SSRIs for mild to moderate depression in primary care: the THREAD study

Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study

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Executive summary

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Executive summary

Background

Guidelines for the management of depression, including the National Institute for Health and Clinical Excellence (NICE) guidelines, recommend that antidepressants should not be used as first-line treatment for patients with depression below the severity threshold for major depressive disorder, yet general practitioners (GPs) in the UK frequently prescribe for such patients. Previous research on antidepressants has mostly been carried out in secondary care settings among patients with relatively severe depression, and there has been relatively little research on mild to moderate depression in primary care. Placebo-controlled trials have suggested that selective serotonin reuptake inhibitor (SSRI) antidepressants can be effective for mild depression, but it is not known if prescribing them is cost-effective in practice. We aimed to determine whether treatment with an SSRI antidepressant plus supportive care is more effective and cost-effective than supportive care alone. Secondary aims were to explore whether treatment is more effective for moderate than for mild depression and to explore patient factors which might predict a beneficial response to antidepressants.

Objectives

Our research objectives were:

1. To determine the effectiveness and cost-effectiveness of SSRI treatment plus supportive care, versus supportive care alone, for mild to moderate depression in patients with somatic symptoms in primary care.
2. To determine the impact of the initial severity of depression on the effectiveness and relative costs of these two approaches.
3. To carry out exploratory analyses of the impact on the effectiveness of these two approaches of demographic and social variables, including age, gender, employment status, life events and difficulties, the patient's self-reported duration of depressive symptoms, the patient's previous experience of antidepressant use, the number of physical symptoms, the patient's attribution of his or her symptoms (physical cause versus non-physical cause) and alcohol consumption.

Methods

Design

The study was a parallel group, open-label, pragmatic randomised controlled trial.

Setting

The study took place in a UK primary care setting: 212 general practices around three academic centres (in Southampton, Liverpool and London) agreed initially to take part. Patients were referred by 177 GPs from 115 practices.

Participants

Patients diagnosed with new episodes of depression by the GP and potentially in need of treatment were referred to the study team. Both the patients and their GPs had to be in equipoise about the need for antidepressant treatment and prepared for the patient to be randomised to being prescribed an SSRI. Inclusion criteria were age 18 or over, symptoms for at least 8 weeks, no antidepressant treatment within the previous 12 months, no current receipt of counselling or psychological therapies, a score of between 12 and 19 on the 17-item Hamilton Depression Rating Scale (HDRS) and at least one physical symptom on the Bradford Somatic Inventory (BSI). Exclusion criteria were a lack of the spoken or written language skills necessary to take part, expressed suicidal intent, reported significant substance misuse and a score of 13 or more on the Alcohol Use Disorders Identification Test (AUDIT) questionnaire. In total, 602 patients were referred to the study team, of whom 220 were randomised into the study.

Interventions

All treatments were delivered by the patients' GPs, reflecting usual practice in the UK. They were asked to provide supportive care to all participants in follow-up consultations 2, 4, 8 and 12 weeks

after the baseline assessment. They were not asked to provide any specific interventions in the follow-up consultations in the supportive care alone arm, but were asked to prescribe an SSRI antidepressant of their choice to those patients in the SSRI plus supportive care arm and to continue treatment for at least 4 months after recovery, in line with guidelines. They could switch antidepressants during treatment if they deemed this to be necessary. They were asked to refrain from prescribing an antidepressant to those randomised to the supportive care alone arm during the initial 12-week treatment period, but could use their judgement to prescribe antidepressants to patients in that arm if they became more depressed and in need of treatment.

Outcome measures

The primary outcome measure was the score on the HDRS at 12-week follow-up. Secondary outcome measures were the HDRS at 26-week follow-up and scores on the Beck Depression Inventory (BDI), Medical Outcomes Study Short Form 36-item (SF-36) questionnaire measure of generic health status, Medical Interview Satisfaction Scale (MISS), modified Client Service Receipt Inventory (CSRI) patient questionnaire for use of health and social services and informal care, and GP medical record data for primary care contacts and drug prescriptions. Inter-rater reliability on the HDRS between researchers in the three centres was checked at four points during recruitment and was found to be high.

Analysis

The primary analysis was by intention to treat using double-sided significance tests. We used analysis of covariance, controlling for baseline value and recruitment site and allowing for clustering by GP, to estimate treatment effectiveness using the HDRS at both follow-ups independently. Longitudinal analysis was also performed, in which 12-week and 26-week outcomes were modelled simultaneously, and both time point and time point × treatment interaction effects were tested in these models. Baseline predictors of a lack of follow-up data were identified by means of logistic regression and the models of predictors of outcomes were refitted to include these variables. Cost-effectiveness was expressed in terms of incremental cost-effectiveness and cost–utility ratios. In addition, cost-effectiveness acceptability curves (CEACs) were generated, synthesising data on costs and outcomes, for varying levels of acceptability of costs.

Results

More than 90% of patients in each arm received supportive care from the GPs, with a mean number of consultations of around four during the 12-week treatment period. Selective serotonin reuptake inhibitor antidepressants were received by 87% of patients in the SSRI plus supportive care arm and also by 20% of patients in the supportive care alone arm. Longitudinal analyses demonstrated statistically significant differences in favour of the SSRI plus supportive care arm in terms of lower HDRS scores, higher scores on the SF-36 mental health subscale and higher scores on the MISS, but not in terms of lower BDI scores. Differences in the SF-36 vitality score were of borderline significance, and the other SF-36 subscales were not significantly different. Significant mean differences in HDRS score adjusted for baseline were found at both follow-up points when analysed separately, but were relatively small: 2.3 points at 12 weeks and 1.7 points at 26 weeks. The numbers needed to treat (NNTs) for remission (to HDRS < 8) were 6 [95% confidence interval (CI) 4 to 26) at 12 weeks and 6 (95% CI 3 to 31) at 26 weeks, and the NNTs for significant improvement (HDRS reduction $\geq 50\%$) were 7 (95% CI 4 to 83) and 5 (95% CI 3 to 13) respectively. Costs were slightly higher in the SSRI plus supportive care arm, but were not significantly different. Incremental cost-effectiveness ratios and cost-effectiveness planes suggested that adding an SSRI to supportive care was probably cost-effective, with mean costs of £90 per point improvement on the HDRS, and £14,854 per quality-adjusted life-year (QALY) gain. The CEAC for utility suggested that adding an SSRI to supportive care was cost-effective at the values of £20,000–£30,000 per QALY used by NICE, with a 65–75% probability. A poorer outcome on the HDRS was significantly related to greater severity at baseline, a higher physical symptom score and being unemployed. The effect size of unemployment was of similar magnitude to that of treatment. None of the other possible predictors was significantly related to outcome or response to treatment. Further analyses are planned of possible relationships between life events and remission, the nature of supportive care received, patterns of change in depressive symptoms and the components of patient satisfaction.

Conclusions

Treatment with an SSRI plus supportive care is more effective than supportive care alone for patients with mild to moderate depression in primary care in the UK, at least for those with symptoms persisting for 8 weeks and with a score of ≥ 12 on the HDRS, equivalent to around 12 on the Patient Health Questionnaire, 9-item version (PHQ-9) and 9 on the Hospital Anxiety and Depression Scale, depression subscale (HADS-D). The additional benefit is relatively small, and may be at least in part a placebo effect, but is probably cost-effective at the level used by NICE to make judgements about recommending treatments within the National Health Service (NHS).

Implications for further research

In order of priority, these are as follows:

- More studies of drug and non-drug treatments for mild depression in primary care are needed, as the evidence base for the treatment of mild depression is still relatively small.
- More research is required on the natural history of mild to moderate depression and predictors of chronicity because, although many patients recover within weeks without treatment, a significant number do not improve over 6 months of follow-up.
- More trials of antidepressant treatment are needed among patients with persistent and/or repeated mild depression, in mild depression in the context of a history of severe depression, in the context of physical illness and in patients over the age of 70 years. There are reasons to believe that antidepressants may be a relatively good or bad idea in these subgroups, rather than to take the blanket view that antidepressants should always be second-line treatments for mild depression (as suggested by NICE). We also know relatively little about the required doses of antidepressants and duration of treatment in these groups.
- More research is needed to identify the most effective elements of supportive care.
- More research is required into the differences between the HDRS, BDI and other measures of depression, to explore whether they measure different aspects of depression and differ in sensitivity to change in relation to drug, psychological and other treatments.
- More economic evaluations are required and the appropriateness of the methods used to generate QALYs should be assessed.
- Better measures of outcome for depression studies, including patient-derived measures, need to be developed.

Trial registration

This trial is registered as ISRCTN84854789.

Publication

Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, *et al*. Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. *Health Technol Assess* 2009;**13**(22).

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

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Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/70/05. The contractual start date was in September 2003. The draft report began editorial review in May 2008 and was accepted for publication in November 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. 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' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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