The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 30, 2021 VOL. 385 NO. 14

Maintenance or Discontinuation of Antidepressants in Primary Care

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ABSTRACT

BACKGROUND

Patients with depression who are treated in primary care practices may receive antidepressants for prolonged periods. Data are limited on the effects of maintaining or discontinuing antidepressant therapy in this setting.

METHODS

We conducted a randomized, double-blind trial involving adults who were being treated in 150 general practices in the United Kingdom. All the patients had a history of at least two depressive episodes or had been taking antidepressants for 2 years or longer and felt well enough to consider stopping antidepressants. Patients who had received citalopram, fluoxetine, sertraline, or mirtazapine were randomly assigned in a 1:1 ratio to maintain their current antidepressant therapy (maintenance group) or to taper and discontinue such therapy with the use of matching placebo (discontinuation group). The primary outcome was the first relapse of depression during the 52-week trial period, as evaluated in a time-to-event analysis. Secondary outcomes were depressive and anxiety symptoms, physical and withdrawal symptoms, quality of life, time to stopping an antidepressant or placebo, and global mood ratings.

RESULTS

A total of 1466 patients underwent screening. Of these patients, 478 were enrolled in the trial (238 in the maintenance group and 240 in the discontinuation group). The average age of the patients was 54 years; 73% were women. Adherence to the trial assignment was 70% in the maintenance group and 52% in the discontinuation group. By 52 weeks, relapse occurred in 92 of 238 patients (39%) in the maintenance group and in 135 of 240 (56%) in the discontinuation group (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. Patients in the discontinuation group had more symptoms of depression, anxiety, and withdrawal than those in the maintenance group.

CONCLUSIONS

Among patients in primary care practices who felt well enough to discontinue antidepressant therapy, those who were assigned to stop their medication had a higher risk of relapse of depression by 52 weeks than those who were assigned to maintain their current therapy. (Funded by the National Institute for Health Research; ANTLER ISRCTN number, ISRCTN15969819.)

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N Engl J Med 2021;385:1257-67.
DOI: 10.1056/NEJMoa2106356

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Antidepressants are often a first-line treatment for depression in primary care.[1] In high-income countries, the number of prescriptions for these medications has risen during the past several decades, mostly due to an increase in the duration of treatment.[2-5] Several systematic reviews of studies have shown a higher rate of relapse among patients who discontinue antidepressant therapy than among those who continue to receive such therapy, but such studies have had several limitations.[6-12] Most trials recruited patients with depression from specialist mental health services, treated them with antidepressants for 3 to 8 months, and randomly assigned patients who had a response to therapy to continue antidepressant therapy or switch to placebo. A few studies have recruited patients who were receiving maintenance antidepressants (mainly tricyclic compounds) for longer than 8 months.[13-15] However, small sample sizes have limited the ability to draw firm conclusions.

We conducted the randomized Antidepressants to Prevent Relapse in Depression (ANTLER) trial to assess the effects of maintenance antidepressant therapy, as 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 their medication.

Methods

Trial Design and Oversight

In this multicenter, randomized, double-blind trial, we recruited patients from 150 general practices across four sites in England (Bristol, London, Southampton, and York). Recruitment was performed through searches of electronic health records, after which we sent potentially eligible patients an invitation letter, or during primary care visits. The trial was approved by the National Research Ethics Service committee of the East of England–Cambridge South region. Clinical trial authorization was granted by the Medicines and Healthcare Products Regulatory Agency. All the patients provided written informed consent.

The trial was conducted according to the Good Clinical Practice guidelines of the International Council for Harmonisation. The trial was sponsored by University College London and funded by the National Institute for Health Research, with no commercial involvement. The first two authors wrote the first draft of the manuscript, which was reviewed by all the authors. A data and safety monitoring committee oversaw the recruitment and retention of patients and evaluated serious adverse events.

Patients

We enrolled patients who were receiving conventional doses of the three most commonly prescribed antidepressants in the United Kingdom (citalopram, sertraline, and fluoxetine)[4,16]; mirtazapine was also included among the trial drugs because of its increasing use in the United Kingdom.[16] We excluded patients who were receiving escitalopram since it is not widely used in U.K. 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 patients were between the ages of 18 and 74 years and had reported at least two prior episodes of depression or had been taking antidepressants for more than 2 years. All the patients had been receiving and adhering to a daily regimen of 20 mg of citalopram, 100 mg of sertraline, 20 mg of fluoxetine, or 30 mg of mirtazapine for at least 9 months, had recovered from their most recent depressive episode, and felt well enough to consider stopping antidepressants. Patients who were receiving other doses of the eligible medications and other antidepressants were excluded from the trial.

The main exclusion criterion was current depression, as defined by the criteria of the International Classification of Diseases, version 10 (ICD-10), at the time of trial entry. In order to exclude patients who were currently depressed at baseline, patients completed the original version of the Clinical Interview Schedule–Revised (CIS-R),[17] a computerized, self-administered, structured interview. The CIS-R asks about depressive symptoms during the past week and determines whether the symptoms indicate a diagnosis that meets the ICD-10 criteria for depressive episodes. The CIS-R also includes a method for scoring the severity of depression on a scale of 0 to 21, with higher scores indicating more severe depression, as determined 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 scores for anxiety, worry, phobias, worries about physical health, and panic sections. Additional details regarding the inclusion and exclusion criteria are provided in the protocol, available with the full text of this article at NEJM.org.

RANDOMIZATION

We used a computerized system and minimization algorithm that included site, medication, and median CIS-R score to attempt to attain a 1:1 ratio of patients who were maintaining their current antidepressant therapy (maintenance group) or were tapering and discontinuing such therapy (discontinuation group). (Details regarding the minimization algorithm are provided in the Supplementary Appendix, available at NEJM.org.) The trial-group assignments were provided to pharmacy staff members, who sent masked trial antidepressants or placebo to the primary care practice for distribution to patients or directly to the patient's home.

TRIAL TREATMENTS AND PROCEDURES

Trial medications contained antidepressants 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. All the capsules were of identical opaque appearance and were provided in identical bottles. The intention of the identical pills and bottles was to keep both patients and practitioners unaware of the trial-group assignments.

During the first month in the discontinuation group, patients who were taking citalopram, sertraline, or mirtazapine at baseline received the medications at half their regular dose. In the second month, they received half-dose antidepressants and placebo on alternate days. Starting in the third month, they received placebo only. Patients who were taking fluoxetine at baseline received 20 mg of fluoxetine and placebo on alternate days in the first month. (Fluoxetine was not available in a 10-mg capsule at the time of enrollment.) Starting in the second month, they received placebo only, since fluoxetine has a long half-life. In the maintenance group, patients received their usual antidepressants at their usual doses. We used a five-item patient-report measure that had been used in two other antidepressant trials[18,19] to determine adherence to the assigned regimen.

The trial was performed during a period of 52 weeks, with follow-up at 6, 12, 26, 39, and 52 weeks. Data were collected by means of questionnaires that were mailed to patients at 6 weeks and by face-to-face interviews conducted at baseline and at 12, 26, 39, and 52 weeks.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the first relapse of depression during the 52-week follow-up, as determined in a time-to-event analysis. This outcome was defined as a new episode of depression, as 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 in the following sections: depression, depressive ideas, fatigue, concentration, and sleep problems. In contrast to the original, the rCIS-R inquired specifically about the patient's experience during the previous 12 weeks. (Details regarding this instrument, including its reliability and validity, are provided in the Supplementary Appendix.)

Our case definition for relapse of depression was an affirmative answer to either of two mandatory rCIS-R questions: First, have you had a spell of feeling sad, miserable, or depressed? And second, have you been unable to enjoy or take an interest in things as much as you usually do? To meet the outcome of a depressive episode, patients also had to report that at least one of the preceding responses had lasted for 2 weeks or more and to describe the occurrence of at least one of the following symptoms: depressive thoughts (which included loss of interest in sex, restlessness, feeling guilty, feeling inferior to others, hopelessness, feeling that life was not worth living, and thoughts of suicide), fatigue, loss of concentration, or sleep disturbance.

We evaluated patients regarding eight secondary outcomes. First, we measured depressive symptoms using the Patient Health Questionnaire 9-item version (PHQ-9), with scores ranging from 0 to 27, with higher scores indicating more severe symptoms. Second, we evaluated generalized anxiety symptoms using the Generalized Anxiety Disorder Assessment 7-item version (GAD-7), with scores ranging from 0 to 21,

with higher scores indicating more severe symptoms. Third, we reviewed physical symptoms that are potentially side effects of antidepressant therapy using a modified 13-item Toronto Side Effect Scale. We report a count of the number of side effects (ranging from 0 to 13) and the proportion of patients who reported at least one side effect.[20] Fourth, we evaluated the frequency of new or worsened drug-withdrawal symptoms on a modified 14-item Discontinuation-Emergent Signs and Symptoms (DESS) checklist[21] (and after consulting with patients, we added a question to the DESS on electric sensations in the brain, leading to a total of 15 items[22]).

Fifth and sixth, we calculated quality-of-life scores for physical and mental health categories on the 12-Item Short-Form Health Survey (SF-12), with scores ranging from 0 to 100, with higher scores indicating a better quality of life. Seventh, we determined the interval between the date of initiation of an antidepressant or placebo and the stopping date. And eighth, we rated the patient's reported global rating of mood (feeling worse [grade 1] or feeling the same or better [grade 0]). Two of the secondary outcomes — the time until stopping the medication and the patient's mood — were prespecified in the statistical analysis plan before the database lock but after the protocol had been published.[24] All outcomes were assessed at every follow-up except for scores on the rCIS-R, SF-12, and adherence scales, which were obtained at every follow-up except at 6 weeks.

ADVERSE EVENTS

Since this was a phase 4 trial of licensed medications within their licensed indications, we recorded adverse events of special interest only, using the Toronto and DESS scales at each follow-up (reported as secondary outcomes). Serious adverse events were recorded by investigators using a recording-and-reporting form created by the trial sponsor. The principal investigator at each site rated each event according to seriousness, causal relationship to a trial medication, severity, and outcome.

STATISTICAL ANALYSIS

We determined that the enrollment of 479 patients would provide the trial with 90% power to detect a hazard ratio of 1.92 for the primary outcome in the discontinuation group on the basis of an estimated relapse frequency of 20% in the maintenance group and 35% in the discontinuation group at a two-sided alpha level of 0.05, assuming 20% attrition.[24] We used Cox proportional-hazards modeling to perform the primary analysis after adjustment for the baseline CIS-R depression score. We performed Kaplan–Meier analysis to determine proportionality and the predicted survival plot, and the assumption was affirmed.

Sensitivity analyses for the primary outcome included adjustment for minimization variables as patient-level explanatory factors and an investigation of missing data with the use of best-case and worst-case scenarios for patients who were not included in the primary analysis. For the best-case and worst-case scenarios, we censored data for patients in the maintenance group on the day of the last follow-up visit or withdrawal from the trial (good outcome, no relapse); for those in the discontinuation group, we determined that they had had a relapse on the day before the last follow-up or on the day of withdrawal (bad outcome, relapse).

We analyzed continuous secondary outcomes at 12, 26, 39, and 52 weeks and prespecified that these outcomes would be analyzed for each follow-up separately after accounting for baseline values, using mixed-effects linear regression with fixed effects for time and randomized group.[1,25] We used logistic-regression analysis to evaluate patients' responses on the global ratings of mood at each follow-up. We used Cox proportional-hazards modeling to evaluate the time until an antidepressant or placebo was stopped, and proportionality was determined according to the method that was used for the primary outcome. Because there was no prespecified plan for the adjustment of confidence intervals for multiple comparisons of secondary outcomes, no definite conclusions can be drawn from these data. For secondary outcomes, except for the time until the stopping of an antidepressant or placebo, we conducted sensitivity analyses that included predictors of missingness at baseline that were identified with the use of univariable logistic regression. We adjusted for variables that were significantly associated with missingness as covariates.

For the primary outcome, we conducted five prespecified subgroup analyses according to antidepressant type, severity of depression, severity

of anxiety, duration of depression, and age of onset of depression. We also conducted post hoc analyses to explore the characteristics of primary care practices, the age and sex of patients who were invited to participate in the trial as compared with those who participated, the level of patients' anxiety at baseline, antidepressant use according to relapse and group, whether patients guessed their group assignment, the number needed to harm, and whether patients were aware of their trial-group assignments (e.g., because of unblinding owing to adverse events). In addition, we reran the primary analyses and classified relapse according to ICD-10 depression criteria and reran secondary analyses using log-transformed PHQ-9 and GAD-7 scores that could be compared with prior studies of minimal clinically important differences.[2,3]

RESULTS

PATIENTS

We invited 23,553 potential patients (23,429 by sending them letters and 124 during general-practice consultations) to participate in the trial (Fig. 1 and Fig. S1 in the Supplementary Appendix). Of these patients, 1466 (6%) underwent screening for suitability, and 606 (41%) were found to be eligible to participate. Among the patients who were eligible, 478 were enrolled and underwent randomization (238 to the maintenance group and 240 to the discontinuation group). All the patients provided final outcome data with respect to relapse, although 10 patients (6 in the maintenance group and 4 in the discontinuation group) did not provide the timing of relapse. Thus, these patients were not included in the primary analysis but were included in the absolute number of patients with relapse.

The two trial groups had similar characteristics at baseline (Table 1). Approximately three quarters of the patients were women, with a mean (±SD) age of 54±13 years; approximately 95% were White. Citalopram was the most commonly used antidepressant, and almost three quarters of the patients had been taking antidepressants for more than 3 years. The median time between randomization and starting an antidepressant or placebo was 9 days (interquartile range [IQR], 6 to 13) in the maintenance group and 8 days (IQR, 6 to 13) in the discontinuation group.

PRIMARY OUTCOME

Relapse of depression occurred in 92 of 238 patients (39%) in the maintenance group and in 135 of 240 (56%) in the discontinuation group during the 52 weeks of the trial (hazard ratio, 2.06; 95% confidence interval [CI], 1.56 to 2.70; P<0.001) (Table 2 and Fig. 2). Sensitivity analyses, including for missing data, were in the same direction as the primary analysis (Table S2).

SECONDARY OUTCOMES

At 12 weeks, secondary outcomes were generally in the same direction as the primary outcome, except for scores on the SF-12 physical-health component and Toronto Side Effect Scale (Table 2). Effect estimates at other time points were also generally in the same direction as those for the primary outcome, although the confidence intervals in several categories crossed the null cutoff (indicating the likelihood of no between-group difference). Since there was no plan for adjustment of confidence intervals for multiple comparisons, no definite conclusions can be drawn regarding these or other differences between groups for secondary outcomes.

The mean score for depressive symptoms as assessed by the PHQ-9 at 12 weeks was 4.1±3.8 in the maintenance group and 6.3±5.1 in the discontinuation group, for an estimated difference of 2.2 points (95% CI, 1.5 to 2.8). The mean score for anxiety symptoms as assessed by the GAD-7 at 12 weeks was 3.1±3.3 in the maintenance group and 5.3±4.6 in the discontinuation group, for an estimated difference of 2.4 points (95% CI, 1.8 to 3.0). The mean score for side effects as assessed on the Toronto scale at 12 weeks was 4.2±2.9 in the maintenance group and 4.6±3.0 in the discontinuation group, for an estimated difference of 0.7 points (95% CI, 0.3 to 1.1). The mean score for withdrawal symptoms at 12 weeks on the modified DESS was 1.3±2.4 in the maintenance group and 3.1±3.5 in the discontinuation group, for an estimated difference of 1.9 points (95% CI, 1.5 to 2.3). The mean score for mental health–related quality of life on the SF-12 at 12 weeks was 46±10 in the maintenance group and 41±11 in the discontinuation group, for an estimated difference of −4.9 points (95% CI, −6.4 to −3.3).

A greater percentage of patients in the discontinuation group than in the maintenance group stopped taking the trial medication before

Figure 1. Enrollment and Outcomes.

Patients who had missed participation in one follow-up assessment could participate in a subsequent assessment. The retrospective Clinical Interview Schedule–Revised (rCIS-R) is a computerized, self-administered interview that asks about depressive symptoms during the previous 12 weeks. A flow chart showing the recruitment of patients and screening process is provided in Figure S1.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Maintenance Group (N=238)	Discontinuation Group (N=240)
Demographic		
Age — yr	54±13	55±12
Female sex — no. (%)	168 (71)	181 (75)
White race — no./total no. (%)†	221/238 (93)	228/235 (97)
Married — no. (%)	146 (61)	161 (67)
Currently employed — no. (%)	140 (59)	152 (63)
Trial site — no. (%)		
London	101 (42)	98 (41)
Bristol	48 (20)	54 (22)
Southampton	48 (20)	48 (20)
York	41 (17)	40 (17)
Clinical		
Antidepressant use — no. (%)		
Sertraline	41 (17)	37 (15)
Citalopram	111 (47)	112 (47)
Fluoxetine	77 (32)	83 (35)
Mirtazapine	9 (4)	8 (3)
Depression score above median value on CIS-R — no./total no. (%)‡	116/237 (49)	110/240 (46)
Age at onset of depression — yr	33±16	32±14
≥3 previous episodes of depression — no./total no. (%)	224/238 (94)	219/239 (92)
Continuous antidepressant use for ≥3 yr — no./total no. (%)§	170/238 (71)	168/239 (70)
Score on Patient Health Questionnaire 9-item version¶	3.9±3.5	3.8±3.6
Score on Generalized Anxiety Disorder 7-item version‖	3.2±3.1	2.8±3.0
Score on 12-Item Short-Form Health Survey**		
Physical component	48±11	50±9
Mental component	47±9	48±9
Score on modified Toronto Side Effect Scale††	4.2±2.7	3.7±2.7
Score on modified DESS‡‡		
No. of new or worsening symptoms	1.0±1.4	0.6±1.0
≥1 new or worsening symptom — no. (%)	118 (50)	95 (40)
Mood worse than 2 wk ago — no./total no. (%)	13/237 (5)	9/239 (4)

* Plus–minus values are means ±SD.
† Race was reported by the patients.
‡ Scores on the Clinical Interview Schedule–Revised (CIS-R) range from 0 to 57, with higher scores indicating worse mental health. Scores on this instrument that were above the median were used for minimization.
§ Continuous use of an antidepressant was defined as receipt without a break of 2 weeks or more, including during a change in medication.
¶ Scores on the Patient Health Questionnaire 9-item version range from 0 to 27, with higher scores indicating more severe symptoms.
‖ Scores on the Generalized Anxiety Disorder 7-item version range from 0 to 21, with higher scores indicating more severe symptoms.
** Scores on the 12-Item Short-Form Health Survey range from 0 to 100, with higher scores indicating a better quality of life.
†† Scores on the modified Toronto Side Effect Scale (which provides a count of side effects) range from 0 to 13.
‡‡ Scores on the modified checklist of Discontinuation-Emergent Signs and Symptoms (DESS) range from 0 to 15, with higher scores indicating more symptoms.

Table 2. Primary and Secondary Outcomes.*

Outcome	Maintenance Group (N=238)	Discontinuation Group (N=240)	Effect Size or Difference (95% CI)†
Primary outcome			
Relapse of depression — no. (%)	92 (39)	135 (56)	Hazard ratio, 2.06 (1.56 to 2.70)
Secondary outcomes			
Score on Patient Health Questionnaire 9-item version			
12 wk	4.1±3.8	6.3±5.1	2.2 (1.5 to 2.8)
26 wk	4.2±3.7	5.0±4.6	0.7 (0.0 to 1.4)
39 wk	3.8±3.9	4.4±4.2	0.6 (–0.1 to 1.2)
52 wk	3.7±3.7	4.0±4.5	0.4 (–0.3 to 1.1)
Score on Generalized Anxiety Disorder 7-item version			
12 wk	3.1±3.3	5.3±4.6	2.4 (1.8 to 3.0)
26 wk	3.4±3.8	4.1±4.4	0.8 (0.1 to 1.4)
39 wk	2.9±3.5	3.8±4.1	1.0 (0.4 to 1.6)
52 wk	3.0±3.7	3.1±3.0	0.3 (–0.4 to 0.9)
Score on modified Toronto Side Effect Scale			
12 wk	4.2±2.9	4.6±3.0	0.7 (0.3 to 1.1)
26 wk	4.0±2.6	3.9±2.8	0.2 (–0.3 to 0.7)
39 wk	3.8±2.5	3.7±2.6	0.2 (–0.3 to 0.6)
52 wk	3.7±2.6	3.5±2.8	0.0 (–0.4 to 0.5)
No. of new or worsening symptoms on modified DESS			
12 wk	1.3±2.4	3.1±3.5	1.9 (1.5 to 2.3)
26 wk	1.4±2.3	1.9±2.9	0.5 (0.1 to 0.9)
39 wk	0.8±1.6	1.7±2.7	0.9 (0.6 to 1.3)
52 wk	0.8±1.8	1.1±2.5	0.3 (–0.0 to 0.6)
Score on physical component of 12-Item Short-Form Health Survey			
12 wk	48±10	50±9	0.4 (–0.9 to 1.8)
26 wk	48±10	49±10	0.2 (–1.3 to 1.6)
39 wk	48±11	51±10	1.5 (–0.1 to 3.0)
52 wk	49±10	49±11	–0.6 (–2.1 to 0.9)
Score on mental component of 12-Item Short-Form Health Survey			
12 wk	46±10	41±11	–4.9 (–6.4 to –3.3)
26 wk	46±11	44±11	–2.6 (–4.4 to –0.8)
39 wk	48±10	45±11	–3.1 (–4.8 to –1.3)
52 wk	47±10	46±11	–1.6 (–3.4 to 0.2)

* Plus–minus values are means ±SD.
† All the listed comparisons are for the discontinuation group as compared with the maintenance group. All the comparisons are differences in means, except for the hazard ratio for the primary analysis.

the end of the trial (48% vs. 30%) (hazard ratio, 2.28; 95% CI, 1.68 to 3.08). Of the patients who stopped their trial medication, the percentage who returned to the use of an antidepressant prescribed by their primary care doctor was 20% (95% CI, 15 to 25) in the maintenance group and

39% (95% CI, 32 to 45) in the discontinuation group.

During the course of the trial, 157 of 225 patients (70%) in the maintenance group adhered to the trial regimen, as compared with 119 of 230 patients (52%) in the discontinuation group (Table S12). At 12 weeks, the patients who reported feeling worse (as compared with the same as or better) than they had felt at 6 weeks included 48 of 228 patients (21%) in the maintenance group and 94 of 216 patients (44%) in the discontinuation group (odds ratio, 2.88; 95% CI, 1.90 to 4.38). Results for all outcomes were similar with the inclusion of predictors of missingness in models (Table S3). Results of subgroup, sensitivity, and post hoc analyses are provided in the Supplementary Appendix.

ADVERSE EVENTS

There were 17 serious adverse events during the trial (9 [4%] in the maintenance group and 8 [3%] in the discontinuation group), and the categories of serious events were similar in the two groups (Table 3). Investigators considered that 2 serious adverse events were unlikely to be related to a trial medication and 15 were unrelated to a trial medication. There were no deaths or suicide attempts during the trial period.

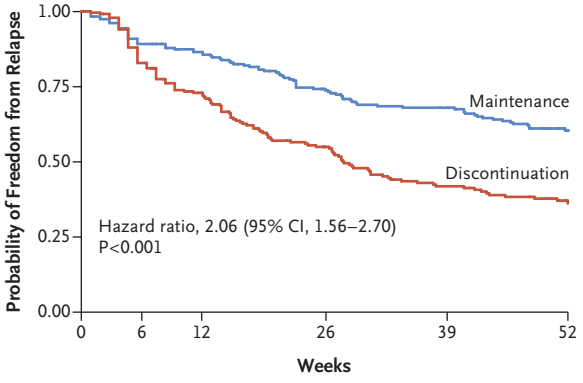

Figure 2. Kaplan–Meier Estimates of the Primary Outcome.

Shown are the results of Kaplan–Meier analysis of the first relapse of depression by 52 weeks (the primary outcome) among those who continued to receive their current antidepressant therapy (maintenance group) and those who tapered and discontinued such therapy (discontinuation group).

Table 3. Serious Adverse Events (Safety Population).*

Event	Maintenance Group (N=238)	Discontinuation Group (N=240)
	no. of patients (%)	
Any serious adverse event	9 (4)	8 (3)
Resulting in death	0	0
Resulting in life-threatening condition	0	1 (<1)
Resulting in hospitalization	8 (3)	7 (3)
Resulting in disability or incapacity	0	0
Resulting in congenital anomaly or birth defect	0	0
Resulting in medically important event	1 (<1)	0

* Serious adverse events are listed according to a 6-item severity rating created by the trial sponsor. The types of serious adverse events are not listed in order to protect patients' confidentiality because each event occurred in only one patient. There were no deaths or suicide attempts during the trial period.

DISCUSSION

Patients in the group assigned to discontinue their antidepressant medication in our trial had a higher frequency of relapse of depression than those who were assigned to keep taking their medication through 52 weeks of follow-up. Secondary outcomes were generally in the same direction as the primary outcome, except for scores on the SF-12 physical health component and the Toronto side-effect scale. By the end of the trial, 39% of the patients in the discontinuation group had returned to taking an antidepressant prescribed by their clinician, which may explain why there was no evidence of between-group differences for secondary outcomes at the last follow-up at 52 weeks.

We investigated only three selective serotonin-reuptake inhibitors that have similar pharmacologic profiles and have similar mechanisms of activity, along with mirtazapine (a noradrenergic and specific serotonergic antidepressant), so we cannot generalize our findings to other classes of antidepressants.[23,26] Another limitation of our trial is that we excluded patients who were taking escitalopram and those who were taking doses of the trial medications that differed from the usual doses for maintenance treatment in the United Kingdom. In addition, only a small percentage of patients who were recruited for the trial ultimately participated, which may have introduced bias into the trial sample. An impor-

tant limitation is that our findings pertain only to patients who felt 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 all the patients were being treated in the U.K. health system, so we cannot generalize our results to non-White patients and to other health systems.[27]

We recruited patients who had been taking antidepressants, usually for many years, and asked them to recall their 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 that patients provided. We also did not have detailed information about the original clinical decision for prescribing the antidepressant or any diagnostic information at that time.

Among patients in primary care practices who had been treated for depression and who were willing to stop their antidepressant medication, the risk of relapse of depression was higher among the patients in the discontinuation group than among those in the maintenance group during 52 weeks. Quality-of-life measures and symptoms of depression, anxiety, and medication withdrawal were generally worse in patients who discontinued their antidepressant therapy.

The views expressed in this article are those of the authors and do not necessarily reflect the views of the National Institute for Health Research, the National Health Service, or the U.K. Department of Health and Social Care.

Supported by the National Institute for Health Research (HTA Program 13/115/48).

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who volunteered to participate in the trial; the staff members in the primary care practices that helped to recruit patients; colleagues who contributed to the trial 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; the members of Clinical Research Networks (CRN) in North Thames, North West London, South London, Thames Valley, and South Midlands; Luton, Essex, and Herts Valley; and West of England and Wessex; CRN staff members Debbie Kelly, Claire Winch, Zara Prem, Andrei Gabzdyl, and Lynsey Wilson; the members of the Biomedical Research Centre, University College London Hospitals; the members of the Biomedical Research Centre at University Hospitals Bristol and the Weston National Health Service Foundation Trust; Allan House, Geoffrey Wong, Jonathan Bisson, Lucy Carr, Chris Dowrick, Rafael Perera-Salazar, and Mike Crawford for serving on the trial steering committee and the data and safety monitoring committee; and Luke Montagu for his advice concerning the modified Discontinuation-Emergent Signs and Symptoms scale.

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