

A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine

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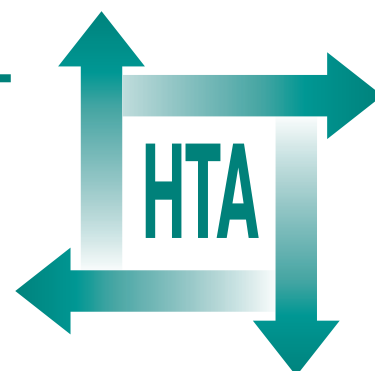
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Executive summary

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Executive summary

Objectives

The main aim of this study was to determine the relative cost-effectiveness of three classes of antidepressant: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and the TCA-related antidepressant lofepramine, as first choice treatments for depression in primary care.

Methods

Design

The study was an open, pragmatic, controlled trial with three randomised arms and one preference arm. Patients were followed up for a total of 12 months.

Setting

The study took place in a UK primary care setting: 73 practices in urban and rural areas in Hampshire, Wiltshire, Dorset, Sussex and Surrey agreed initially to take part. Patients were referred by 87 GPs from 55 practices.

Participants

Patients with a new episode of depressive illness according to GP diagnosis were assessed. In total, 388 patients were referred to the study team.

Interventions

Patients were randomised to receive a TCA (amitriptyline dothiepin or imipramine), an SSRI (fluoxetine, sertraline or paroxetine) or lofepramine. Standardised recommendations about dose and dose escalation based on the British National Formulary were issued to GPs. Patients or GPs were able to choose an alternative treatment if preferred.

Main outcome measures

At baseline the Clinical Interview Schedule, Revised (CIS-R PROQSY computerised version) was administered to establish symptom profiles. Outcome measures over the 12-month follow-up included the Hospital Anxiety and Depression Scale self-rating of depression (HAD-D), CIS-R, EuroQol 5 Dimensions for quality of life, Short Form 36 for generic health status, and patient and practice records of use of health and social services. The primary effectiveness outcome was the number of

depression-free weeks (HAD-D <8, with interpolation of intervening values) and the primary cost outcome total direct NHS costs. Quality-adjusted life-years (QALYs) were used as the outcome measure in a secondary analysis. Incremental cost-effectiveness ratios and cost-effectiveness acceptability curves were computed. Estimates were bootstrapped with 5000 replications.

Results

In total, 327 patients were randomised. Follow-up rates were 78% at 3 months and 52% at 1 year. Linear regression analysis revealed no significant differences between groups in number of depression-free weeks when adjusted for baseline HAD-D. A higher proportion of patients randomised to TCAs entered the preference arm than those allocated to the other choices. Switching to another class of antidepressant in the first few weeks of treatment occurred significantly more often in the lofepramine arm and less in the preference arm. There were no significant differences between arms in mean cost per depression-free week. For values placed on an additional QALY of over £5000, treatment with SSRIs was likely to be the most cost-effective strategy. TCAs were the least likely to be cost-effective as first choice of antidepressant for most values of a depression-free week or QALY, but these differences were relatively modest.

Conclusions

Given the low probability of significant differences in cost-effectiveness, the authors conclude that it is appropriate to base the first choice between these three classes of antidepressant in primary care on doctor and patient preferences. Adopting this policy may lead to less switching of medication subsequently. Choosing lofepramine is likely to lead to a greater proportion of patients switching treatment in the first few weeks.

Recommendations for research

Recruitment to trials in primary care remains a difficult problem to solve. The following

strategies may be helpful and should be investigated further:

- financially rewarding recruitment to high-quality research studies (those funded by the partnership organisations, the MRC, NHS R&D, and AMRC charities), by giving practices points in the General Medical Services performance-related contract, which is to be revised in 2006.
- funding nurse time in the practices, as in the MRC GP research framework
- using practitioners with a track record of recruiting to other studies
- working extensively with practitioners and support staff in a smaller number of practices, rather than stretching resources thinly over a large number of practices
- building in a pilot phase to test recruitment, and including qualitative interviews with patients, especially those declining to take part in the trial
- keeping the inclusion and exclusion criteria as brief and clear as possible
- keeping the information sheet as short as possible, but in keeping with giving enough information
- IT support including better email links with practices, and a website with study information

- pop-up screens on practice computers to remind practitioners to consider referral of patients with the relevant conditions.

Further research is still needed to address other important questions surrounding the management of depressive illness in primary care. This should address areas such as the optimum severity threshold at which medication should be used; the feasibility and effectiveness of adopting structured management programmes in the UK context; the importance of factors such as physical co-morbidity and recent life events in GP's prescribing decisions; alternative ways of collecting data, for example using telephone follow-up or payment for data; and factors that give rise to many patients being reluctant to accept medication and discontinue treatment early.

Publication

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The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

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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.

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