Antidepressant medication to prevent depression relapse in primary care: the ANTLER RCT

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Scientific summary

The ANTLER RCT

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Scientific summary

Background

Depression is the leading cause of ill health and disability worldwide, with > 300 million people now living with depression. Depression causes marked emotional distress and interferes with daily function not only of the individual, but also of society. It has been estimated that depression reduces England's national income (gross national product) by over 4% (approximately £80M) every year. This reduction results from increased unemployment, a larger number of sick days and reduced productivity. It is also accompanied by increased welfare expenditure.

Antidepressants are often a first-line treatment for depressive symptoms and are also used for maintenance treatment, that is, to prevent relapse once an individual has recovered. It has been estimated that 90% of antidepressant prescriptions in the UK were used for maintenance between 1993 and 2005. A more recent UK study has also demonstrated a steady increase in the duration of long-term treatment between 2001 and 2012. In a Scottish study involving 78 practices, 8.6% of the registered population were prescribed an antidepressant, and half had been taking antidepressants for > 2 years (Johnson CF, MacDonald HJ, Atkinson P, Buchanan AI, Downes N, Dougall N. Reviewing long-term antidepressants can reduce drug burden: a prospective observational cohort study. *Br J Gen Pract* 2012;**62**:e773–9). This trend is similar in other high-income countries.

The National Institute for Health and Care Excellence (NICE) in England recommends that antidepressant maintenance treatments should continue to be used for 2 years for those at risk of relapse. However, NICE also recognises the uncertainty about the benefit of long-term maintenance treatment and has recommended further research into its psychological and pharmacological effects. Continuing maintenance treatment in the first few months after remission has been extensively studied and reduces relapse rates. However, the evidence for a treatment period longer than 8 months is insufficient to justify long-term maintenance treatment. The studies were conducted during the 1980s or early 1990s in secondary care by pharmaceutical companies for regulatory purposes; one was investigating tricyclic antidepressants that are no longer used for depression. All were very small studies ($n < 20$ participants in total) and had a poor follow-up rate.

Aim

The overall aim of the ANTLER trial was to answer the following research question: 'What is the clinical effectiveness and cost-effectiveness in UK primary care of continuing on long-term maintenance antidepressants compared with a placebo in preventing relapse of depression in those who have taken antidepressants for more than 9 months and who are now well enough to consider stopping maintenance treatment?'. The trial was embedded in primary care and had broad inclusion criteria to increase the generalisability to the population currently receiving maintenance antidepressants.

Methods

The trial was a Phase IV, double-blind, pragmatic, multisite, individually randomised parallel-group controlled trial, with follow-up at 6, 12, 26, 39 and 52 weeks.

We recruited primary care patients who were taking one of four of the most commonly used antidepressant medications. At the point of recruitment, the patients were well enough to consider stopping their medication. Participants were recruited from 150 primary care practices in four UK sites: London, Bristol, Southampton and York. We recruited the first participant in March 2017, and within 2 years we randomised 238 participants to antidepressant continuation and 240 participants to discontinuation. The participants were individuals aged 18–74 years who had experienced at least two episodes of depression and had been taking antidepressants for ≥ 9 months but felt well enough to consider stopping their medication. Participants were excluded if they met *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, criteria for depressive illness assessed with the clinical interview schedule – Revised (CIS-R) (see below); had bipolar disorder, psychotic illness, dementia or terminal illness; could not understand questionnaires in English; had contraindications to the medication or placebo ingredients; were taking monoamine oxidase inhibitors; or were enrolled in another clinical trial. Women were excluded if they were pregnant, planning pregnancy or breastfeeding. At baseline, participants were taking citalopram 20 mg, sertraline 100 mg, fluoxetine 20 mg or mirtazapine 30 mg. They were randomised to either remain on their current medication or switch to placebo after a tapering period of 1 (fluoxetine) or 2 (citalopram, sertraline or mirtazapine) months. The trial compared continuing antidepressant medication with discontinuing medication by replacing it with an identical placebo after a tapering period.

The primary outcome was the time, in weeks, to the beginning of the first depressive episode after randomisation. This was measured by a shortened CIS-R that assessed the onset of a depressive episode in the previous 12 weeks and was conducted at 12, 26, 39 and 52 weeks. We called the new assessment the retrospective CIS-R (rCIS-R) and conducted a test–retest reliability study, which was nested within the ANTLER trial. The ANTLER trial participants were asked to complete the rCIS-R twice, at the beginning and the end of one of the follow-up appointments, and 396 participants provided data. The depression-related resource use was collected over 12 months and for the 6 months preceding baseline from medical records and patient-completed questionnaires. Quality-adjusted life-years (QALYs) were calculated using the EuroQol-5 Dimensions, five-level version.

Results

Recruitment began on 9 March 2017 and the last participant was randomised on 1 March 2019. The general practitioner record search identified 23,429 potentially eligible patients, who were sent an invitation letter. Another 124 potentially eligible patients were referred during general practitioner consultation, resulting in 1466 patients wanting to take part. Of these patients, 606 were eligible. In total, 478 participants were randomised: 238 to maintenance antidepressant and 240 to placebo. A total of 390 participants (82%) completed the trial. All participants provided data on whether or not they relapsed; however, 10 (maintenance group, $n = 6$; discontinuation group, $n = 4$) participants did not provide data on timing of relapse, so could not be included in the analysis of the primary outcome.

The groups were well balanced at baseline, with a mean age of 54 years [standard deviation (SD) 13 years] in the maintenance group and 55 years (SD 12 years) in the discontinuation group. Just over 40% of participants were recruited from London, 20% from each of Bristol and Southampton and 17% from York. Under half were taking citalopram, one-third fluoxetine, one-sixth sertraline and under one-twentieth mirtazapine. Almost three-quarters of participants had taken antidepressants for > 3 years, with over one-third taking them for ≥ 6 years.

The hazard ratio for relapse in the discontinuation group was 2.06 [95% confidence interval (CI) 1.56 to 2.70; $p < 0.0001$], with 39% of those who continued antidepressants and 56% who discontinued experiencing relapse. In other words, over a 52-week period, one in every six patients who stopped antidepressants would experience a relapse that may not have occurred if they had remained on their antidepressants. A similar pattern was observed for the secondary outcomes, for which participants in the

discontinuation group at 12 weeks had more depressive and anxious symptoms (coefficients Patient Health Questionnaire-9 items 2.12, 95% CI 1.37 to 2.86; Generalised Anxiety Disorder-7 2.24, 95% CI 1.59 to 2.89) and poorer mental health quality of life (coefficient Short Form questionnaire-12 items −4.61, 95% CI −6.42 to −2.81) than those in the maintenance group, and had more than twice the odds of feeling worse using the Global Rating Question (odds ratio 2.88, 95% CI 1.90 to 4.38). In the discontinuation group, 37% (95% CI 28% to 45%) of participants remained on their randomised medication until the end of the trial, and 39% (95% CI 32% to 45%) returned to their original antidepressant compared with 20% (95% CI 15% to 25%) of participants in maintenance group.

People who discontinued antidepressants experienced more withdrawal symptoms than those who remained on medication, with the largest difference at 12 weeks (coefficient 1.81, 95% CI 1.40 to 2.23) and reducing thereafter. Among those who relapsed in the discontinuation group, 53% of participants chose to return to an antidepressant prescribed by their doctor.

The health economic evaluation found that participants randomised to discontinuation had worse utility scores at 3 months (−0.037, 95% CI −0.059 to −0.015) and fewer QALYs over 12 months (−0.019, 95% CI −0.035 to −0.003) than those randomised to the maintenance group. The discontinuation group was dominated by the maintenance group in that the discontinuation pathway, besides giving worse outcomes, also cost more (extra £2.71 per patient over 12 months, 95% CI −£36.10 to £37.07), although the cost difference was not statistically significant. There was only a 12% probability that discontinuing antidepressants was sufficiently cost-effective compared with maintenance therapy at a cost-effectiveness threshold of £30,000 per QALY gained.

Conclusions

Our trial found that primary care patients who discontinue long-term maintenance antidepressants were at increased risk of relapse and withdrawal symptoms, particularly in the first few months after ending antidepressants. The results of our economic evaluation suggest that discontinuing antidepressant medication would not be recommended by national decision-makers on the grounds of cost-effectiveness. Some individuals may choose to taper and stop antidepressants to see if they can manage without antidepressants. For example, a substantial proportion of patients are still able to discontinue even if they relapse. Our findings will give patients and clinicians an estimate of the likely benefits and harms of stopping long-term maintenance antidepressants and improve shared decision-making. It supports the policy that there should be regular medical review of long-term maintenance antidepressant medication.

Trial registration

This trial is registered as ISRCTN15969819 and EudraCT 2015-004210-26.

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This report

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