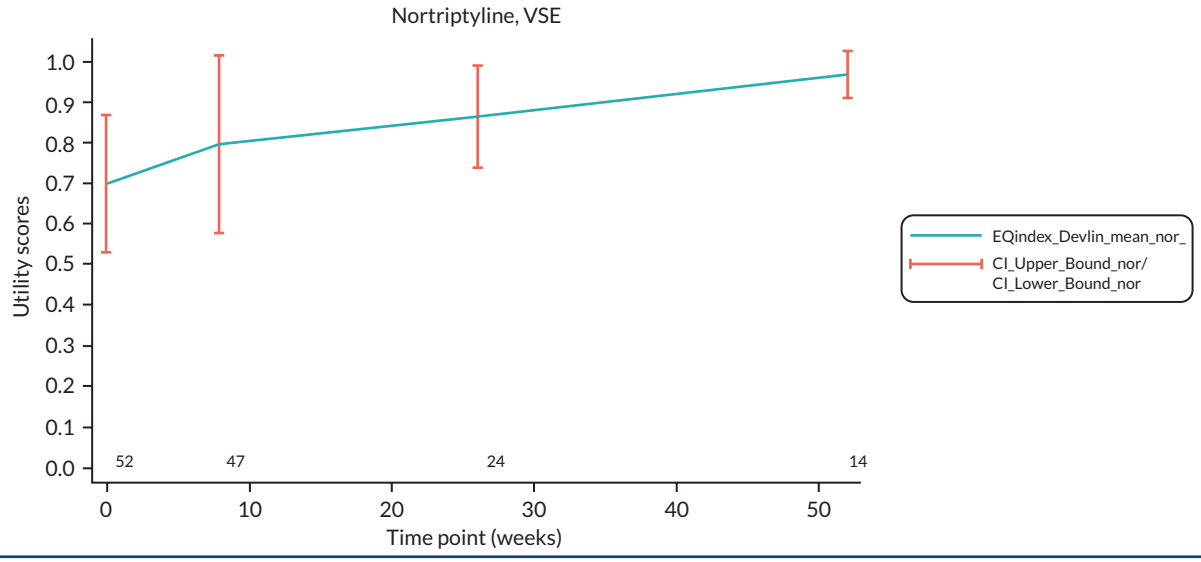

FIGURE 14 Mean unadjusted utility scores by time point for participants on nortriptyline, from the responses to the EQ-5D-5L, valued using the Devlin Value Set for England tariff (secondary analysis).

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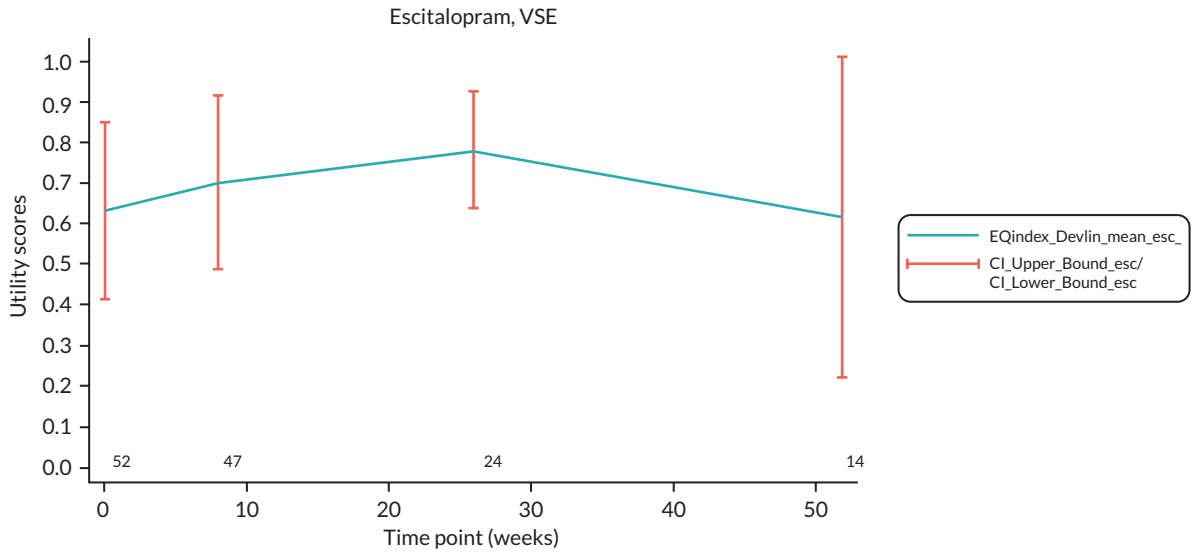

FIGURE 15 Mean unadjusted utility scores by time point for participants on escitalopram, from the responses to the EQ-5D-5L, valued using the Devlin Value Set for England tariff (secondary analysis).

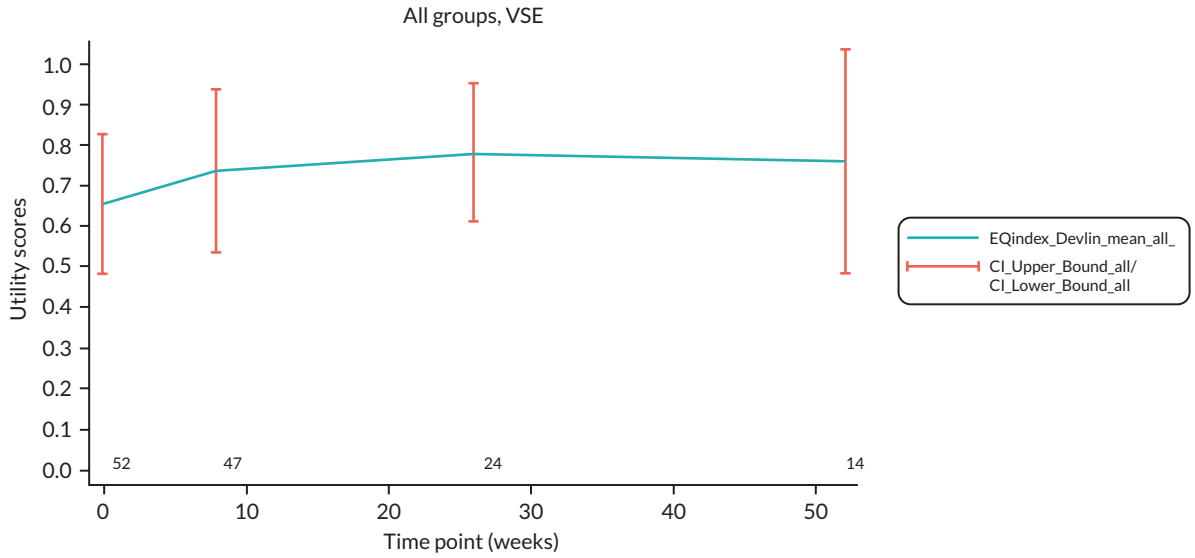

FIGURE 16 Mean unadjusted utility scores by time point for all participants, from the responses to the EQ-5D-5L, valued using the Devlin Value Set for England tariff (secondary analysis).

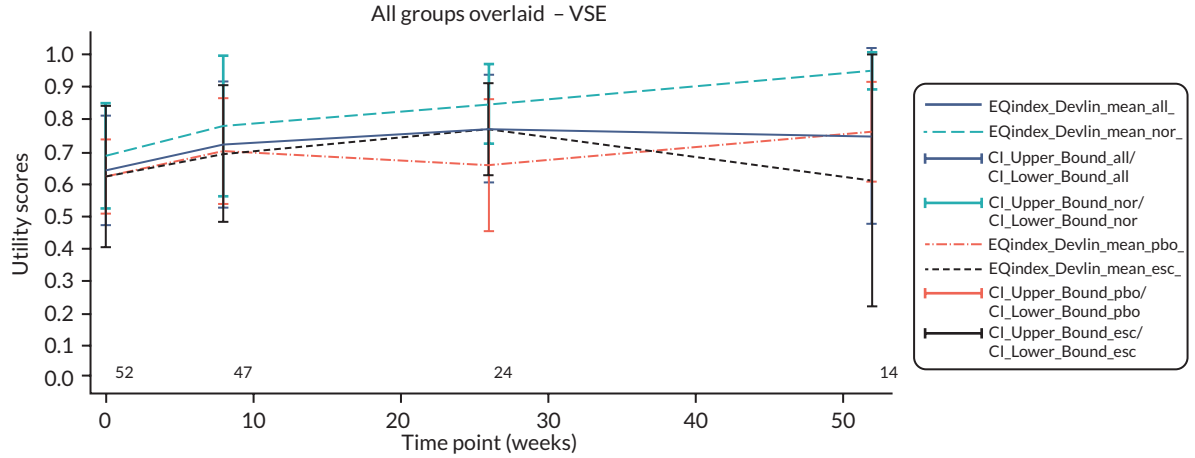

FIGURE 17 Mean unadjusted utility scores by time point for participants overlaid, from the responses to the EQ-5D-5L, valued using the Devlin Value Set for England tariff (secondary analysis).

Appendix 3 Mean unadjusted capability scores by time point, from the responses to the ICEpop CAPability measure – Older people version, valued using the standard tariff

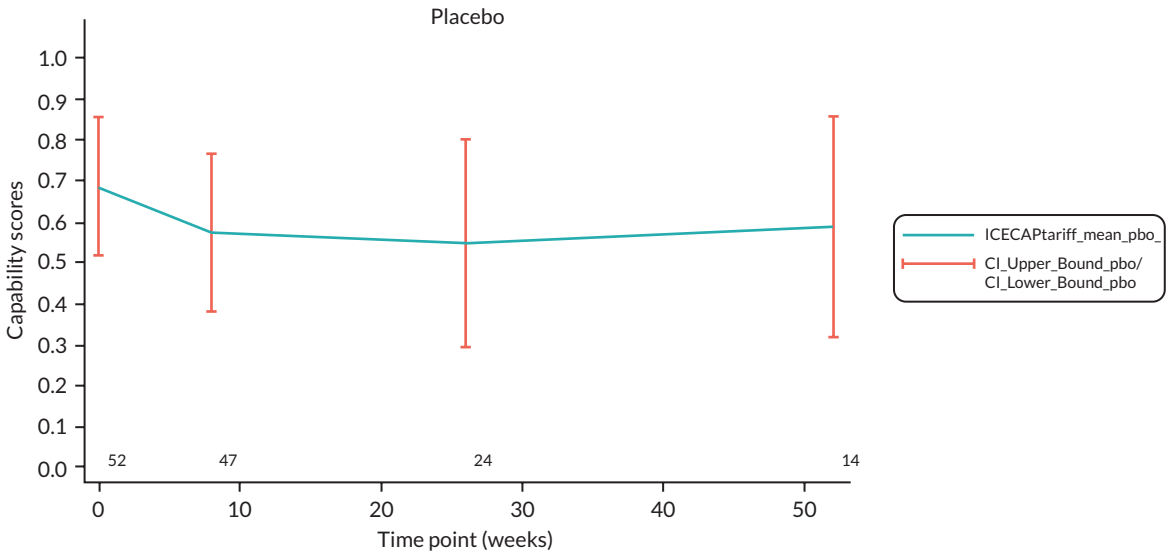

FIGURE 18 Mean unadjusted capability scores by time point for participants on placebo, from the responses to the ICECAP-O, valued using the standard tariff.

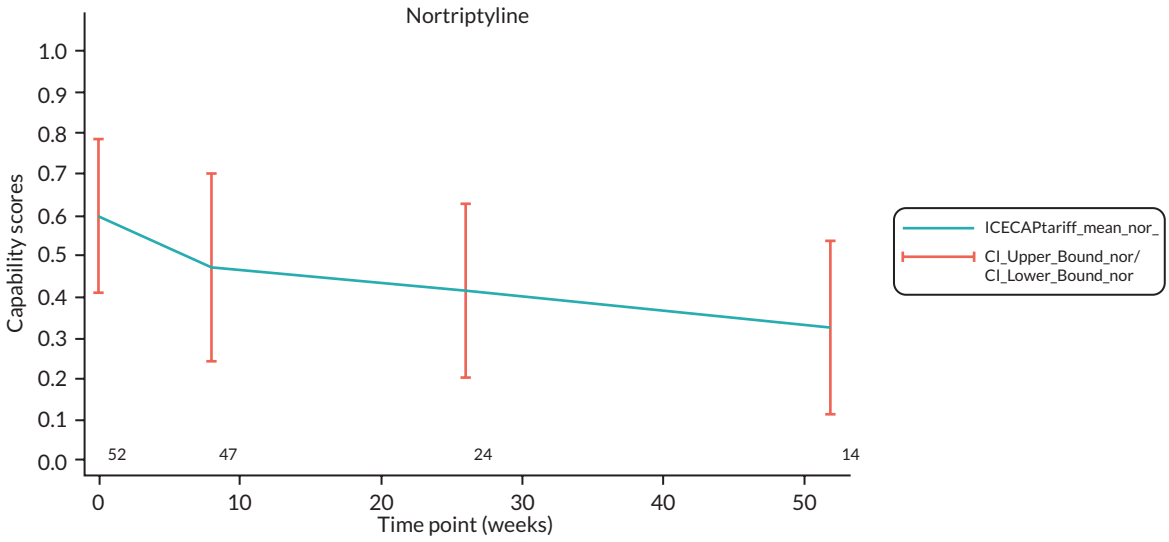

FIGURE 19 Mean unadjusted capability scores by time point for participants on nortriptyline, from the responses to the ICECAP-O, valued using the standard tariff.

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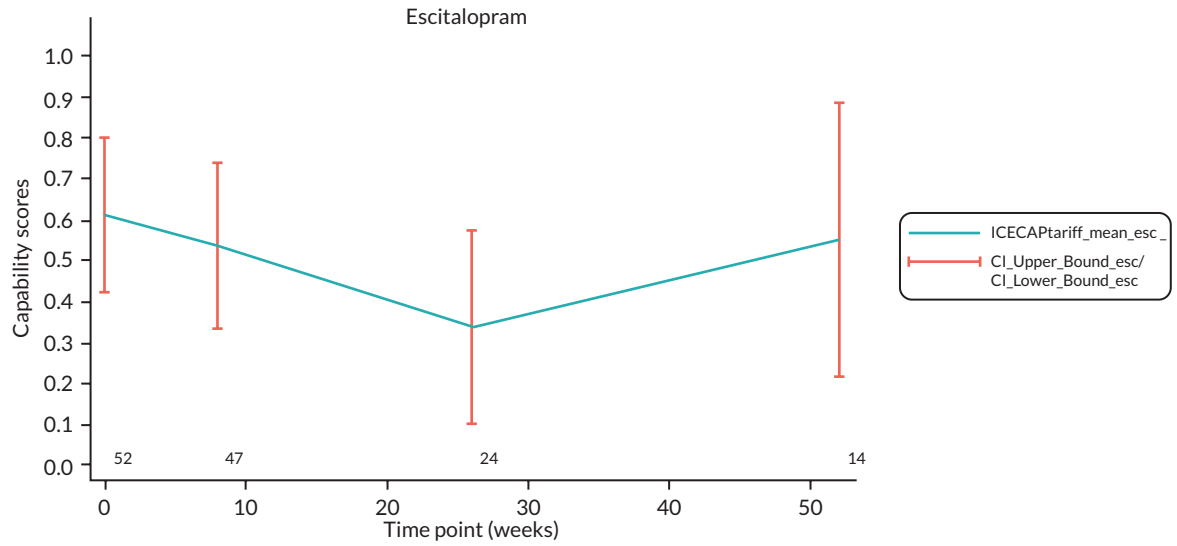

FIGURE 20 Mean unadjusted capability scores by time point for participants on escitalopram, from the responses to the ICECAP-O, valued using the standard tariff.

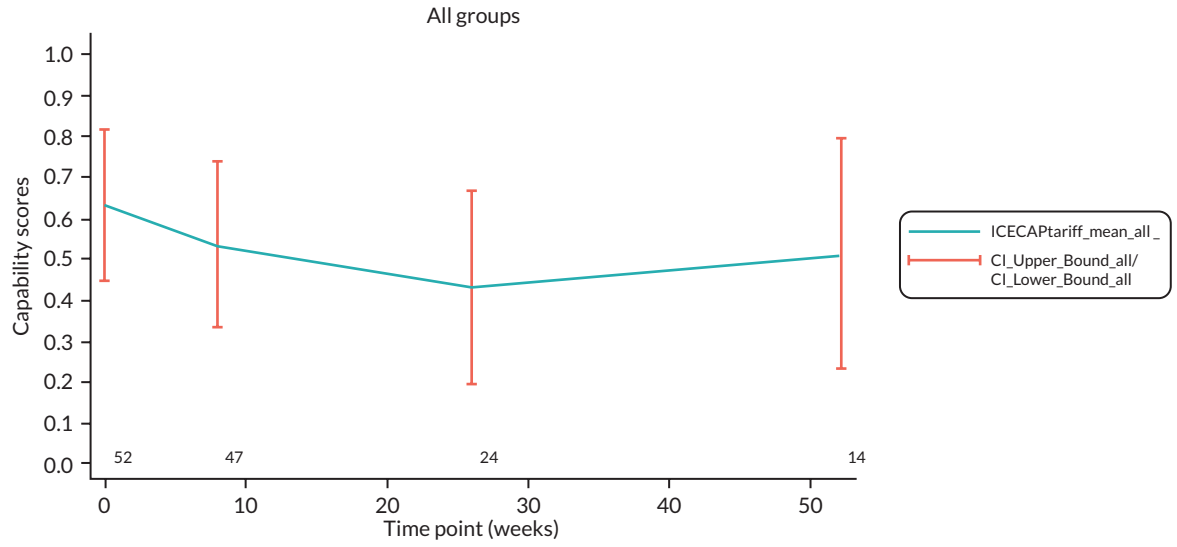

FIGURE 21 Mean unadjusted capability scores by time point for all participants, from the responses to the ICECAP-O, valued using the standard tariff.

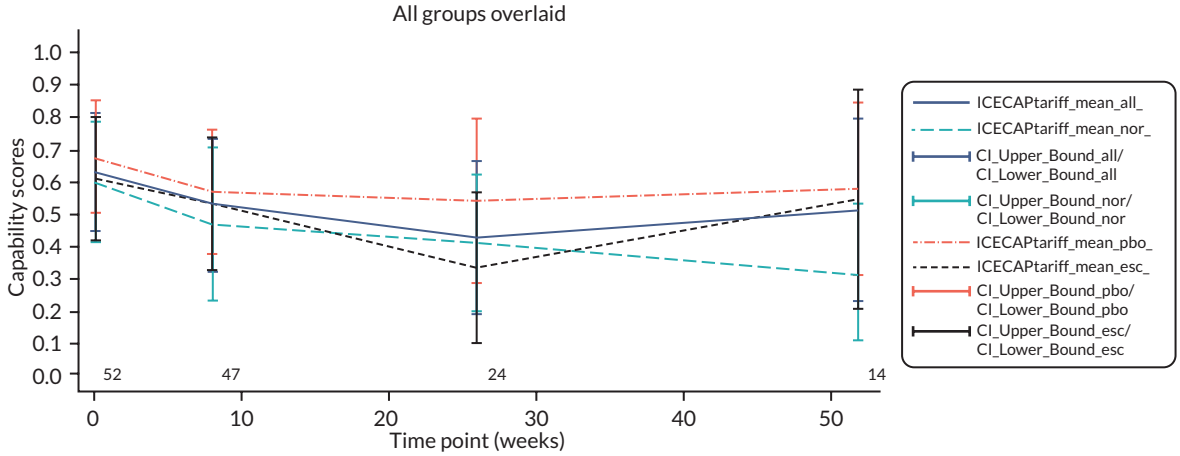

FIGURE 22 Mean unadjusted capability scores by time point for all participants overlaid, from the responses to the ICECAP-O, valued using the standard tariff.

Appendix 4 Mean unadjusted utility scores by time point for carers, from the responses to the EuroQol-5 Dimensions, five-level version, and valued by mapping to the EuroQol-5 Dimensions, three-level version tariff, as currently preferred by the National Institute for Health and Care Excellence (base-case analysis)

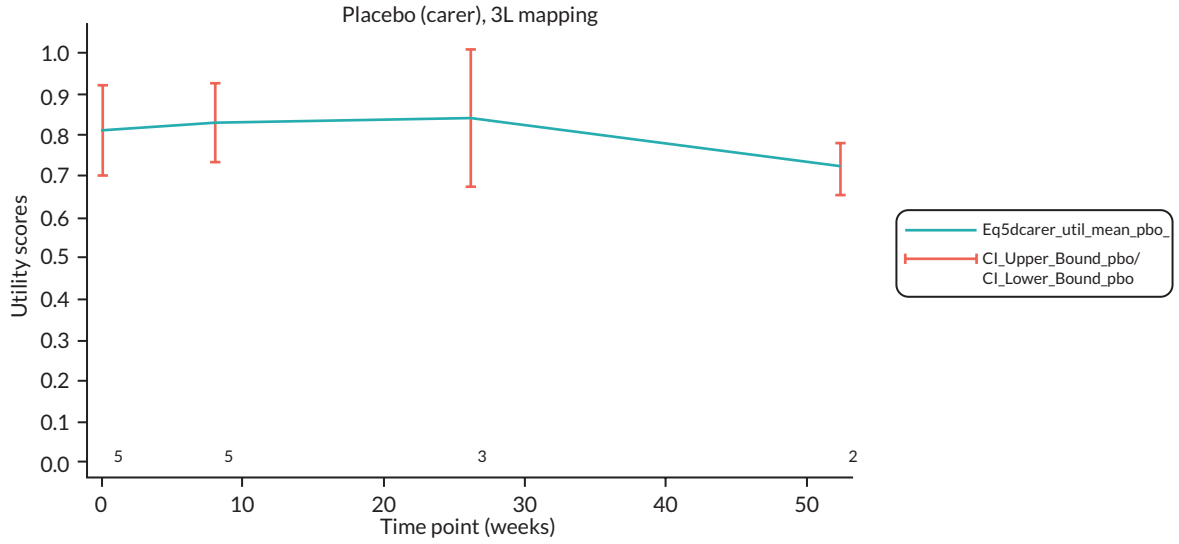

FIGURE 23 Mean unadjusted utility scores by time point for carers for patients on placebo, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

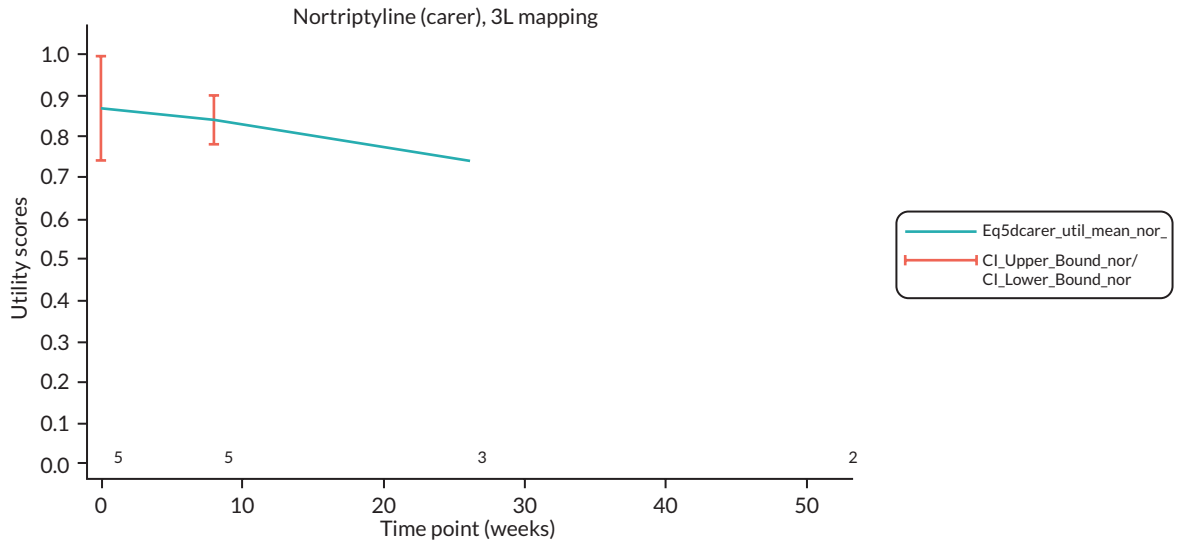

FIGURE 24 Mean unadjusted utility scores by time point for carers for patients on nortriptyline, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

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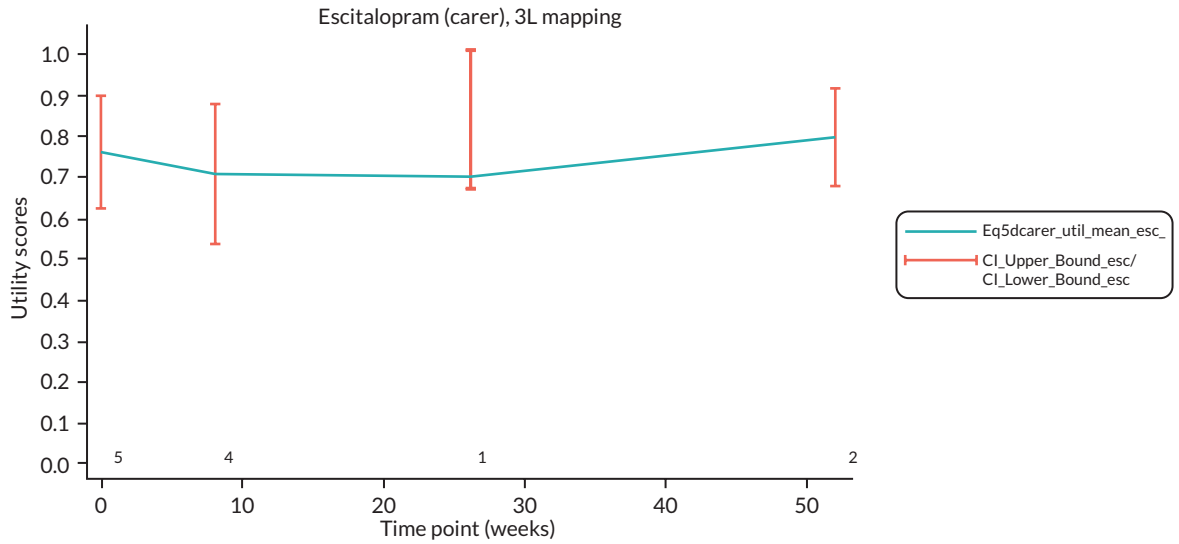

FIGURE 25 Mean unadjusted utility scores by time point for carers for patients on escitalopram, from the responses to the EQ-5D-5L and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

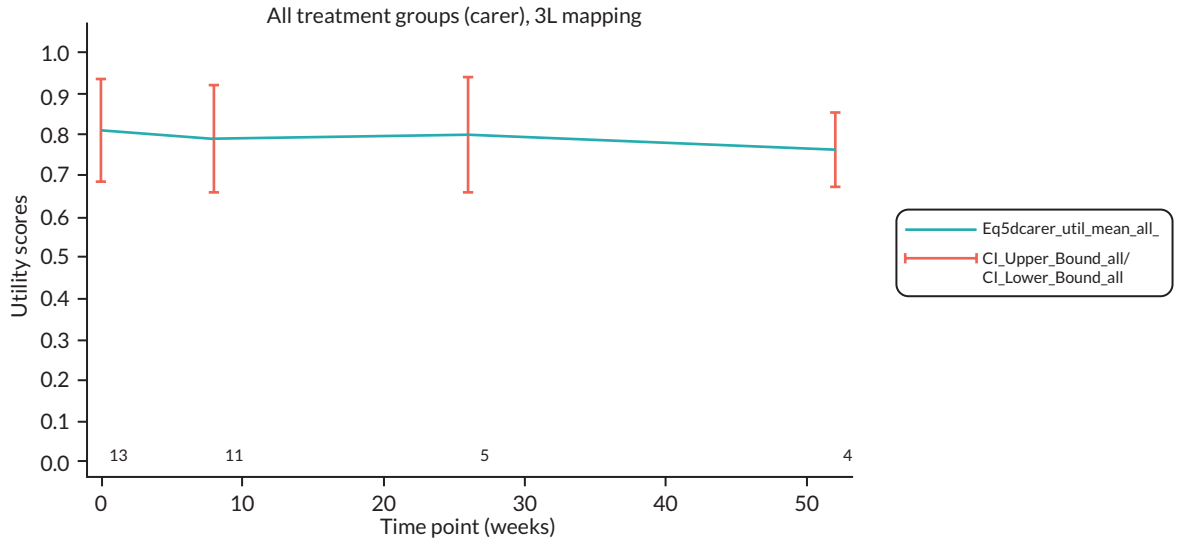

FIGURE 26 Mean unadjusted utility scores by time point for carers for patients on all treatment groups, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

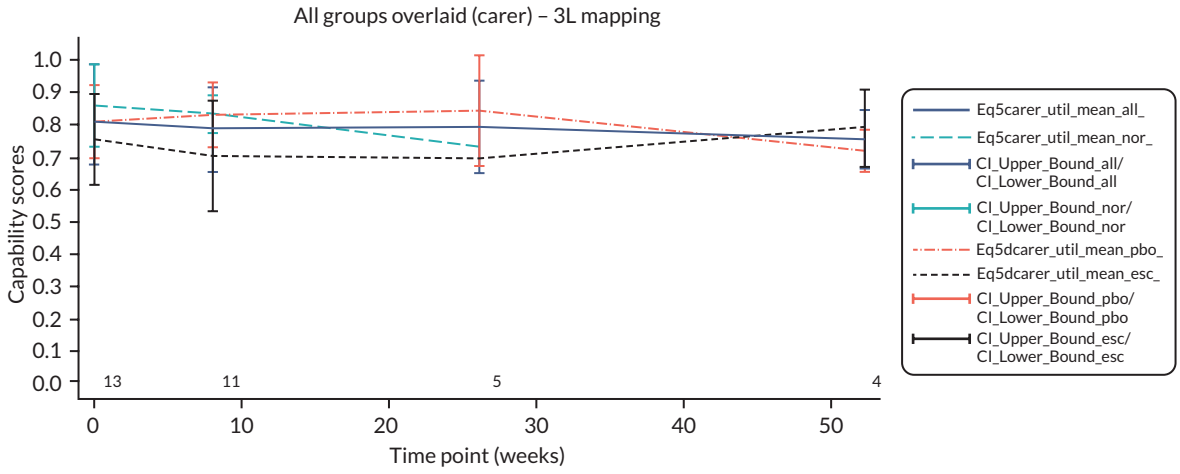

FIGURE 27 Mean unadjusted utility scores by time point for carers, from the responses to the EQ-5D-5L and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis).

Appendix 5 Mean unadjusted utility scores by time point for carers, from the responses to the EuroQol-5 Dimensions, five-level version and valued using the Devlin Value Set for England tariff (secondary analysis)

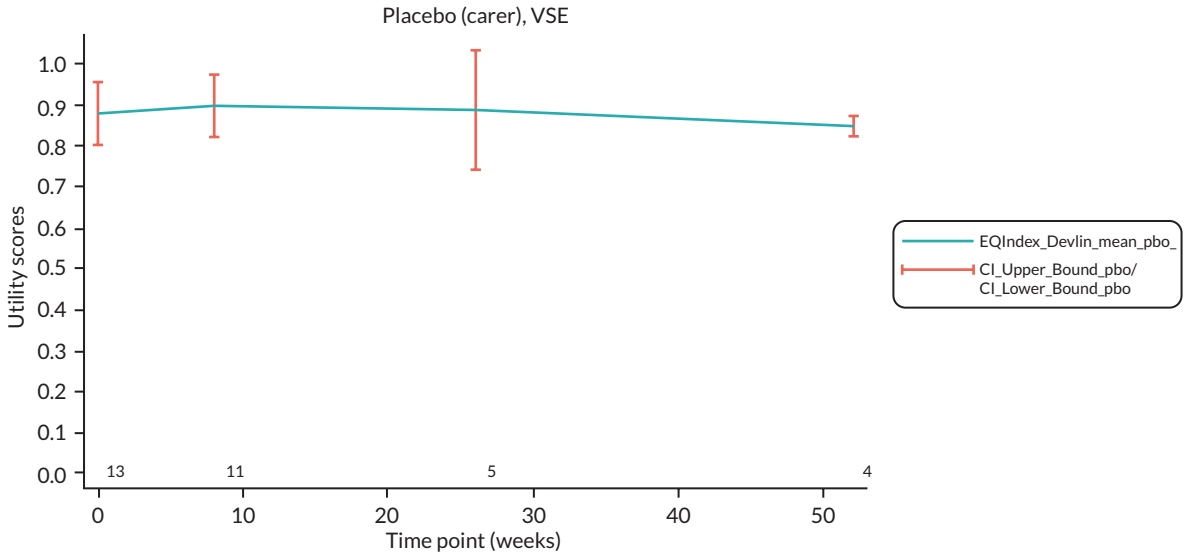

FIGURE 28 Mean unadjusted utility scores by time point for carers for patients on placebo, from the responses to the EQ-5D-5L and valued using the Devlin Value Set for England tariff (secondary analysis).

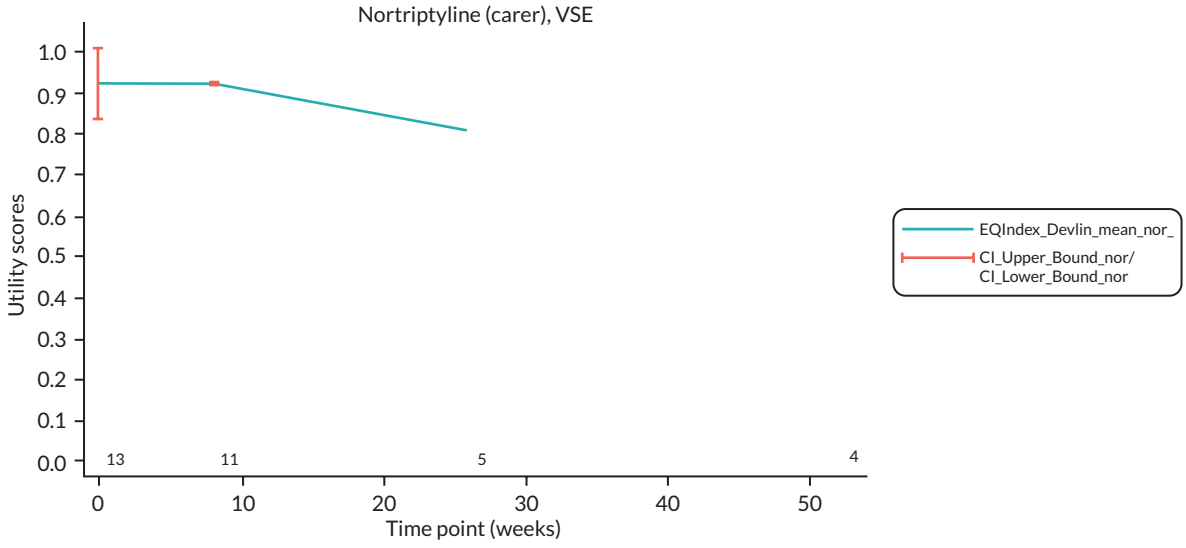

FIGURE 29 Mean unadjusted utility scores by time point for carers for patients on nortriptyline, from the responses to the EQ-5D-5L and valued using the Devlin Value Set for England tariff (secondary analysis).

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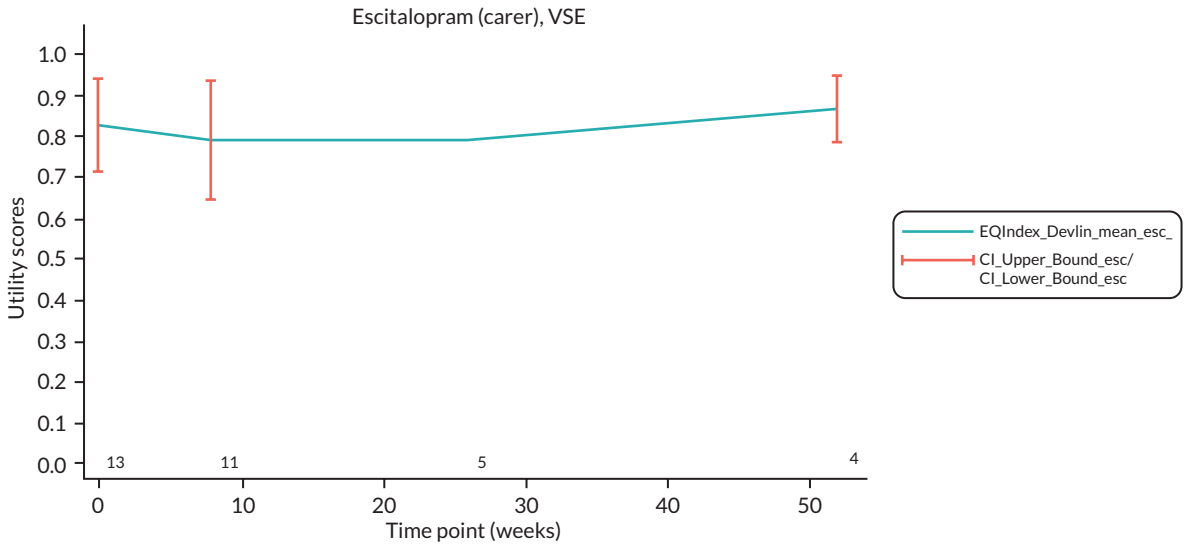

FIGURE 30 Mean unadjusted utility scores by time point for carers for patients on escitalopram from the responses to the EQ-5D-5L and valued using the Devlin Value Set for England tariff (secondary analysis).

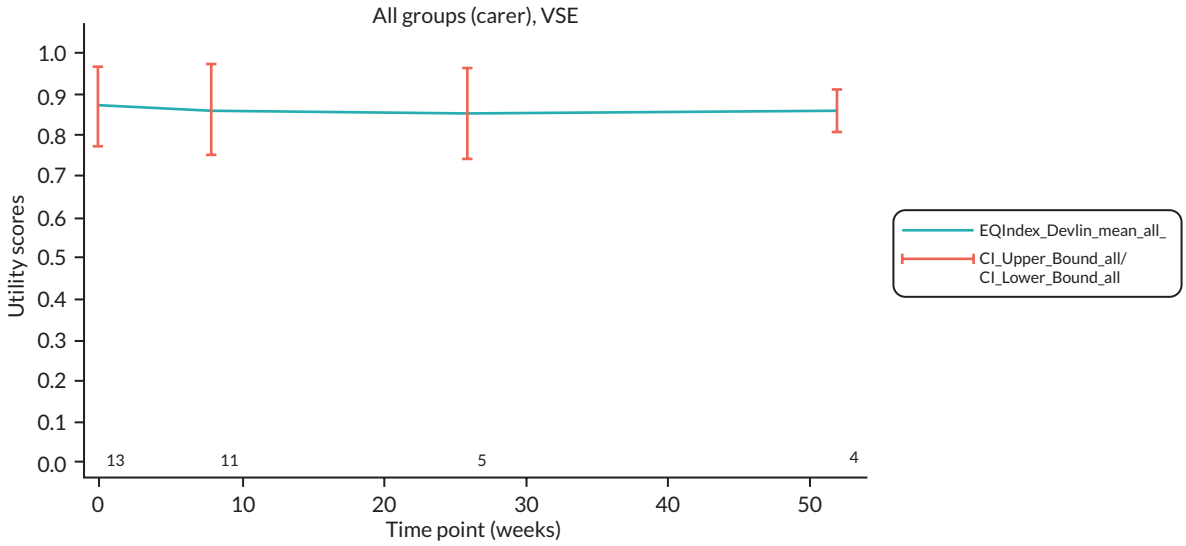

FIGURE 31 Mean unadjusted utility scores by time point for carers for patients from all groups, from the responses to the EQ-5D-5L and valued using the Devlin Value Set for England tariff (secondary analysis).

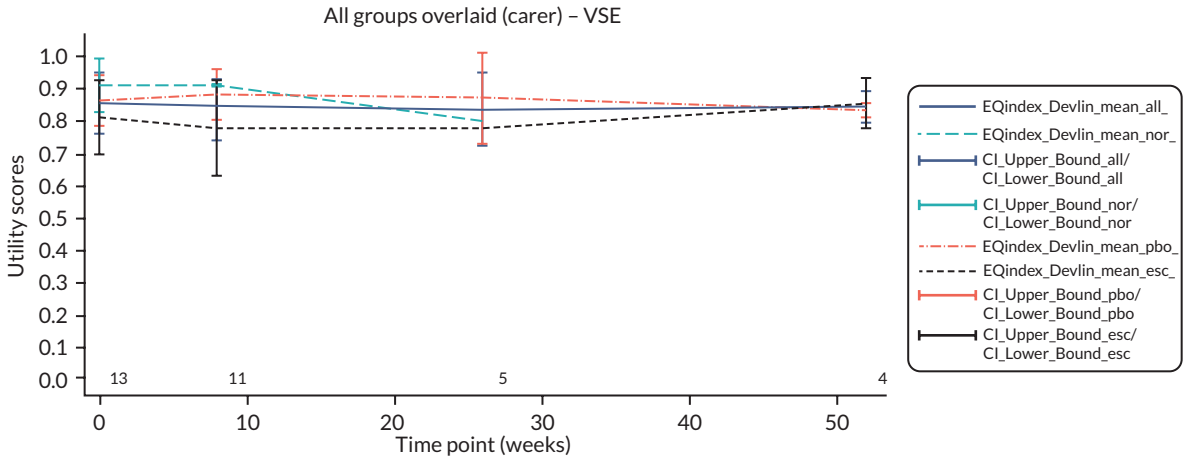

FIGURE 32 Mean unadjusted utility scores by time point for carers, from the responses to the EQ-5D-5L and valued using the Devlin Value Set for England tariff (secondary analysis).

Appendix 6 Mean unadjusted utility scores and mean 8-week quality-adjusted life-years and quality-adjusted life-weeks

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TABLE 43 Mean unadjusted utility scores and mean 8-week QALYs and QALWs (unadjusted and adjusted for baseline utility with bootstrapping) for participants, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis)

Utility scores – EQ-5D-5L mapping from 3L – participants												
	Placebo			Nortriptyline			Escitalopram			Overall		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Utility at baseline	19	0.559	0.104	16	0.627	0.172	17	0.533	0.229	52	0.571	0.175
Utility at 8 weeks	17	0.627	0.211	14	0.727	0.222	16	0.621	0.225	47	0.655	0.219
Utility at 26 weeks	7	0.569	0.215	10	0.808	0.176	7	0.651	0.208	24	0.692	0.215
Utility at 52 weeks	6	0.688	0.188	3	0.935	0.112	5	0.507	0.417	14	0.677	0.309
Unadjusted												
8-weekQALYs	17	0.092	0.021	14	0.105	0.025	16	0.089	0.034	47	0.095	0.027
8-weekQALWs	17	4.776	1.103	14	5.443	1.294	16	4.603	1.766	47	4.916	1.428
Adjusted and bootstrapped	***n***	**Mean**	**SE**	***n***	**Mean**	**SE**	***n***	**Mean**	**SE**	***n***	**Mean**	**SE**
8-weekQALYs	17	0.146	0.033	14	0.161	0.031	16	0.138	0.015	47	0.144	0.011
8-weekQALWs	17	7.573	1.729	14	8.352	1.612	16	7.166	0.771	47	7.491	0.596

n, sample size; SE, standard error.

TABLE 44 Mean unadjusted utility scores and mean 8-week QALYs and QALWs (unadjusted, and adjusted for baseline utility with bootstrapping) for participants, from the responses to the EQ-5D-5L, and valued using the Devlin Value Set for England tariff (secondary analysis)

Utility scores – EQ-5D-5L VSE tariff secondary analysis – participants												
	Placebo			Nortriptyline			Escitalopram			Overall		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Utility at baseline	19	0.634	0.118	16	0.698	0.165	17	0.634	0.221	52	0.654	0.171
Utility at 8 weeks	17	0.713	0.168	14	0.793	0.220	16	0.705	0.214	47	0.734	0.20
Utility at 26 weeks	7	0.669	0.210	10	0.864	0.123	7	0.784	0.142	24	0.784	0.172
Utility at 52 weeks	6	0.774	0.158	3	0.967	0.058	5	0.622	0.399	14	0.761	0.276
Unadjusted												
8-week QALYs	17	0.104	0.020	14	0.115	0.023	16	0.103	0.032	47	0.107	0.026
8-week QALWs	17	5.416	1.027	14	5.992	1.197	16	5.346	1.685	47	5.564	1.334
Adjusted and bootstrapped	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***
8-week QALYs	17	0.136	0.025	14	0.132	0.037	16	0.136	0.016	47	0.137	0.009
8-week QALWs	17	7.054	1.309	14	6.848	1.921	16	7.094	0.825	47	7.109	0.490

n, sample size; SE, standard error.

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TABLE 45 Mean unadjusted capability scores and mean 8-week CALYs and CALWs (unadjusted, and adjusted for baseline capability with bootstrapping) for participants, from the responses to the ICECAP-O, valued using the standard tariff

Capability scores – ICECAP-O – participants												
	Placebo			Nortriptyline			Escitalopram			Overall		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Utility at baseline	19	0.673	0.169	16	0.596	0.185	17	0.607	0.188	52	0.628	0.180
Utility at 8 weeks	17	0.566	0.186	14	0.470	0.230	16	0.532	0.201	47	0.526	0.204
Utility at 26 weeks	7	0.539	0.250	10	0.412	0.211	7	0.335	0.232	24	0.427	0.233
Utility at 52 weeks	6	0.577	0.264	3	0.325	0.209	5	0.546	0.331	14	0.512	0.279
Unadjusted												
8-weekCALYs	17	0.095	0.024	14	0.082	0.028	16	0.088	0.027	47	0.089	0.026
8-week CALWs	17	4.930	1.232	14	4.288	1.455	16	4.553	1.393	47	4.611	1.353
Adjusted and bootstrapped	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***
8-week CALYs	17	0.116	0.020	14	0.120	0.024	16	0.122	0.017	47	0.120	0.010
8-week CALWs	17	6.025	1.062	14	6.243	1.228	16	6.322	0.897	47	6.256	0.520

n, sample size; SE, standard error.

TABLE 46 Mean unadjusted utility scores and mean 8-week QALYs and QALWs (unadjusted, and adjusted for baseline utility with bootstrapping) for carers, from the responses to the EQ-5D-5L, and valued by mapping to the EQ-5D-3L tariff, as currently preferred by NICE (base-case analysis)

Utility scores – EQ-5D-5L mapping from 3L – carers												
	Placebo			Nortriptyline			Escitalopram			Overall		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Utility at baseline	5	0.815	0.114	3	0.862	0.127	5	0.759	0.140	13	0.805	0.124
Utility at 8 weeks	5	0.833	0.099	2	0.838	0.059	4	0.707	0.169	11	0.788	0.130
Utility at 26 weeks	3	0.848	0.170	1	0.736	N/A	1	0.698	N/A	5	0.795	0.141
Utility at 52 weeks	2	0.723	0.064	0	N/A	N/A	2	0.794	0.120	4	0.759	0.088
Unadjusted												
8-weekQALYs	5	0.127	0.012	2	0.132	0.009	4	0.110	0.021	11	0.122	0.017
8-weekQALWs	5	6.595	0.635	2	6.850	0.472	4	5.745	1.109	11	6.332	0.882
Adjusted and bootstrapped	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***
8-weekQALYs	5	0.084	0.127	2	[a]	[a]	4	0.131	0.077	11	0.108	0.022
8-weekQALWs	5	4.370	6.590	2	[a]	[a]	4	6.834	4.020	11	5.615	1.148

n, sample size; N/A, not applicable; SE, standard error.
a Bootstrapping could not be performed for the nortriptyline group as there were too few data points.

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TABLE 47 Mean unadjusted utility scores and mean 8-week QALYs and QALWs (unadjusted, and adjusted for baseline utility with bootstrapping) for carers, from the responses to the EQ-5D-5L, and valued using the Devlin Value Set for England tariff (secondary analysis)

Utility scores – EQ-5D-5L Devlin tariff secondary analysis – carers												
	Placebo			Nortriptyline			Escitalopram			Overall		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Utility at baseline	5	0.875	0.078	3	0.923	0.084	5	0.824	0.113	13	0.867	0.095
Utility at 8 weeks	5	0.892	0.074	2	0.919	0.004	4	0.786	0.145	11	0.859	0.109
Utility at 26 weeks	3	0.882	0.142	1	0.809	N/A	1	0.790	N/A	5	0.849	0.110
Utility at 52 weeks	2	0.844	0.021	0	N/A	N/A	2	0.865	0.081	4	0.855	0.050
Unadjusted												
8-weekQALYs	5	0.136	0.010	2	0.141	0.009	4	0.122	0.018	11	0.132	0.014
8-weekQALWs	5	7.070	0.504	2	7.342	0.455	4	6.344	0.913	11	6.856	0.740
Adjusted and bootstrapped	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***	***n***	***Mean***	***SE***
8-weekQALYs	5	0.104	0.102	2	[a]	[a]	4	0.130	0.110	11	0.125	0.021
8-weekQALWs	5	5.388	5.289	2	[a]	[a]	4	6.763	5.723	11	6.489	1.101

n, sample size; N/A, not applicable; SE, standard error.
a Bootstrapping could not be performed for the nortriptyline group as there were too few data points.

Appendix 7 Numbers of bottles of medication dispensed, by arm and by time point

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TABLE 48 Numbers of bottles of medication dispensed, by arm and by time point

	Placebo					Nortriptyline					Escitalopram					Overall				
	n	Mean	SD	Median	IQR	*n*	Mean	SD	Median	IQR	*n*	Mean	SD	Median	IQR	*n*	Mean	SD	Median	IQR
Week 1	19	1.42	0.51	1.0	1.0	16	1.63	0.50	2.0	1.0	17	1.65	0.49	2.0	1.0	52	1.56	0.50	2.0	1.0
Week 12	13	1.46	0.52	1.0	1.0	10	1.70	0.48	2.0	1.0	10	1.70	0.48	2.0	1.0	33	1.61	0.50	2.0	1.0
Week 26	8	1.50	0.53	1.50	1.0	8	1.75	0.46	2.0	0.50	8	1.63	0.52	2.0	1.0	24	1.63	0.49	2.0	1.0
Week 39	7	1.43	0.53	1.0	1.0	6	1.83	0.41	2.0	0.0	5	1.80	0.45	2.0	0.0	18	1.67	0.49	2.0	1.0

n, sample size; IQR, interquartile range.

Appendix 8 Costs (£, BNF 2023) for medications dispensed in the two active medication arms, by arm and by time point

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TABLE 49 Costs (£, BNF 2023) for medications dispensed in the two active medication arms, by arm and by time point

	Nortriptyline					Escitalopram				
	n	Mean	SD	Median	IQR	*n*	Mean	SD	Median	IQR
Week 1	16	7.61	2.34	9.36	4.68	17	12.51	3.74	15.20	7.60
Week 12	10	7.96	2.26	9.36	4.68	10	12.92	3.67	15.20	7.60
Week 26	8	8.19	2.17	9.36	2.34	8	12.35	3.93	15.20	7.60
Week 39	6	8.58	1.91	9.36	0.0	5	13.68	3.40	15.20	0.0

n, sample size; IQR, interquartile range.

EME
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HTA
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This report presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

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