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**Trial of Discontinuation vs Maintenance of Antidepressants in Primary Care**

Authors: Gemma Lewis, Ph.D.,1\* Louise Marston, Ph.D.,2\* Larisa Duffy, B.Sc.,1 Nick Freemantle, Ph.D.,3 Simon Gilbody, Ph.D.,4 Rachael Hunter, M.Sc.,2 Tony Kendrick, M.D.,5 David Kessler, M.D.,6 Dee Mangin, F.R.N.Z.C.G.P.,7 Michael King, Ph.D.,1 Paul Lanham, B.A.,1 Michael Moore, F.R.C.G.P.,5 Irwin Nazareth, Ph.D.,2 Nicola Wiles, Ph.D.,8 Faye Bacon, B.Sc.,1 Molly Bird, M.Sc.,1 Sally Brabyn, 4 Alison Burns, 8 Caroline S. Clarke, Ph.D.,2 Anna Hunt, 5 Jodi Pervin, 4 Glyn Lewis, Ph.D..1

1Division of Psychiatry, Faculty of Brain Sciences, University College London, UK.

2Research Department of Primary Care and Population Health, UCL, London, UK, and Priment Clinical Trials Unit, UCL, London, UK.

3Institute of Clinical Trials and Methodology, UCL, London, UK.

4Department of Health Sciences & Hull York Medical School, University of York UK.

5Primary Care Population Sciences and Medical Education, Faculty of Medicine. University of Southampton.

6Population Health Sciences, Bristol Medical School, University of Bristol UK.

7Department of Family Medicine, McMaster University.

8Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol UK.

\*These authors contributed equally to the manuscript

Contact information for one (1) corresponding author: Dr Gemma Lewis, University College London - Division of Psychiatry149 Tottenham Court Road 6th Floor, Maple House London, London W1T 7NF; email: gemma.lewis@ucl.ac.uk

**Abstract**

**Background:** Patients in primary care practices with depression may receive antidepressants for prolonged periods. There has been limited evaluation of the effects of maintaining or discontinuing antidepressants in this setting.

**Methods:** This was a randomized,double-blind trial in adults from 150 UK general practices who had experienced at least two depressive episodes or been taking antidepressants for two years or longer, had been receiving antidepressants for at least the 9 previous months, and felt well enough to consider stopping antidepressants. Participants who had been on citalopram, fluoxetine, sertraline or mirtazapine were randomly assigned in a 1:1 ratio to continue or taper and discontinue antidepressants. The primary outcome was time to relapse of depression over 52 weeks. Secondary outcomes assessed depressive and anxiety symptoms, physical and withdrawal symptoms, quality of life, time to stopping medication, and global mood ratings.

**Results:** A total of 1466 patients were screened and 478 enrolled;238 were assigned to continue and 240 to tapering and discontinuing antidepressants. Their average age was 54 and 73% were women. Adherence to trial assignment was 70% vs 52% in the maintenance and discontinuation groups, respectively. Relapse occurred in 92 of 238 (39%) patients in the maintenance group and 135 of 240 (54%) in the discontinuation group. The primary outcome of estimated time to relapse was 13.3 weeks vs 19.0 weeks, for discontinuation and maintenance, respectively (hazard ratio, 2.06; 95% confidence interval, 1.56 to 2.70; p<0.001). Secondary outcomes were generally in the same direction as the primary outcome. Participants who discontinued antidepressants experienced more depressive, anxiety and withdrawal symptoms and stopped study medication sooner.

**Conclusions:** Selectedpatients in primary care practices, who felt well enough to discontinue antidepressants after at least 9 months of continuous use, had higher rates of depression relapse with tapering and discontinuation of medication compared to those who remained on medication.

 (Funded by the National Institute for Health Research Health Technology Assessment Programme (13/115/48); ISRCTN15969819)

**Introduction**

Antidepressants are often a first-line treatment for depression in primary care1 and the number of prescriptions of these medications has risen in high-income countries in the last several decades, mostly due to an increase in the duration of treatment.2–5 Several systematic reviews have reported increased relapse rates in people who discontinue antidepressants compared with those on maintenance treatment, but trials have had several limitations.7–13 Most trials recruited patients with depression from specialist mental health services, treated them with an antidepressant for between 3 and 8 months, and randomized responders to continue antidepressants or switch to placebo. There are also a few studies of patients receiving maintenance antidepressants, mainly of tricyclic compounds for longer than 8 months 14–16 but small sample sizes and their non-randomized limited conclusions.

We conducted a randomized trial to assess the effects of maintenance antidepressants compared with discontinuation of treatment in primary care patients who had been taking antidepressants for more than 9 months and felt well enough to consider stopping medication.

**Methods**

This was a two-arm, multicenter, randomized, double-blind parallel trial, with participants recruited from 150 general practices across four sites in England (Bristol, London, Southampton and York). Recruitment was through electronic health record searches (those potentially eligible were sent an invitation letter) or during primary care visits. The trial was approved by the National Research Ethics Service committee, East of England - Cambridge South. Clinical trial authorization was granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). All participants provided written informed consent. The trial was conducted in accord with the revised Helsinki Guidelines. The trial was sponsored by University College London and there was no commercial involvement in the trial. GL, NF, SG, RH, TK, DK, MK, MM, IN, PL and NW designed the trial, LM and NF conducted main analyses and GeL and LM wrote the first draft of the paper. A Data Monitoring Committee monitored recruitment, retention and serious adverse events.

We enrolled patients receiving conventional doses of the most commonly prescribed antidepressants in the UK (citalopram , sertraline, and fluoxetine)4,17,18 as well as mirtazapine, due to its increasing use in the U.K.17,18 We excluded patients using escitalopram because it is not widely used in UK primary care, paroxetine because prescription rates are dropping and discontinuation can lead to marked withdrawal symptoms, and venlafaxine because its discontinuation also causes withdrawal symptoms and most clinical guidelines recommend it as second-line treatment.

Eligible participants were aged 18 to 74, had reported at least two prior episodes of depression, or been taking antidepressants for over 2 years, had been receiving and adhering to citalopram 20mg, sertraline 100mg, fluoxetine 20mg or mirtazapine 30mg for at least 9 months, had recovered from their most recent depressive episode, and were considering stopping antidepressants. Patients receiving other doses and other antidepressant medications were excluded. The main exclusion criterion was current depression as defined by ICD-10 criteria at the time of trial entry, assessed with the clinical interview schedule-revised (CIS-R).21 Full inclusion and exclusion criteria are in the protocol, available with the full text of this paper at NEJM.org.

Randomization was conducted with the intent of attaining a 1:1 ratio of trial assignments to continuing or discontinuing antidepressant using a computerized system and minimization algorithm that included site, medication and median CIS-R score (see Supplement available at NJEM.org for minimization algorithm). The allocation was provided to an unblinded pharmacy, which sent masked trial medications to the primary care practice for distribution to patients or sent medications directly to patients’ homes. The first six participants were erroneously randomized using simple 1:1 randomization.

**Trial treatments**

Trial medications contained active antidepressant at full or half doses, or lactose (placebo), as required for each phase of the trial in lactose film-coated, over-encapsulated capsules, all manufactured by Capsugel and B&C Group (Belgium; complying with Good Manufacturing Practices). All capsules were of identical opaque appearance and were provided in identical bottles of 31 capsules. The intention of the identical pills and bottles was to mask patients and practitioners to trial assignment During the first month, participants in the discontinuation group were prescribed antidepressants at half their regular dose. In the second month, they received half dose antidepressants and placebo on alternate days. From the third month, they were prescribed placebo. Participants taking fluoxetine at baseline were prescribed fluoxetine 20 mg and placebo on alternate days in the first month and from the second month, they received placebo as fluoxetine has a long half-life. In the maintenance group, participants were prescribed their usual antidepressants at their usual doses. We used a five-item self-report measure of medication adherence that has been used in two other antidepressant trials. 19,20

The trial was 52 weeks long, with follow-up at 6, 12, 26, 39 and 52 weeks. Data were collected using postal questionnaires at 6 weeks and by face-to-face interviews at baseline and 12, 26, 39 and 52 weeks. In order to exclude patients who were currently depressed at baseline, patients completed the original version of the Clinical Interview Schedule-Revised (CIS-R),21 a computerized, self-administered, structured interview. The CIS-R asks about depressive symptoms over the past week and determined if the symptoms indicated a diagnosis meeting ICD-10 criteria for depressive episodes, and a depression severity score (available range 0–21) created by the sum of the following five sections of the instrument: depression, depressive ideas, fatigue, concentration, and sleep problems. Anxiety scores were also generated as a sum of the anxiety, worry, phobias, worries about physical health and panic sections.

**Outcomes**

Primary outcome

The primary outcome was time to relapse of depression, defined as a new episode of depression, determined by components of a modified retrospective CIS-R (rCIS-R) that was adapted for the purpose of this trial. The rCIS-R used questions from the original CIS-R from the following sections: depression, depressive ideas, sleep, fatigue, concentration. In contrast to the original, the rCIS-R enquired specifically about the previous 12 weeks (see Supplement available at NJEM.org for full details, including reliability and validity of this instrument). Our case definition for relapse of depression was an affirmative answer to either of two mandatory CIS-R questions: 1) have you had a spell of feeling sad, miserable or depressed? and 2) have you been able to enjoy or take an interest in things as much as you usually do? To meet the outcome of an episode of depressive patients also had to report at least one of these symptoms lasting for two weeks and also to report at least one of the following: depressive thoughts (which included loss of interest in sex, restlessness, feeling guilty, feeling as though they were not as good as others, hopelessness, feeling that life was not worth living, thoughts of killing self), fatigue, concentration, or sleep disturbance.

Secondary outcomes

There were 8 clinical secondary outcomes: 1) depressive symptoms using the Patient Health Questionnaire 9-item version (PHQ-9, range 0 to 27, higher scores indicating more severe symptoms); 2) generalized anxiety symptoms using the Generalized Anxiety Disorder Assessment 7-item version (GAD-7, range 0 to 21, higher scores indicating more severe symptoms); 3) physical symptoms that were potentially antidepressant side-effects assessed with a modified 13-item Toronto scale (range 13-52, higher scores indicating a greater number and frequency of side effects );22 4) frequency of new or worsened withdrawal symptoms using a modified 14-item discontinuation-emergent signs and symptoms checklist (DESS).23 (After consulting with patients, we added a question to the DESS on electric sensations in the brain, leading to a total of 15 items; see Supplement available at NEJM.org for details);24 5) physical and 6) mental health-related quality of life scores using the 12-item Short-Form Health Survey (SF-12, range for each, 0 to 100 with lower scores indicating worse quality of life); 7) time to stopping study medication (i.e. choosing not to take the study medication) as a secondary outcome. The start date was taken from the latest of: receiving study medication, starting medication or, when the former were missing, date of randomization. The stop date was the earliest of: the date participants reported stopping study medication or final follow-up); 8) global ratings of mood rated as “Compared to when we last saw you, how have your moods and feelings changed?” Responses were: ‘I feel a lot better’; ‘I feel slightly better’; ‘I feel about the same’; ‘I feel slightly worse’; ‘I feel a lot worse’., creating a dichotomous outcome of: feeling worse (1) or feeling the same or better (0). This outcome and time to stopping medication were pre-specified secondary outcomes in the statistical analysis plan prior to database lock but after the protocol was published.26

As this was a phase IV trial of licensed medications within their licensed indications, we recorded adverse events of special interest only, using the Toronto and DESS scales at each follow-up (reported as secondary outcomes). Serious adverse events (SAEs) were recorded by researchers using an SAE recording and reporting form created by the study Sponsor (the Joint Research Office, University College London). The principal investigator at each site rated each event according to seriousness, causal relationship to study medication, severity, and outcome using a recording and reporting log (see Supplemental Appendix). Results of the EuroQol five-dimensional (EQ-5D-5L), primary healthcare resource use, Client Service Receipt Inventory and emotional processing tasks were also completed but have not been analyzed. All outcomes were assessed at every time-point except the retrospective CIS-R, SF-12 and adherence scales, which were obtained at every time-point except 6 weeks.

**Statistical analysis**

To detect a hazard ratio of 0.52 for the primary outcome of relapse rate comparing discontinuation to maintenance groups, based on 20% anticipated relapsing in the maintenance group and 35% in discontinuation groups, with 90% power and 5% significance (two sided), inflating for 20% drop out (see SAP)26 we determined that 479 participants would need to be recruited. The primary outcome, time to relapse, was analyzed using Cox Proportional Hazards modelling, adjusted for baseline CIS-R depression score. Proportionality was determined using a Kaplan Meier and predicted survival plot and the assumption was affirmed. No imputation was conducted for missing data in the primary analysis but there were 10 people with missing primary outcome data (relapsed but time of relapse not known). Sensitivity analyses for the primary outcome included adjusting for minimization variables as participant level explanatory factors and investigating missing data using best- and worst-case scenarios for participants not included in the primary analysis. For the best- and worst-case scenarios, those in the maintenance group with missing primary outcome data were censored at date of last follow-up or study withdrawal (good outcome, no relapse) and for those in the discontinuation group with missing primary outcome data, relapse on the day before last follow-up or withdrawal (bad outcome, relapse).

Continuous secondary outcomes were analyzed at 12, 26, 39 and 52 weeks follow-up and prespecified to be analyzed for each time-point separately, accounting for baseline value, using mixed effects linear regression with fixed effects for time and randomized group using baseline and follow up values for each time point (see Statistical Plan available at NJEM.org).1 The Global Rating Question was analyzed using logistic regression at each time-point. Time to stopping study medication was analyzed using Cox Proportional Hazards modelling. proportionality was determined as for the primary outcome. Because there was no prespecified plan for adjustment of confidence intervals for multiple comparisons of secondary outcomes, no definite conclusions can be drawn from these data. For secondary outcomes, except time to stopping study medication, we conducted sensitivity analyses including predictors of missingness at baseline identified using univariable logistic regression. We adjusted for variables that were associated (statistically significant at the 5% level) with missingness as covariates.

For the primary outcome, we conducted four pre-specified subgroup analyses as indicated in the Statistical Analysis Plan. We conducted post hoc analyses to explore characteristics of primary care practices, age and gender of invited participants, number of participants experiencing anxiety at baseline, antidepressant use according to relapse and group, whether participants guessed their allocation, number needed to harm, and whether participants were unblinded. We re-ran the primary analyses, classifying relapse according to ICD-10 depression criteria. We re-ran secondary analyses using log transformed PHQ-9 and GAD-7 scores that could be compared to prior studies of minimal clinically important differences.2,3

**Results**

We invited 23,429 potential participants by letter and 124 during GP consultation (Figure 1). Of these, 1,466 (6%) responded; of whom 606 (41%) were screened for eligibility and 478 were enrolled; 238 were assigned to the maintenance group and 240 to the discontinuation group. All participants provided final outcome data on relapse, however 10 (6 in the maintenance group, 4 in discontinuation) participants did not provide the timing of relapse and are not included in the analysis of estimated time to relapse but are reported with the absolute number who relapsed. Therefore, 232 of 238 in the maintenance group and 236 of 240 in the discontinuation group were included in the primary outcome analysis of time to relapse.

Groups were similar in baseline characteristics (Table 1). Approximately three quarters were women, with a mean age in the total population of 54 years (SD 13) and approximately 95% were white. Citalopram was the most commonly used antidepressant and almost three-quarters of participants had been on antidepressants for more than three years. The median time between randomization and starting trial medication was 9 days (IQR 6, 13) in the maintenance group and 8 days (IQR 6, 13) in the discontinuation group.

**Primary outcome**

Relapse of depression occurred in 92 of 238 (39%) in the maintenance group and 135 of 240 (56%) of the discontinuation group during the 52 weeks of the trial. The primary outcome of estimated median time to relapse was 13.3 weeks (IQR 6.0, 26.6) in the discontinuation groups and 19.0 weeks (IQR 6.0, 28.0) in the maintenance group (hazard ratio, 2.06; 95% confidence interval [CI], 1.56 to 2.70; p<0.001) (Table 2, Figure 2). Sensitivity analyses, including for missing data, were in the same direction as the primary analysis (Table S2).

**Secondary outcomes**

For secondary outcomes at 12-weeks, except SF-12 physical component and Toronto side effect scores but were generally in the same direction as the primary outcome and confidence intervals for hazard ratios did not include one at that time point (Table 2). Hazard ratios at other time points were also generally in the same direction as the primary outcome but confidence intervals variably included one. As there was no plan for adjustment of confidence intervals for multiple comparisons, no conclusions can be drawn regarding these or other differences between groups for secondary outcomes. Depressive symptoms assessed by PHQ-9 scores at 12 weeks were mean 6.3 (SD 5.1) and 4.1 (SD 3.8) for the discontinuation and maintenance groups respectively; estimated difference 2.16 (95% CI, 1.47 to 2.84). Anxiety symptoms assessed by GAD-7 scores at 12 weeks were 5.3 (SD 4.6) and 3.1 (SD 3.3) for discontinuation and maintenance groups respectively; estimated difference 2.40 (95% CI, 1.81 to 2.99) (Table 2). Withdrawal symptoms at 12 weeks using the modified DESS were a mean of 3.1 (SD 3.5) in the discontinuation group and 1.3 (SD 2.4) in the maintenance group; estimated difference in means 1.87 (95% CI, 1.46 to 2.28). Side effects assessed by the Toronto scale at 12 weeks were mean 4.6 (SD 3.0) and 4.2 (SD 2.9) for the discontinuation and maintenance groups respectively; estimated difference 0.68 (95% CI, 0.25 to 1.11). Participants in the discontinuation group had a mean SF-12 mental health related quality of life score at 12 weeks of 41 (SD 11) and those in the maintenance group 46 (SD 10), estimated difference 4.86 (95% CI, -6.44 to -3.29).

The median time to stopping study medication was 14.7 weeks (IQR, 10.1 to 25.7) in the discontinuation group and 26.9 weeks (IQR, 13.3 to 40.4) in maintenance (hazard ratio 2.28 (95% CI, 1.68 to 3.08)). A greater percentage of the discontinuation group stopped taking study medication before the end of the trial (48% versus 30%). Of the 48% in the discontinuation group who stopped study medication, 39% (95% CI, 32% to 45%) returned to use of an antidepressant prescribed by their primary care doctor. Of the 30% of the maintenance group who stopped study medication, 20% (95% CI, 15% to 25%) returned to use of an antidepressant prescribed by their GP. Over the course of the trial, 157 (70%) patients in the maintenance group adhered to study medication compared with 119 (52%) in discontinuation (Table S12). At 12, weeks, 21% (48/228) of the maintenance group and 44% (94/216) of the discontinuation group reported feeling worse rather than the same or better; odds ratio 2.88 (95% CI, 1.90 to 4.38). Results for all outcomes were similar when including predictors of missingness in models (Table S3). Results for subgroup, sensitivity, and post hoc analyses are shown in the supplement.

Safety and Adverse Events

There were 17 SAEs during the trial and these were similar in the two groups; 9 (5%) in the maintenance group and 8 (4%) in the discontinuation group (Table 3). Two SAEs were classed as unlikely to be related to study medication and 15 as unrelated to study medication (Table S7). There were deaths and no suicides or suicide attempts.

**Discussion**

Patients who discontinued maintenance antidepressant medications in our trial had higher rates of relapse of depression than those who remained on medication through 52-weeks of follow-up. Secondary outcomes were generally in the same direction as the primary analysis except for SF-12 physical health scale and Toronto side effect score. By the end of the trial, 39% of the discontinuation group had returned to an antidepressant prescribed by their clinician, which may explain why there was no evidence for group differences for secondary outcomes at the last trial time-point of 52 weeks.

We investigated three SSRIs that have a similar pharmacological profiles and act via similar mechanisms. Our results may not generalize to other classes of antidepressants.25,28 A limitation of our study is that we excluded people on escitalopram and those receiving doses different to usual antidepressant maintenance treatment in the UK. A further limitation is that only a small proportion of patients who were invited ultimately participated, which may have introduced bias into the trial population and the results pertain only to patients with self-assessment that they were ready to discontinue medication. The method of determining depression relapse was adapted from conventional instruments for the purpose of the trial, in part because of the need to have patients retrospectively assess symptoms over the prior 12 weeks. Our trial population also lacked ethnic diversity and was conducted in the U.K. health system that may not generalize to other health systems.30

We recruited individuals who had been taking antidepressants, usually for many years, and asked them to recall history of depression and its treatment. Although recall bias is unlikely to affect the validity of our findings, it could influence the accuracy of the information participants provided. We also did not have detailed information about the original clinical decision for prescribing the antidepressant or any diagnostic information at that time.

In conclusion, among patients in primary care practices with depression and who were willing to stop their SSRI antidepressants, rates of relapse of depression were higher with discontinuation than with maintenance of antidepressants. Quality of life, depressive, anxiety and withdrawal symptoms were generally worse in patients who discontinued antidepressants.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

**Acknowledgments**

We thank the staff in participating general practitioner surgeries for their help with recruitment and all participants who took part in the study. We also thank colleagues who have contributed to the study through recruitment, administrative help, and other advice - in particular Yvonne Donkor, Carmen Sinclair, Nomsa Chari, Paula Beharry, Sungmin Hahn, Vivien Jones, Catherine Derrick and Mahsa Rezaei. We have been supported by the following clinical research networks (CRNs): North Thames CRN, CRN North West London, CRN South London, Thame Valley and South Midlands CRN; Luton, Essex and Herts Valley CRN; CRN West of England and Wessex CRN. We especially thank the following CRN staff: Debbie Kelly, Claire Winch, Zara Prem, Andrei Gabzdyl, Lynsey Wilson. We also acknowledge the support of the University College London Hospitals Biomedical Research Centre Mental Health theme. We acknowledge the support of the NIHR Biomedical Research Centre (BRC) at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. This study was also supported by the NIHR University College London Hospitals BRC. We also thank Allan House, Geoffrey Wong, Jonathan Bisson, Lucy Carr, Chris Dowrick, Rafael Perera-Salazar and Mike Crawford for generously agreeing to sit on either the trial steering committee or data monitoring committee.

**Sources of support**

The ANTLER trial is independent research commissioned by the National Institute for Health Research HTA Programme 13/115/48. The views expressed in this publication are those of the author(s) and not necessarily those of the sponsor, UK National Health Service, NIHR, or UK Department of Health and Social Care.

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Figure Legends

Figure 1. CONSORT diagram

Figure 2: Kaplan Meier plot for estimated time to depression relapse.

TABLES

Table 1: Baseline demographic and clinical characteristics by randomized group

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| --- | --- | --- |
| **Characteristic** | **Maintenance** | **Discontinuation** |
| **Demographic** |  |  |  |  |
| Age years mean (SD) | 54 | (13) | 55 | (12) |
| Female n/N % | 168/238 | 71 | 181/240 | 75 |
| White ethnicity n/N % | 221/238 | 93 | 228/235 | 97 |
| Married n/N % | 146/238 | 61 | 161/240 | 67 |
| Employed n/N % | 140/238 | 59 | 152/240 | 63 |
| Site n/N % |  |  |  |  |
|  London | 101/238 | 42 | 98/240 | 41 |
|  Bristol | 48/238 | 20 | 54/240 | 23 |
|  Southampton | 48/238 | 20 | 48/240 | 20 |
|  York | 41/238 | 17 | 40/240 | 17 |
| **Clinical** |  |  |  |  |
| Antidepressant n/N % |  |  |  |  |
|  Sertraline | 41/238 | 17 | 37/240 | 15 |
|  Citalopram | 111/238 | 47 | 112/240 | 47 |
|  Fluoxetine | 77/238 | 32 | 83/240 | 35 |
|  Mirtazapine | 9/238 | 4 | 8/240 | 3 |
| CIS-R depression score above the median n/N % | 116/237 | 49 | 110/240 | 46 |
| Age at onset of depression mean (SD) | 33 | (16) | 32 | (14) |
| Three or more previous episodes of depression n/N % | 224/238 | 94 | 219/239 | 92 |
| Taking antidepressants for 3 or more years n/N %\*\* | 170/238 | 71 | 168/239 | 70 |
| PHQ-9 mean (SD)† | 3.9 | (3.5) | 3.8 | (3.6) |
| GAD-7 mean (SD)‡ | 3.2 | (3.1) | 2.8 | (3.0) |
| SF-12 physical mean (SD)§ | 48 | (11) | 50 | (9) |
| SF-12 mental mean (SD)§ | 47 | (9) | 48 | (9) |
| Modified Toronto Side Effects Scale mean (SD)‖ | 4.2 | (2.7) | 3.7 | (2.7) |
| Number of new or worsening symptoms using modified DESS mean (SD)¶ | 1.0 | (1.4) | 0.6 | (1.0) |
| At least one new or worsening symptom using modified DESS n/N %¶ | 118/238 | 50 | 95/240 | 40 |
| Mood worse than 2 weeks ago n/N % | 13/237 | 5 | 9/239 | 4 |

\* CIS-R - revised Clinical Interview Schedule, range 0 to 57. CIS-R depression scores above the median were used for minimisation.

† PHQ-9 - Patient Health Questionnaire 9, range 0 to 27.

‡ GAD-7 – Generalised anxiety disorder 7, range 0 to 21

§ SF-12 – Short form 12 questions, range 0 to 100

‖ Modified Toronto Side Effects Scale (count of side effects), range 0 to 13

¶ Modified DESS - Discontinuation-emergent signs and symptoms (DESS) checklist, range 0 to 15

\*\* Without a break of two weeks or more (including changed antidepressants without taking a break)

Table 2: Primary and secondary outcomes (maintenance group as reference)

|  |  |  |  |
| --- | --- | --- | --- |
| Primary outcome | Maintenance (232) | Discontinuation (236) | Comparison between groups |
| Median | (IQR) | Median | (IQR) | Hazard ratio | 95% CI |
| Time to first depression relapse weeks N=468\* | 19.0 | (6.0, 28.0) | 13.3 | (6.0, 26.6) | 2.06 | (1.56, 2.70) |
|  |  |  |  |  |  |  |
| Secondary outcomes | Maintenance | Discontinuation |  |  |
| PHQ-9 † | Mean | (SD) | Mean | (SD) | Difference in means | 95% CI |
|  12 weeks N=477 | 4.1 | (3.8) | 6.3 | (5.1) | 2.16 | (1.47, 2.84) |
|  26 weeks N=477 | 4.2 | (3.7) | 5.0 | (4.6) | 0.72 | (0.02, 1.42) |
|  39 weeks N=477 | 3.8 | (3.9) | 4.4 | (4.2) | 0.55 | (-0.14, 1.24) |
|  52 weeks N=477 | 3.7 | (3.7) | 4.0 | (4.5) | 0.38 | (-0.32, 1.07) |
| GAD-7 ‡ |  |  |  |  |  |  |
|  12 weeks N=477 | 3.1 | (3.3) | 5.3 | (4.6) | 2.40 | (1.81, 2.99) |
|  26 weeks N=477 | 3.4 | (3.8) | 4.1 | (4.4) | 0.79 | (0.13, 1.45) |
|  39 weeks N=477 | 2.9 | (3.5) | 3.8 | (4.1) | 0.99 | (0.36, 1.62) |
|  52 weeks N=477 | 3.0 | (3.7) | 3.1 | 3.0 | 0.27 | (-0.36, 0.89) |
| Modified Toronto Side Effects Scale § |  |  |  |  |  |  |
|  12 weeks N=477 | 4.2 | (2.9) | 4.6 | (3.0) | 0.68 | (0.25, 1.11) |
|  26 weeks N=477 | 4.0 | (2.6) | 3.9 | (2.8) | 0.20 | (-0.26, 0.66) |
|  39 weeks N=476 | 3.8 | (2.5) | 3.7 | (2.6) | 0.16 | (-0.30, 0.62) |
|  52 weeks N=475 | 3.7 | (2.6) | 3.5 | (2.8) | 0.04 | (-0.41, 0.49) |
| Number of new or worsening symptoms using modified DESS ‖  |  |  |  |  |  |  |
|  12 weeks N=478 | 1.3 | (2.4) | 3.1 | (3.5) | 1.87 | (1.46, 2.28) |
|  26 weeks N=478 | 1.4 | (2.3) | 1.9 | (2.9) | 0.50 | (0.12, 0.89) |
|  39 weeks N=478 | 0.8 | (1.6) | 1.7 | (2.7) | 0.94 | (0.60, 1.28) |
|  52 weeks N=478 | 0.8 | (1.8) | 1.1 | (2.5) | 0.32 | (-0.02, 0.65) |
| SF-12 physical ¶ |  |  |  |  |  |  |
|  12 weeks N=476 | 48 | (10) | 50 | (9) | 0.44 | (-0.91, 1.78) |
|  26 weeks N=476 | 48 | (10) | 49 | (10) | 0.15 | (-1.33, 1.62) |
|  39 weeks N=476 | 48 | (11) | 51 | (10) | 1.49 | (-0.06, 3.04) |
|  52 weeks N=476 | 49 | (10) | 49 | (11) | -0.59 | (-2.09, 0.92) |
| SF-12 mental ¶ |  |  |  |  |  |  |
|  12 weeks N=476 | 46 | (10) | 41 | (11) | -4.86 | (-6.44, -3.29) |
|  26 weeks N=476 | 46 | (11) | 44 | (11) | -2.56 | (-4.35, -0.77) |
|  39 weeks N=476 | 48 | (10) | 45 | (11) | -3.07 | (-4.84, -1.31) |
|  52 weeks N=476 | 47 | (10) | 46 | (11) | -1.59 | (-3.43, 0.25) |

\* Median (IQR) time to relapse in weeks was for those who relapsed only: N=86 maintenance; N=131 discontinuation

† PHQ-9 - Patient Health Questionnaire 9, range 0 to 27, higher scores indicating more severe symptoms.

‡ GAD-7 – Generalized anxiety disorder 7, range 0 to 21, higher scores indicating more severe symptoms.

§ Modified Toronto Side Effects Scale (count of side effects), range 0 to 13, higher scores indicating more frequent and severe symptoms.

‖ Modified DESS - Discontinuation-emergent signs and symptoms (DESS) checklist, range 0 to 15, higher scores indicating more severe symptoms.

¶ SF-12 – Short form 12 questions, range 0 to 100, lower scores indicating worse quality of life.

N is number of participants included in the main models

As there was no pre-specified plan for adjustment for multiple comparisons for the secondary outcomes, no clinical conclusions can be drawn from the data.

Table 3. Serious adverse events.

|  |  |  |
| --- | --- | --- |
| Event  | Maintenance (n=238) | Discontinuation (n=240)  |
| Total number of serious adverse events / adverse events, n(%) | 10 (4%) | 8 (3%) |
| Grade 1: Resulted in death | 0 | 0 |
| Grade 2: Life threatening | 0 | 1 |
| Grade 3: Required hospitalization  | 8 | 7 |
| Grade 4: Resulted in disability/incapacity | 0 | 0 |
| Grade 5: Resulted in congenital anomaly/birth defect | 0 | 0 |
| Grade 6: Important medical event | 1 | 0 |

Serious adverse events are categorized using a severity rating created by the study sponsor (University College London): 1=Resulted in Death, 2=life Threatening, 3=required inpatient or prolonged existing hospitalization, 4=resulted in persistent or significant disability/incapacity, 5=resulted in congenital anomaly/birth defect, 6= Important Medical Event.

The names of individual serious adverse events are not listed to protect participant confidentiality because each event occurred in ≤1 patient.