Study of the use of antidepressants for depression in dementia: the HTA-SADD trial – a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine

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Executive summary

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Executive summary

Background

Dementia is one of the most common and serious disorders in later life. Worldwide it affects 35 million people, and this will treble by 2050. In the UK there are 750,000 people with dementia and 200,000 new cases every year. It causes irreversible decline in global intellectual, social and physical functioning. In the UK dementia costs around £17B per year; worldwide, its annual cost is US$600B, with this set to at least triple in the next 20 years. The negative impacts of dementia on those with the disorder, in terms of deteriorating function, and on carers are profound. Dementia has a devastating impact across culture, gender, ethnicity and class. The need to improve care for people with dementia is a policy priority.

Depression is common in dementia, with prevalence of $>20\%$, causing distress, reducing quality of life, exacerbating cognitive and functional impairment, increasing mortality, and increasing carer stress and depression. Treating depression is therefore a key clinical priority to improve the well-being, quality of life and level of function of people with Alzheimer's disease (AD).

A Cochrane review (Bains J, Birks JS, Dening TR. The efficacy of antidepressants in the treatment of depression in dementia. *Cochrane Database Syst Rev* 2002;**4**:CD003944) identified only three studies, comprising 107 subjects, which had data that could be subject to a meta-analysis of efficacy. It concluded that, despite its clinical seriousness, there was only weak evidence of the effectiveness of antidepressants in dementia. Two studies used tricyclic antidepressants – 'drugs not commonly used in this population' (because of anticholinergic side effects that may negatively affect cognition, and cardiac side effects); only one used the most commonly used class (selective serotonin reuptake inhibitors). None covered newer classes of antidepressants and all were of short duration. Subsequently, the Depression in Alzheimer's Disease Study-II (DIADS)-II compared 67 people prescribed sertraline with 64 given placebo. In contrast with the DIADS study included in the Cochrane review, they found no benefit whatsoever of sertraline.

Despite the equivocal evidence, current practice is to use antidepressants, often sertraline, as a first-line treatment for depression in dementia. Given the limited evidence in this clinically important area, the Health Technology Assessment (HTA) programme of the UK National Institute for Health Research prioritised antidepressant treatment of depression in dementia as an area for primary research. They commissioned the study reported here to fill gaps in the evidence base definitively and enable the formulation of good-quality guidance on care for people with dementia and their carers.

Trial design

Multicentre parallel group double-blind placebo-controlled randomised controlled trial of the clinical effectiveness of sertraline and mirtazapine with 13- and 39-week follow-up.

Methods

Participants

This was a pragmatic trial, with inclusion criteria designed to mirror clinical practice closely. Those eligible met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable or possible AD and co-existing depression of at least 4 weeks' duration with a Cornell Scale for Depression in Dementia (CSDD) of 8+. The only exclusions were being too critical for randomisation (e.g. suicide risk); absolute contraindication

to trial medications; currently taking antidepressants; being in another trial; and having no informant to give collateral information. Participants were recruited from community old-age psychiatry services in nine English centres.

Interventions

There were three groups, (1) sertraline, (2) mirtazapine and (3) placebo, all with normal clinical care. The target dose for all participants was 150 mg of sertraline or 45 mg of mirtazapine per day.

Primary outcomes

Depression in dementia, measured by CSDD, and costs measured by the Client Service Receipt Inventory at 13 weeks.

Secondary outcomes and moderators

These included disease-specific health-related quality of life [Dementia Quality of Life (DEMQOL) and DEMQOL-Proxy]; generic quality of life [European Quality of Life-5 Dimensions (EQ-5D) interview administered to carer]; withdrawal from treatment; cognitive impairment (Mini Mental State Examination); medication adherence; adverse events; carer mental health [General Health Questionnaire version 12 (GHQ-12)]; carer quality of life (Short Form questionnaire-12 items version 2; SF-12v2); carer burden (Zarit Scale); behavioural disorder [Neuropsychiatric Inventory (NPI)]; and (at baseline) a dementia vascularity index (modified Hachinski scale).

Sample size

Initially a sample size of 507 was calculated to provide 90% power to detect a two-point CSDD difference [standard deviation (SD) 5; standardised effect size 0.4] for the sertraline–placebo and the mirtazapine–placebo comparisons at 13 weeks, and 86% power at 39 weeks.

Change to protocol

Owing to a call for extra funding following slower recruitment than predicted, the sample size needed for the trial was reassessed by statistical review by the Data Monitoring and Ethics Committee when there were 75 subjects available with 13-week follow-up data. The parameters of the sample size calculation were not changed, but the new target was calculated on the basis of reported values with greater precision than pre-study assumptions. An extended recruitment was agreed with a revised target of 339 participants.

Randomisation

Participants were allocated to placebo, sertraline or mirtazapine (1 : 1 : 1) through the Clinical Trials Unit (CTU) after baseline assessment and obtaining consent. The CTU database programmer independently undertook treatment allocation. Random allocation was stratified by centre and undertaken with a computer-generated randomisation sequence with randomly varying block sizes.

Blinding

The trial was double blind, with medication and placebo identical in appearance for each antidepressant. Referring clinicians and research workers completing assessments were kept blind to group allocation, as were patients and pharmacies. Statisticians were blind to group identity until after the analyses were completed.

Statistical methods

Significance was tested at 5%. Analyses were pragmatic, based on intention to treat. CSDD differences between treatment groups (sertraline–placebo and mirtazapine–placebo), were estimated with mixed linear regression models. Covariates were treatment group, baseline CSDD score, time and the stratification factor, and centre. A time-by-treatment interaction term was included to allow estimates at the individual time points to be summarised. The model for the CSDD incorporated random intercepts by participant. Model assumptions were checked by use of diagnostic plots. We compared categorical variables by use

of Fisher's exact test. We analysed secondary outcomes with mixed linear regression models with random participant intercepts and a time-by-treatment interaction term; covariates in the model were treatment group, baseline value of outcome, time, and treatment centre. NPI analyses utilised the generalised linear model framework, specifying a negative binomial distribution and logit link.

Health economics method

The primary economic evaluation was a cost-effectiveness analysis comparing differences in treatment costs for patients receiving sertraline, mirtazapine or placebo with CSDD score, over 0–13 weeks and 0–39 weeks. The secondary analysis was a cost–utility analysis using quality-adjusted life-years (QALYs) computed from the EQ-5D and societal weights. Both the primary and secondary economic evaluations were undertaken from the perspective of (a) health and social care agencies and (b) health, social care agencies and informal carers. Health and social care costs for 0–13 months and 0–39 months (and health, social care and costs of informal care costs for the parallel analysis from the broader perspective for the same time periods) were regressed in turn on treatment allocation, baseline cost, baseline CSDD and centre. To mitigate the effects of skewness, non-parametric bootstrapping methods were used to estimate 95% confidence intervals for mean costs. Estimates of bootstrapped mean cost and effectiveness were used to estimate an incremental cost-effectiveness ratio for each analysis. The value of health effects was then expressed in terms of QALYs. Uncertainty around the costs and effectiveness estimates was addressed by plotting cost-effectiveness acceptability curves.

Results

Trial recruitment

A total of 664 individuals were screened; 326 (49%) were randomised – 111 to placebo, 107 to sertraline and 108 to mirtazapine. Groups were evenly matched, and the majority of participants were female, with a mean age of 79 years; 146 (45%) were married.

Outcomes and estimation

Primary outcome: Cornell Scale for Depression in Dementia

The absolute change from baseline at 13 weeks was greatest for placebo, –5.6 (SD 4.7), compared with –3.9 (SD 5.1) for sertraline and –5.0 (SD 4.9) for mirtazapine. This difference was maintained through to 39 weeks, with change scores of –4.8 (SD 5.5) for placebo, –4.0 (SD 5.2) for sertraline and –5.0 (SD 6.1) for mirtazapine. The results from the linear-mixed modelling, after adjusting for baseline depression and centre, made clear that there was no evidence of a difference between sertraline and placebo or mirtazapine and placebo, on the CSDD score at 13 or 39 weeks. This analysis provides robust evidence of an absence of clinical effectiveness of the antidepressants tested here compared with placebo.

Secondary outcomes

There were fewer neuropsychiatric symptoms and higher carer-rated health-related quality-of-life (HRQL) scores (DEMQOL-Proxy) in participants given mirtazapine compared with sertraline; these differences did not persist to 39 weeks. Carers whose relatives were receiving placebo had higher HRQL scores at 13 weeks (SF-12v2 mental component score) and higher mental-health scores (GHQ-12) than did those whose relatives were on sertraline. Carers of participants in the mirtazapine group had better quality of life as measured by HRQL score (SF-12v2 mental component score) at 13 weeks than did those in the sertraline group.

Safety data

A total of 19 participants reported 240 adverse reactions: 29/111 (26%) in the placebo group had adverse reactions compared with 46/107 (43%) in the sertraline group ($p = 0.010$) and 44/108 (41%) in the mirtazapine group ($p = 0.031$; overall p-value for placebo vs either drug = 0.017). Overall, the number of serious adverse events reported did not differ between groups but more of these events were severe in

those on antidepressants compared with placebo ($p = 0.003$). Mortality did not differ between groups (five deaths in each group by 39 weeks).

Economic analyses

In the 0- to 13-week period, there were no differences in service use between the treatment groups reaching statistical significance. However, taking the whole 0- to 39-week period, it was striking that the mean number of hours per week spent by unpaid carers caring for patients in the placebo-treated group and the sertraline group was almost twice that for patients in the mirtazapine-treated group. This difference in unpaid carer time between the placebo and mirtazapine-treated group was statistically significant at the 5% level. On the secondary measure of outcome, the mean QALY gain at 39 weeks between placebo and sertraline was 0.03 (95% CI –0.09 to 0.03); between placebo and mirtazapine 0.05 (95% CI –0.10 to 0.10); and between mirtazapine and sertraline 0.02 (95% CI –0.03 to 0.07). There were no statistically significant differences in either the primary or secondary measure of outcome between groups at 13 or 39 weeks. After adjustment for baseline costs, CSDD score at baseline and site, there were no statistically significant differences in health and social care costs (or health, social care and unpaid carer costs) in any pair-wise comparison in either time period. Mirtazapine had a low likelihood (around 30%) of being more cost-effective than placebo if society was not willing to pay anything for a unit improvement in the CSDD depression score, with this rising to 80% if society was willing to pay £5000 for a unit improvement in CSDD score. In the secondary economic evaluation, where costs were considered alongside QALYs, mirtazapine was 89% likely to be more cost-effective than placebo even if society was willing to pay nothing for a QALY gain.

Conclusions

This is a trial with negative findings but important clinical implications. The data suggest that the antidepressants tested, given with normal care, are not clinically effective (compared with placebo) for clinically significant depression in AD. The data do not support the use of antidepressants as the first-line treatment of depression in AD.

As far as we are aware, this is the first study to explore the cost-effectiveness of mirtazapine and sertraline in treating depression in dementia. Our results show that mirtazapine and sertraline are not cost-effective compared with placebo as a treatment for depression in dementia when looking at the primary outcome of change in depressive symptoms. However, mirtazapine did halve unpaid carer time and therefore carer costs. So, when costs were considered alongside QALY gains, a different picture emerged. Mirtazapine had the highest likelihood of cost-effectiveness compared with sertraline and placebo.

We considered possible reasons for the finding that mirtazapine treatment had a good chance of being cost-effective compared with placebo or sertraline when the outcome under consideration is the QALY. The trend towards lower incremental costs for mirtazapine was driven by the statistically significantly lower unpaid carer inputs. The small improvements in quality of life for mirtazapine relative to the other treatments also contributed to the cost-effectiveness result, and can, perhaps, be mediated plausibly via the putative ability of mirtazapine to ameliorate sleep disturbances and anxiety. Improvements in sleep could potentially improve life quality and therefore patient-reported EQ-5D scores; they could also release carer time directly and so ameliorate an important source of carer distress. In this way mirtazapine might have a general effect, beneficial for both the patient and the carer, without exerting a specific antidepressant effect. The potential positive effects of mirtazapine seem to act more in the realm of general behavioural and psychological symptoms in dementia than depression per se.

The data from this study provide evidence to support antidepressants not being prescribed as a first-line treatment for people with depression in AD, who are referred to old-age psychiatry, for all but the most critical of cases (by reason, for example, of self-harm or other risk), as many cases will resolve with usual care and without sertraline or mirtazapine. Alternatives to antidepressants include the stepped

care, with 'watchful waiting', which is advocated currently as best practice for the general treatment of depression (without dementia) in the community. The first step is provision of 'low-intensity psychosocial interventions', with more complex psychosocial interventions as an alternative to antidepressants at the next stage of severity. Those recruited into the trial will have received non-drug 'treatment as usual' provided by the community mental-health teams to whom they were referred. This will have included a broad range of supportive and problem-solving interventions, commonly delivered by a community psychiatric nurse, often in their own household. This will have focused on problems encountered by the person with dementia and the carer, covering aspects of dementia as well as depression, and ranging in intensity from low to high as needed. Identifying which components of 'usual care' may be effective is an important area for future research. Other explanations for the observed changes for all cases over time include regression to the mean, and Hawthorne and placebo effects. As we find no evidence to support the use of antidepressants, we suggest that potential cases might be more appropriately managed by specialist services that are able to offer non-drug interventions for depression, perhaps avoiding the use of medication with potential for adverse reactions.

From the data generated we formulated the following recommendations for future work.

1. The secondary analyses presented here suggest that there would be value in carrying out a placebo-controlled trial of the clinical effectiveness and cost-effectiveness of mirtazapine in the management of Behavioural and Psychological Symptoms of Dementia.
2. A conclusion from this study is that it remains both ethical and essential for trials of new medication for depression in dementia to have a placebo arm.
3. Further research is required to evaluate the impact that treatments for depression in people with dementia can have on their carers, not only in terms of any impacts on their quality of life, but also the time they spend care-giving.
4. There is a need for research into alternative biological and psychological therapies for depression in dementia. These could include evaluations of new classes of antidepressants (such as venlafaxine) or antidementia medication (e.g. cholinesterase inhibitors).
5. Research is needed to investigate the natural history of depression in dementia in the community when cases are not referred to secondary care services.
6. Further work is needed to investigate the cost modelling results in this rich data set, investigating carer burden and possible moderators to the treatment effects.
7. There is scope for reanalysis of the primary outcome in terms of carer and participant CSDD results.

Trial registration

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The 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 programme 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'.

For more information about the HTA programme please visit the website: http://www.hta.ac.uk/

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