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

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AS	Alzheimer's Society
BADL	Bristol Activities of Daily Living
BPSD	Behavioural and Psychological Symptoms of Dementia
CEAC	Cost-Effectiveness Acceptability Curves
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CSDD	Cornell Scale for Depression in Dementia
CSRI	Client Service Receipt Inventory
DEMQOL	Dementia Quality of Life
DeNDRoN	Dementia and Neurodegenerative Disease Research Network
DIADS	Depression in Alzheimer's Disease Study
DMEC	Data Monitoring Committee
DSM	Diagnostic & Statistical Manual
ENT	Ear, Nose & Throat
EQ5D	EuroQol version 5D
GHQ-12	General Health Questionnaire version 12
GP	General Practitioner
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
MH&N CTU	Mental Health & Neurosciences Clinical Trials Unit
MHRN	Mental Health Research Network
MMSE	Mini-Mental State Examination
NASSA	Noradrenergic and Specific Serotonergic Antidepressant
NB	Net Benefit
NHS	National Health Service
NICE/SCIE	National Institute for Health and Clinical Excellence/ Social Care Institute for Excellence
NIHR	National Institute for Health Research
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
OR	Odds Ratio
QALY	Quality Adjusted Life Years
QRD	Quality Research in Dementia
RCT	Randomised Controlled Trial
SADD	Study of Antidepressants for Depression in Dementia
SD	Standard Deviation
SE	Standard Error
SES	Standardised Effect Size
SF-12	Short Form 12 Health Survey
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TSC	Trial Steering Committee
UK	United Kingdom
VAS	Visual Analogue Scale

EXECUTIVE SUMMARY

Background

Dementia is one of the most common and serious disorders in later life. Worldwide it affects 35 million, 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 £17 billion per year; worldwide, its annual cost is $600 billion 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 over 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.

The Cochrane review *Antidepressants for treating depression in dementia* identified only three studies, comprising 107 subjects that 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 tricyclics "drugs not commonly used in this population" (because anticholinergic side effects may negatively affect cognition, and cardiac side effects); only one used the most commonly used class (SSRIs). None covered newer classes of antidepressants and all were of short duration. Subsequently, the DIADS-II study compared 67 people prescribed sertraline, with 64 given placebo. In contrast to 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 NIHR 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

Multi-centre parallel group double-blind placebo-controlled RCT 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 NINCDS/ADRDA criteria for probable or possible Alzheimer's Disease and co-existing depression of at least four weeks duration with a CSDD of 8+. The only exclusions were: too critical for randomisation (eg suicide risk); absolute contra-indication 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 was for all participants was 150mg sertraline or 45mg mirtazapine per day.

Primary outcomes: Depression in dementia, measured by CSDD, and costs measured by the Client Service Receipt Inventory (CSRI) at 13 weeks.

Secondary Outcomes and moderators: These included: disease-specific health related quality of life (DEMQOL and DEMQOL-Proxy); generic quality of life (EQ-5D interview administered to carer); withdrawal from treatment; cognitive impairment (Mini Mental State Examination MMSE); medication adherence; adverse events; carer mental health (General Health Questionnaire GHQ-12); carer quality of life (SF-12v2); and 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 2 point CSDD difference (SD 5; SES 0.4) for the sertraline/placebo and the mirtazapine/placebo comparisons at 13 weeks, and 86% power at 39 weeks.

Change to protocol: Due 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 (DMEC) 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 done 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 an 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, 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%CIs for mean costs. Estimates of bootstrapped mean cost and effectiveness were used to estimate an incremental cost-effectiveness ratio (ICER) for each analysis. The value of health effects was then expressed in terms of quality-adjusted life years (QALYs). Uncertainty around the costs and effectiveness estimates was addressed by plotting cost-effectiveness acceptability curves (CEAC).

Results

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

Outcomes and estimation - primary outcome: CSDD The absolute change from baseline at 13 weeks was greatest for placebo -5.6 (SD 4.7), compared to -3.9 (5.1) for sertraline and -5.0 (4.9) for mirtazapine. This was difference was maintained through to 39 weeks, change scores of -4.8 (5.5) for placebo, -4.0 (5.2) for sertraline and -5.0 (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-12 mental component score) and higher mental health scores (GHQ-12) than did those on sertraline. Carers of participants in the mirtazapine group had HRQL scores (SF-12 mental component score) at 13 weeks than did those in the sertraline group.

Safety data: 119 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 0-13 week period, there were no differences in service use between the treatment groups reaching statistical significance. However, taking the whole 0-39 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 were 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 (-0.09 to 0.03); between placebo and mirtazapine 0.05 (-0.10 to 0.01); and between mirtazapine and sertraline 0.02 (-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 pairwise comparison in either time period. Mirtazapine had a low likelihood (around 30%) of being more cost-effective than placebo if society were not willing to pay anything for a unit improvement in the CSDD depression score with this rising to 80% if society were willing to pay £5,000 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 Alzheimer's disease. The data do not support the use of antidepressants as the first line treatment of depression in Alzheimer's disease.

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 to 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 to sertraline and placebo.

We considered possible reasons for the finding that mirtazapine treatment had a good chance of being cost-effective compared to 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 (BPSD) 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 Alzheimer's disease 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' that 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 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 focussed on problems encountered by the person

with dementia and the carer, covering aspects of dementia as well 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 use of antidepressants, it suggests 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.

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CHAPTER 1: INTRODUCTION

Scientific background

Dementia is one of the most common and serious disorders in later life with a prevalence of 5% and an incidence of 2% per year in the over 65s.[1,2] Worldwide it affects 35 million, and this will treble by 2050.[3] In the UK there are 750,000 people with dementia currently[4] and 200,000 new cases every year. It causes irreversible decline in global intellectual, social and physical functioning. Abnormalities in behaviour, insight and judgement are part of the disorder, as are neuropsychiatric symptoms such as psychosis, anxiety and depression. The economic cost of caring for people with dementia is immense. In the UK the costs of dementia are around £17 billion per year[4], greater than stroke (£3 billion), heart disease (£4 billion) and cancer (£2 billion).[5] Worldwide, its annual cost is $600 billion, 1% of world GDP,[6] and these are set to at least triple in the next 20 years.[6,7] The need to improve care for people with dementia is a policy priority.[8.9,10,11] More importantly, the negative impacts of dementia on those with the disorder, in terms of deteriorating function, and on carers[12,13] are profound. Dementia has a devastating impact across culture, gender, ethnicity and class.

Depression is common in dementia with prevalence over 20%,[14,15] causing distress, reducing quality of life, exacerbating cognitive and functional impairment, increasing mortality, and increasing carer stress and depression.[16,17,18] 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.

We searched the PubMed and Cochrane Library databases to March 1, 2011, without language restrictions for full articles reporting randomised controlled trials, systematic reviews, and meta-analyses with the search terms "depression", "dementia", "Alzheimer's disease", antidepressant", "meta-analysis", and "CSDD". We excluded trials without recognised depression outcome measures, placebo controls, or specified thresholds for depressive disorder. We identified one Cochrane review[19] and three systematic reviews.[20,21,22]

The Cochrane review completed in July 2002 *Antidepressants for treating depression in dementia*[19] identified six studies with 739 subjects meeting inclusion criteria ("all relatively unconfounded, double-blind, randomized trials comparing any antidepressant drug…with placebo, for patients diagnosed as having dementia and

diagnosed as having a depression according to established criteria"). Only three studies, comprising 107 subjects, had data that could be subject to a meta-analysis of efficacy. Petracca et al[23] studied 24 subjects in a neurological out-patient clinic in Argentina in a double blind placebo controlled crossover trial of clomipramine (a tricyclic antidepressant [TCA]) with two 6 week treatment periods with a 2 week washout period. There was a mean change of -10.7 on the Hamilton depression scale in the intervention group and –4.5 in the control group, an equivocal outcome. Reifler et al[24] selected 61 subjects from two university outpatient clinics in an 8 week double blind trial of imipramine (a TCA). The study showed no treatment effect. The third trial included[25] was an interim analysis of data on 22 subjects that subsequently were reported fully in Lyketsos et al[26]. These final data from DIADS were not available to the Cochrane review. In the final study 44 subjects were recruited from a single university out-patient clinic into a 12 week double-blind placebo controlled trial of sertraline (a specific serotonin reuptake inhibitor [SSRI]). An effect size of 0.51 was reported with a mean change of -10.5 on the Hamilton depression scale in the intervention group and –4.5 in the control group and –9.9 and –3.2 in on the Cornell Scale for Depression in Dementia (CSDD[27]). Other than the further data on the additional 22 cases reported in Lyketsos et al,[26] and the groups subsequent DIADS-II study[28] which was negative and which is discussed below, we are not aware of any other studies published since that would have met the criteria for inclusion in the Cochrane review.

The Cochrane review concluded that, despite its clinical seriousness, there was only weak evidence of the effectiveness of antidepressants in dementia. Two studies used TCAs "drugs not commonly used in this population" (because anticholinergic side effects may negatively affect cognition, and cardiac side effects); only one used the most commonly used class (SSRIs). None covered newer classes of antidepressants and all were of short duration. Lyketsos et al[26] acknowledged the need for research into the efficacy of antidepressants in a wider range of depression type and severity, longer-term treatment, and the comparative efficacy of different classes of antidepressants. They therefore completed a follow up study, the DIADS-II study. This compared 67 people prescribed sertraline with 64 given placebo. In contrast to DIADS, they found no benefit whatsoever of sertraline at 12 or 24 weeks and concluded that this was not a function of depression severity, depression type or severity of dementia.[28,29]

One systematic review[20] used a different quality assessment and included data from five studies of 165 participants, and concluded that antidepressants were better than

was placebo for treatment response (odds ratio [OR] 2·32, 95% CI 1·04–5·16) and remission of depression (2·75, 1·13–6·65) with rates of discontinuation equivalent to placebo. This did not include the DIADS-II data. The positive message of the meta-analysis of the 2010 systematic review[21] is questionable because, although it includes the DIADS-II data,[28,29] it seems to count the data from the first DIADS trial twice (ie, by treating the interim[25] and the final trial data[26] as separate datasets when the first is a subset of the second). Finally, the 2011 study[20] concluded that the efficacy of antidepressants in people with depression and dementia is not established. The reviews and meta-analyses taken together are not conclusive but all reported that limitations of previous trials were their small sizes, low numbers of participants taking drugs that were used in clinical practice, and short follow-up.

It is clear that the subjects recruited into all the trials discussed above were highly selected and so there may be limitations in the generalisability of the data derived from them. One element of this is the severity of depression recruited, with Lyketsos et al[26] and Reifler et al[24] requiring depression to meet DSM criteria for major depressive episode. Such disorders form only a small proportion of clinically significant depression requiring intervention in older adults in the community.

All of these studies except DIADS-II, were of short duration, and so could not tackle the crucial issue of whether there is longer term benefit associated with antidepressant treatment. It is unclear whether the differential efficacy between the published studies relates to the choice of antidepressant, differences in study design and power or chance variation. Importantly, the literature does indicate that the successful resolution of depression may be associated with cognitive and functional improvements[30]. There are however several cautions. For example, one study of the tricyclic antidepressant imipramine indicated that active treatment increased cognitive impairment and disability, whilst several studies of falls indicate that most antidepressants increase risk of falling. In addition, there have been safety concerns relating to the SSRI sertraline and gastrointestinal bleeding 31 and the SSRI paroxetine and withdrawal.

Despite the equivocal evidence, current practice is to use antidepressants, often sertraline, as a first line treatment for depression in dementia. The Quality Standards Subcommittee of the American Academy of Neurology[32] cited only “moderate clinical certainty” for antidepressants in treating depression in dementia, but concluded that “SSRIs may offer some benefit with greater tolerability”. A UK primary care guideline suggests antidepressants as the only form of management for depression in

dementia[33] and the UK NICE/SCIE Clinical Guideline on Dementia[34] also advocates antidepressants for depression in dementia.

Given limited evidence in this clinically important area, the Health Technology Assessment (HTA) Programme of the UK NIHR 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.

Explanation of rationale

Experimental – Inclusion of an arm of the study using tricyclic antidepressants
As discussed above, there are unanswered questions concerning what class of antidepressant to choose and how long to treat. This trial was designed to attempt provide best-quality data on all these clinically important areas.

One possible area of contention is the appropriateness of including a tricyclic antidepressant (TCA) arm in the trial. This was referred to in the original research brief. Prior to our initial submission we carried out a local consultation with people with dementia, family carers and clinicians in London, Manchester and within the Alzheimer's Society. The findings of this exercise were clear. Patients, carers and clinicians all believed that it would be unacceptable to randomise people with dementia to medication with a predictable set of negative (anticholinergic eg constipation, increased confusion, blurred vision, low blood pressure, drowsiness) side effects even given the fact that the competing classes of medication had their own profile of side effects.

In addition, clinicians reported to us that their clinical practice was not to use TCAs as a first line treatment for depression in dementia and that they believed people with dementia to be at a higher risk of harm from TCA side effects than people without dementia. They therefore raised questions of the clinical acceptability of a trial that included the possibility of randomisation to a TCA. To be successful we needed a large number of clinical teams to take part in case finding and if the trial were to generate real effectiveness data then these participants needed to be an unbiased sample of all potential prescribers. On these grounds we therefore decided not to include a tricyclic antidepressant arm but instead to compare the clinical and cost-

effectiveness (including discontinuation and adverse events) of examples of the two classes of antidepressants most in use.

In the subsequent feedback from the HTA Commissioning Board we were invited to reconsider our decision not to include a TCA arm. We therefore consulted the Alzheimer's Society Quality Research in Dementia (QRD) Network. This was a panel made up of people with dementia and their carers that advised the UK Alzheimer's Society (AS) on research issues. The consultation was carried out by the AS Director of Research (Prof Clive Ballard). He consulted regional co-ordinators of the Alzheimer Society's (QRD) and individual members of the network, representing the views of 45 QRD members; most with experience of caring for someone with dementia who has been treated with antidepressants. The purpose was to inform them about key aspects of the study, in particular whether it was appropriate to include TCAs as one of the treatments. All but one of the people responding strongly expressed the view that TCAs were an inappropriate treatment for people with dementia, describing a number of personal experiences where serious falls, increased confusion, urinary retention and other adverse events had resulted in a serious detrimental impact to the quality of life of the person with dementia.

We also consulted clinicians through the potential collaborating centres more widely and again there was a near unanimous view that it was not clinically supportable to initiate people with depression in dementia on a TCA. They also reported that the existence of such a possibility in randomisation would discourage them from entering patients into the trial. At the very least it was therefore likely that there would be substantial selection bias (both in patient acceptability and clinician referral) introduced by the inclusion of a TCA arm. We therefore decided not to include a TCA arm.

Experimental – Choice of antidepressants

The selection of the best candidate antidepressants for this trial is not straightforward. Cost and power considerations dictate that an optimal design should include two active antidepressant treatments and a placebo. There are however several cautions. One previous small RCT has indicated equivocal benefit with the TCA clomipramine,[23] but other data indicate marked side effects and exacerbation of disability associated with TCA treatment. For example, one study of the tricyclic antidepressant imipramine, indicated that active treatment increased cognitive impairment and disability,[24] whilst several studies of falls indicate that most

antidepressants increase falls risk.[35] In addition, there have been safety concerns with SSRIs, with respect to withdrawal effects and the potential risk of self-harm.

Within this framework, the choice of specific antidepressant agents required careful consideration. For example, the best evidence of efficacy in people with dementia at the time of the trial design was for the SSRI sertraline since that was the compound used in the original DIADS study.[26] But this was a very small trial and other SSRIs such as citalopram have also been reported to be effective in treating depression in later life, including those with dementia, but in less well designed studies.[36] Citalopram may have less interactions with other drugs than other SSRIs and people with dementia are usually recipients of polypharmacy. The most effective antidepressant in people without dementia available at that time was probably venlafaxine,[37] but there are no RCTs in people with dementia and there are potential concerns regarding side effects in these individuals.[38] A newer antidepressant, mirtazapine, appeared to have a good safety profile and a different mode of effect and was becoming widely used in clinical practice to treat depression in people with dementia, but had not been evaluated in an RCT for this indication.

In order to design and cost a trial of this sort there is a need to identify the compounds to be tested. We therefore made the decision that our trial design should include sertraline (the SSRI with the best evidence and which would be off licence by the end of the trial) and mirtazapine (the novel antidepressant with the least safety concerns). The doses chosen reflect common clinical practice for the treatment of depression in dementia and (in the case of sertraline) direct trial evidence,[26] with higher doses than those suggested here (ie over 150mg of sertraline or 45mg of mirtazapine) being seen as less appropriate in people with dementia as well as depression.

Controls – use of placebo

The research brief referred to comparison with standard care. Despite the evidence base, standard care for depression in dementia is the provision of antidepressants with SSRIs the most commonly used drugs.[32] Standard secondary care (and it was stipulated in the brief that the study should be people referred to secondary care) is however much more than just medication. It involves a detailed multidisciplinary assessment of the person with dementia and their family carers with the generation of an individualised care package for each, often with continuing monitoring and follow-up.[39] We therefore developed a study design whereby all participants receive

full standard care with only the antidepressant element subject to investigation against placebo and between classes of compound.

We concluded that at the time of the trial design, that there was little convincing evidence that anti-depressant treatments were more effective than placebo in treating depression in dementia in real-world clinical practice. As discussed above, the data available were generally from small-scale studies of highly selected groups of patients with depression in dementia. The research brief required a trial which could take the evidence base and clinical practice forward significantly. In these circumstances we came to the belief that a placebo group was not just ethical, but essential. If antidepressants were indeed not effective, then the placebo group might do better as they should have had fewer side effects. We carried out a further consultation exercise on the acceptability of the inclusion of a placebo group with local people with dementia, family carers and clinicians. They were supportive of the strategy of using placebo in these circumstances as long as its use was minimised and that the information derived from the trial would yield a definitive answer.

Run-in period

One possible element of a trial such as this is the inclusion of a run in period. The potential value of this is to identify a group of people more likely to comply with subsequent data collection (ie to minimise loss to follow-up) and to identify a group of people with depression who are less likely to spontaneously recover.[40,41,42] It is also possible that depression scores may be reduced by psychosocial interventions,[43] some of which may be provided as part of routine care. The result of these factors is a potentially high placebo response rate in clinical trials. The research brief was clear in its call for an evaluation of antidepressants in routine clinical practice and it is not routine clinical practice to precede the prescription of antidepressants for depression in dementia with a trial of a non-pharmacological treatment such as exercise. Instead we proposed the clinically relevant inclusion criterion for the trial that the depression should have been present for at least 4 weeks.

Specific Objectives

The primary objective was to determine the clinical and cost effectiveness of an SSRI (sertraline) and a Noradrenergic and Specific Serotonergic Antidepressant (NASSA, mirtazapine) in reducing depression (measured by CSDD) 13 weeks post randomisation compared with placebo.

Secondary objectives included: clinical effectiveness at 39 weeks; differences in adverse events; other outcomes (eg quality of life, cognition, carer burden, carer quality of life); and the influence of clinical characteristics (eg dementia severity, dementia type, depression type, depression severity, and neuropsychiatric symptoms).

CHAPTER 2: METHODS

Trial design

A multi-centre parallel group double-blind placebo-controlled RCT of the clinical effectiveness of two antidepressants, mirtazapine with 13 and 39 week follow up (1:1:1 allocation).

Participants

Eligibility

This was a pragmatic trial, with inclusion criteria designed to mirror clinical practice closely. Those eligible met NINCDS/ADRDA criteria for probable or possible Alzheimer's Disease[44] and co-existing depression of at least four weeks duration. A local research worker then assessed their depression severity using the CSDD.[27] Those scoring 8+ were eligible for the trial. The only exclusions were: clinically too critical for randomisation (eg suicide risk); absolute contra-indication to trial medications; currently taking antidepressants; being in another trial; and having no family or professional carer to give collateral information.

Settings and location

Participants were recruited from community old age psychiatry services in nine English centres (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, North London, Southampton, and South London & Kent).

Interventions

There were three groups: (1) sertraline, (2) mirtazapine, and (3) placebo, all with normal clinical care. The target dose was for all participants was 150mg sertraline or 45mg mirtazapine per day. Drugs and their placebo were identically presented with participants aiming to take six tablets orally once a day (up to three sertraline 50mgs or sertraline placebo; and up to three mirtazapine 15mgs or mirtazapine placebo).

Outcomes

Co-primary Outcomes

Depression in dementia, measured by CSDD,[27] and costs measured by the Client Service Receipt Inventory (CSRI)[45] at 13 weeks.

Secondary Outcomes and moderators

These included: disease-specific health related quality of life (DEMQOL and DEMQOL-Proxy);[46] generic quality of life (EQ-5D interview administered to carer);[47] withdrawal from treatment; cognitive impairment (Mini Mental State Examination MMSE);[48] medication adherence; adverse events; carer mental health (General Health Questionnaire GHQ-12)[49]; carer quality of life (SF-12v2);[50] and carer burden (Zarit Scale);[51] behavioural disorder (Neuropsychiatric Inventory NPI);[52] and (at baseline) a dementia vascularity index (modified Hachinski scale).[53]

Data Entry

The data arising from each baseline or follow-up interview were entered at each centre via the internet using the InferMed Macro electronic data capture system by the researchers as the study proceeded. The data entry system used was Macro version 3.0. Prior to data base lock, all of the primary outcome measures and 10% of all other outcome measures were source data verified. Table 1 summarises the measures that were used at each assessment time point.

Table 1: Research assessment by time point

	Informant	Screening	Baseline & randomisation	Wk 4	Wk 8	Wk 13	Wk 39	Treatment discontin[a]
Verbal consent to referral to Recruiting PI	Patient / Carer	X By Referring Investigator						
Eligibility assessment	Referring & Recruiting PI/RW	X						
Informed consent	Patient / Carer	X						
NINCSD-ADRDA (for dementia)	Referring PI	X						
Modified Hachinski Ischemic Scale	Carer		X					
DSM-IV (for Depression)	Carer		X			X	X	
Olin (Depression in Dementia)	Carer		X			X	X	
Cornell Scale for Depression in Dementia (CSDD)	Patient/ Carer		X	X	X	X	X	X
Participant demographics	Carer		X					
Carer demographics	Carer		X					
Client Service Receipt Inventory (CSRI)	Carer		X			X	X	
DEMQOL	Patient		X			X	X	
DEMQOL-Proxy	Carer		X			X	X	
EuroQol (Participant)	Patient		X			X	X	
EuroQol (Carer)	Carer		X			X	X	
SF-12 v2 (Carer)	Carer		X			X	X	
Standardised Mini-Mental State Examination (MMSE)	Patient		X			X	X	
GHQ-12 (Carer)	Carer		X			X	X	
Zarit Carer Burden Scale	Carer		X			X	X	
Neuropsychiatric Inventory (NPI)	Carer		X			X	X	
Bristol Activities of Daily Living (BADL)	Carer		X			X	X	
Carer global impression	Carer					X	X	
Medical history	Carer		X					

Sample size

Initially a sample size of 507 was calculated to provide 90% power to detect a 2 point CSDD difference (standard deviation [sd] 5; SES 0.4) for the sertraline/placebo and the mirtazapine/placebo comparisons at 13 weeks, and 86% power at 39 weeks. This allowed 20% loss to follow-up, correlation between baseline and outcome CSDD ≥ 0.6, and up to 12.5% of participants to either drop-out or drop-in using an analysis of covariance with 2-sided 5% significance levels. This allowed for two-sided 95% confidence intervals for the difference in the proportion of adverse events between the groups of (a clinically significant) 10%.

Change to protocol

Due 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 (SD 5; SES 0·4), but the new target was calculated on the basis of reported values that had greater precision than did the pre-study assumptions. An extended recruitment period was agreed with a revised target of 339 participants for the sample (113 in every group). This change involved unmasking of a statistician (Clare Rutterford, Clinical Trials Unit, King's College London, UK), who was not involved in the final analyses, to the identity of patients in the placebo group.

Randomisation

Participants were allocated to placebo, sertraline or mirtazapine (1:1:1) through the Mental Health & Neurosciences Clinical Trials Unit (MH&N CTU) after baseline assessment and obtaining consent. The MH&N CTU database programmer independently undertook treatment allocation. Random allocation was stratified by centre and done with a computer-generated randomisation sequence with randomly varying block sizes (block sizes of 3 or 6). Allocation was physically carried out during working hours Monday to Friday

Blinding

The trial was double-blind with medication and placebo identical in appearance for each antidepressant. Referring clinicians and research workers completing baseline and follow-up 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

The statistical analysis plan was finalised and approved by the Trial Steering and the Data Monitoring and Ethics Committees. Significance was tested at 5% level for all

analyses. Analyses were completed in Stata 11.0. Analyses were pragmatic, based an intention to treat sample.

Descriptive statistics

All baseline data were summarised by treatment groups. Only descriptive statistics were utilised, no formal statistical comparisons were undertaken. Continuous variables were reported as means and standard deviations (SD), categorical variables are presented as frequencies (n) and percentages (%).

The primary analyses

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, 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 did modelling with the assumption that data were missing at random, and included predictors of missing data (treatment group and centre) in the modelling. We used a logistic model to assess predictors of missing data (examination of all baseline clinical and demographic variables).

Secondary Analyses

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. The more detailed NPI analyses utilised the generalised linear model framework; specifying a negative binomial distribution and logit link. The modelling was cross sectional at each time point (13 and 39 weeks), covariates in the model were treatment group, baseline value of outcome and treatment centre. All analyses results are summarised at 13 weeks and 39 weeks with two-sided 95% Confidence Intervals (CIs)

Health Economics – Methods

Economic evaluation

The primary economic evaluation was a cost-effectiveness analysis comparing differences in treatment costs for patients receiving sertraline, mirtazapine or placebo with differences in effectiveness as measured by the primary outcome, total CSDD score, over two time periods: 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 over those same periods. 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. A measure of quality of life was appropriate for the secondary analysis as it was recognised that trial medication not only has a potential impact on depressive symptoms, but also may affect areas of functioning including self-care and usual activities.

Resource use

Resource use data for each person were collected over a retrospective period of 6 months before randomisation. At 13 weeks, follow-up data were collected retrospectively for a 3-month period and at 39 weeks for a retrospective period of 6 months. Services and support received by the study participants were recorded on a resource use questionnaire adapted from the Client Service Receipt Inventory (CSRI),[54] including inpatient stays, outpatient attendances, day hospital treatment, visits to social clubs, meals at lunch clubs, day care visits, hours spent in contact with community-based professionals such as community teams for older people, community psychologist, community psychiatrist, general practitioners, nurses (either practice, district or community psychiatric), social workers, occupational therapist, paid home help or care workers, physiotherapist. The study also collected data on the use of voluntary organisation services such as volunteer support, befriending and telephone care-line support, and also on unpaid support provided by friends and relatives. Contacts made with voluntary support and support provided by friends and relatives were also measured in physical units, such as hours of care support time. The prescribed daily doses for the medications were calculated from the trial medication log, and prescribing periods were weighted to the changing dose regime.

Unit costs

All unit costs were estimated at 2009/2010 prices and were collected from sources in the public domain. Unit costs are summarised in Table 2. Costs per unit of

measurement for each type of service (such as per inpatient day, per appointment, per attendance, per visit or per contact with health and community based professionals including voluntary services) were taken from Curtis.[55] The National Health Service Schedule of Reference Costs[56] was used to estimate the cost of outpatient attendances. The unit cost of medication was obtained from the British National Formulary.[57]

We collected information on the volume and nature of informal care inputs, mindful of the difficulties of measuring such dimensions and of their interpretation as inputs to the care process. Costs were attached to informal care inputs using a replacement cost – the unit cost of a paid local authority home care worker.[55] This approach allowed us to quantify how much it would cost to replace the informal carer with the services from the market. In sensitivity analyses we examined whether the cost-effectiveness results would change under other assumptions.

Table 2 Unit cost for 2009-2010

Service	Unit cost (£)	Source
Inpatient (bed days)	299	Curtis 2010[55]
Day hospital (attendance)	50-205	NHS Reference costs 2009-10[56]; Curtis 2007[58]; Curtis 2010
Outpatient (appointment)	21-165	NHS Reference costs 2009-10
Accident and emergency (attendance)	37; 97	Curtis 2010
General practitioner (per surgery consultation)	28	Curtis 2010
Geriatrician (min)	1.83	Curtis 2010
Nurse (min) [1]	0.43-0.52	Curtis 2010
Occupational therapist (min)	0.65	Curtis 2010
Community psychiatrist (min)	1.83	Curtis 2010
Counsellor (min)	0.57	Curtis 2010
Psychologist (min)	1.20	Curtis 2010
Chiropodist (contact)	0.37	Curtis 2010
Social worker (min)	0.67	Curtis 2010
Care manager (min)	0.82	Curtis 2010
Home care worker/care attendant (min)	0.35	Curtis 2010
Sitting scheme (min)	0.45	Curtis 2010
Self-help group (min)	0.57	Curtis 2010

Meals on wheels (meal)	4.8	http://www.ic.nhs.uk/webfiles/publications/009_Social_Care/pss0910expfinal/pss0910updateOct2011/Personal_Social_Services_Expenditure_Report_2009_10.pdf
Dentist (min)	2.90	NHS Reference costs 2009-10
Optician (min)	0.48	Individual calculation [2]
Day care (day)	42-66	Curtis 2010
Lunch club (meal)	7	http://cash-online.org.uk/content/1/6/3/ ; uprated using the Consumer Price Index (CPI)
Social club (session)	5	Cost of adult social club at 2004/05 uprated using the pay and prices inflator (Curtis 2010)

Notes:

1. Practice nurse, district nurse health visitor, community psychiatric, cardiac nurse, incontinence nurse
2. There is a recommended fee payable to for ophthalmic medical practitioners who administer sight tests, however Optometrists undertake the majority of tests. The salaries of Optometrists can vary depending on the setting in which they practice (private or hospital or combination of the two). The range of typical salaries in private practice based on salary data collected June 2009 (http://www.prospects.ac.uk/optometrist_salary.htm) was £19,500 - £28,000 while in hospital optometrist are usually covered by the Agenda for Change pay scale consisting of nine pay bands. Typical salaries for the pre-registration year start at £18,152 (band 4). Typical starting salaries range from £25,472 - £34,189 (band 6). Specialist optometrists can earn £30,460 - £40,157 (band 7) and principal optometrists £38,851 - £55,945 (band 8a/8b).Typical salaries for consultant optometrists range from £54,454 - £80,810 (band 8c/8d). Working hours are usually nine to five thirty, Monday to Saturday. Hours worked can vary but Optometrist generally work 38 hours per week. The average salary for private practice was used. The cost per hour was estimated based on 41 weeks per annum, 38 hours per week.

Cost estimation

Three main categories of costs were analysed: medication costs, aggregated health and social care costs (primary care and hospital outpatient visits, inpatient admissions and community-based health and social care) and cost of time spent care-giving by relatives and friends. Cost were categorised in this way to facilitate the comparison of costs alongside measures of effectiveness from the perspectives for the economic analysis previously defined. The costs of services and support used by patients were derived by combining medication, health and social care resource utilisation data with estimated unit costs. Costs were calculated for the periods 0-13 weeks and for the period 0-39 weeks.

Statistical analysis

Cost data were analysed in a similar way to the effectiveness data. 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 skew-ness, non-parametric bootstrapping methods – which avoid the distributional assumptions of parametric testing by use of re-sampling – were used to estimate 95% CIs for mean costs.

Where the bias-corrected 95% CIs of between-group change scores excluded zero, they could be judged to be significant at p=0·05.

Estimates of bootstrapped mean cost and effectiveness were used to estimate an incremental cost-effectiveness ratio (ICER) for each analysis. The incremental cost-effectiveness ratio for each replication was calculated as [($cost_b$ – $cost_a$)/ ($effect_b$ – $effect_a$)], which summarises the cost difference between two treatments per incremental difference in the outcome (CSDD and EQ-5D in turn). The EQ-5D was measured directly from patients – as recommended by NICE guidelines (2008) – and weighted by a valuation of changes in quality of life reported from UK population data. The value of health effects was then expressed in terms of quality-adjusted life years (QALYs). The ratio statistic compared the treatments in terms of observed differences in costs and effects, regardless of whether the difference in costs and effects were statistical significant.

Uncertainty around the costs and effectiveness estimates was addressed by plotting cost-effectiveness acceptability curves (CEAC). A CEAC assesses trade-offs between costs and outcomes, showing the likelihood of each of the two medications in turn being seen as cost-effective relative to the other or relative to placebo, given different (implicit monetary) values placed on incremental outcome improvements. In this *net benefit approach*, monetary values of incremental effects and incremental costs for each case are combined, and the net benefit derived as:

$NB = \lambda \times (effect_b - effect_a) – (cost_b – cost_a)$,

Where: a = control, b = drug treatment, NB = net benefit, λ = willingness to pay for unit improvement in CSDD-depression severity score or an additional QALY.

The impact on costs given uncertainty around the value attached to informal care inputs was assessed in one-dimensional sensitivity analysis.

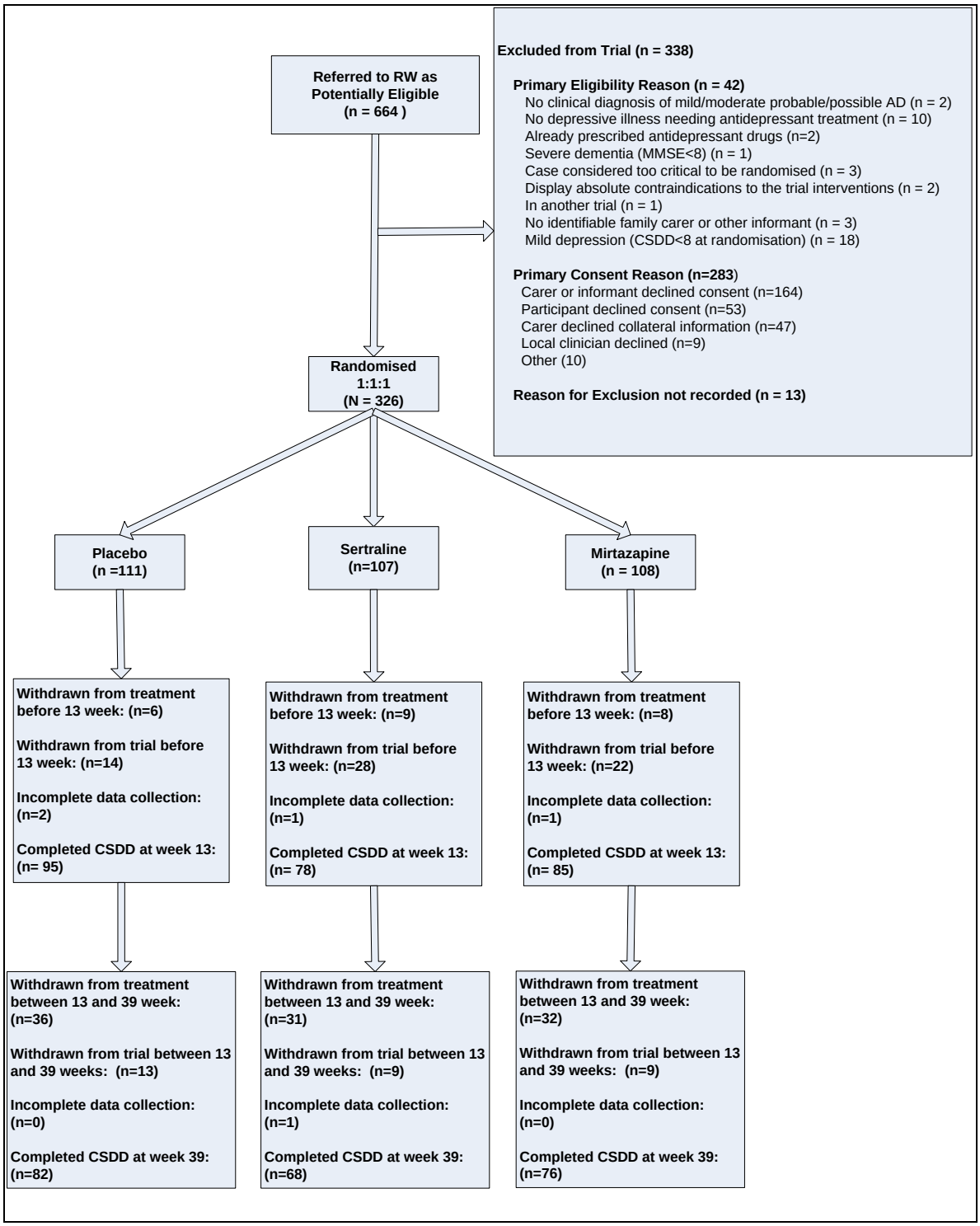
All analyses were done in Stata (version 11) and SPSS 17.

CHAPTER 3: RESULTS

Participant flows

The CONSORT diagram shows the flow of participants through the trial, Figure 1.

Figure 1: Participant flows in the HTA-SADD Trial



Withdrawal from treatment implies that the participant remains in the trial. Withdrawal from the trial implies the participant withdrawal from the trial and treatment. These two categories

are mutually exclusive. MMSE = mini-mental state examination. CSDD = Cornell scale for depression in dementia.

Trial Recruitment

Over the course of the trial there were 9 recruiting sites, all in the UK. These were Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, north London, Southampton and South London. Randomisation was stratified by site; all sites successfully recruited. Recruitment began in December 2006 and ended in January 2010. Follow-up interviews were completed by October 2010. In total, 664 individuals were screened as potential participants, of these 326 (49%) were randomised. The overall recruitment rate is shown in Figure 2. The number of participants recruited per site ranged from 7 to 60 (Table 3).

Figure 2: Cumulative recruitment over the trial period (revised target)

Baseline Data

In total 326 participants were randomised in the trial; 111 to the placebo arm, 107 to the sertraline arm and 108 to the mirtazapine group. All participants completed the CSDD baseline questionnaire. Baseline demographics are summarised for

participant and carers. The total number of collected questionnaires completed is featured. Table 3 shows the participant and carer demographics, data collected on clinical characteristics is summarised in Table 3. Groups were evenly matched

The majority of participants were female, and had a mean age 79 years; ranging from 47 to 98 years. 146 (45%) of participants were married and the majority ethnicity was white.

The carers ranged in age from 22 to 95 years, mean age was 61 . Again the majority were female, a higher proportion of the carers were married (63%) compared to the participants. On average 23% of carers were paid workers.

Table 3: Baseline demographics of participants and carers

	Participant			**Carer**		
	Placebo (n=111)	Sertraline (n=107)	Mirtazapine (n=108)	Placebo (n=111)	Sertraline (n=107)	Mirtazapine (n=108)
Age (years)	79 (8.8)	80 (8.4)	79 (8.4)	59 (14.8)	61 (13.9)	61 (17.1)
Sex (male)	40 (36%)	34 (32%)	31 (29%)	46 (30%)	37 (30%)	48 (35%)
Ethnicity (white)	104(94%)	98 (92%)	101 (94%)	119 (79%)	109 (89%)	119 (86%)
Marital status (married)	48 (43%)	51 (48%)	60 (56%)	93 (62%)	82 (67%)	85 (61%)
Residence (lives in care home)	20 (18%)	13 (12%)	17 (16%)	-	-	-
Relation to participant (paid carer)	-	-	-	40 (26%)	19 (15%)	34 (24%)

Data are mean (sd) or n (%)

Clinical characteristics of participants and carers are shown in Table 4. Completeness of data varies from 74%, MMSE to 100% CSDD, primary outcome measure. Clinical characteristics are balanced over treatment arms. Participant qualities of life have worst outcomes when rated by carers in comparison to the participant rating of equivalent scales.

The mean overall dosages (including participants who withdrew from medication) were 70mg (SD 52) per day for sertraline and 24 mg (16) per day for mirtazapine. For participants who remained on prescribed medication the mean dose was 95 mg (36) per day for sertraline and 30 mg (23) per day for mirtazapine.

Table 4: Baseline participant and carer clinical characteristics

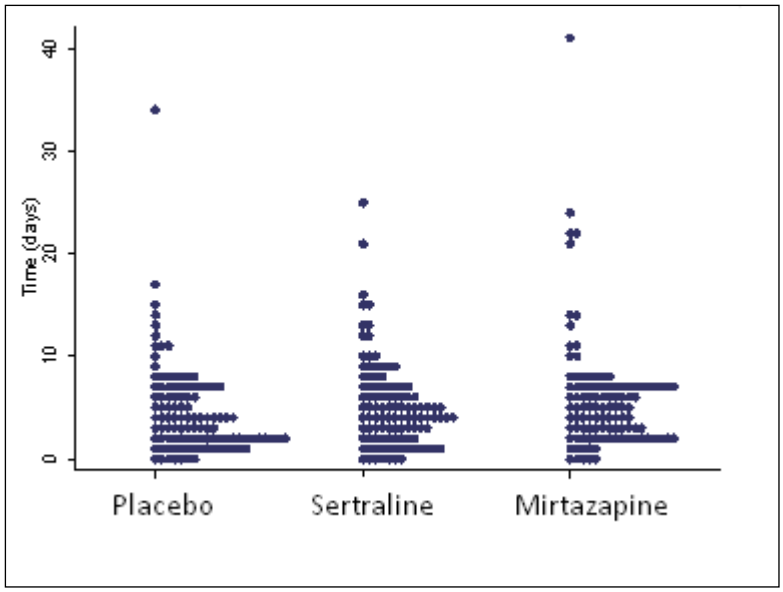
	Placebo	Sertraline	Mirtazapine
Duration of Depression			
Data available	111 (100%)	102 (95%)	106 (98%)
1 month	7 (6%)	3 (3%)	-
1-2 months	4 (4%)	6 (6%)	10 (9%)
2-6 months	24 (22%)	18 (17%)	26 (25%)
>6 months	76 (68%)	75 (71%)	70 (66%)
Severity of depression			
CSDD 8 -11	43 (39%)	45 (42%)	54 (50%)
CSDD ≥12	68 (61%)	64 (58%)	54 (50%)
Dementia vascularity	2.1 (1.3)	2.2 (1.3)	2.2 (1.3)
Carer-rated scores			
Participant SF-12			
Data available	103(93%)	101 (94%)	96 (89%)
Physical component (0-100)	43.2 (10.6)	45.2 (11.2)	44.9 (12.4)
Mental Component (0-100)	50.1 (11.8)	47.9 (11.1)	46.1 (12.5)
Participant generic quality of life			
Data available	109 (99%)	106 (99%)	105 (97%)
EuroQOL VAS (0-100)	52.3 (21.1)	53.8 (19.6)	51.9 (22.4)
Participant depression			
Data available	111 (100%0	107 (100%)	108 (100%)
CSDD (0-38)	13.6 (5.2)	12.8 (3.6)	12.5 (3.7)
Participant activity limitation			
Data available	111 (100%)	106 (99%)	107 (99%)
BADL (0-60)	18.2 (11.1)	16.6 (11.2)	18.4 (10.9)
Participant quality of life			
Data available	91 (82%)	97 (91%)	91 (84%)
DEMQOL proxy (31 -124)	88.4 (15.3)	86.5 (15.6)	86.9 (13.1)
Carer mental health			
Data available	105 (95%)	103 (96%)	98 (91%)
GHQ-12 (0-36)	12.6 (5.1)	12.5 (4.9)	13.0 (5.9)
Carer burden			
Data available	87 (78%0)	93 (87%)	91 (84%)
Zarit (0-88)	27.2 (16.6)	27.8 (14.7)	26.1 (16.0)
Participant neuropsychiatric symptoms			
Data available	106 (95%)	104 (97%)	108 (100%)
NPI (0-144)	30.2 (17.6)	26.9 (16.8)	29.9 (20.9)
Participant–rated scores			
Participant cognition			
Data available	82 (74%)	79. (74%)	90 (83%)
Standardised MMSE (0 -33)	18.2 (7.4)	18.5 (6.7)	17.6 (6.0)
Participant generic quality of life			
Data available	92 (83%)	86 (80%)	91 (84%)
EuroQOL VAS (0-100)	60.3 (24.1)	66.6 (17.8)	66.9 (18.5)
Participant generic quality of life			
Data available	87 (78%)	82 (77%)	91 (84%)
DEMQOL (28-122)	83.7 (17.2)	82.5 (14.3)	85.1 (12.8)

Data are n(%) or mean(SD). SF = short form health survey. VAS=visual analogue scale. CSDD= Cornell scale for depression in dementia. BADL=Bristol Activities of Daily Living. GHQ=general health questionnaire. NPI =Neuropsychiatric inventory. MMSE=mini mental state examination.

Data collection

The mean (SD) time interval between randomisation and completion of questionnaires was 18.2 (14.19) weeks at the 13-week assessment time point and 42.15 (10.7) weeks at the 39 week assessment. The distribution of initiation of treatment following randomisation is shown in Figure 3. Out of the 326 participants randomised, 321 received allocated treatment.

Figure 3: Distribution of initiation of treatment from randomisation



Numbers analysed

111 participants were randomised to placebo, 107 to sertraline, and 108 to mirtazapine. The number of participants included in each analysis is indicated in the tables.

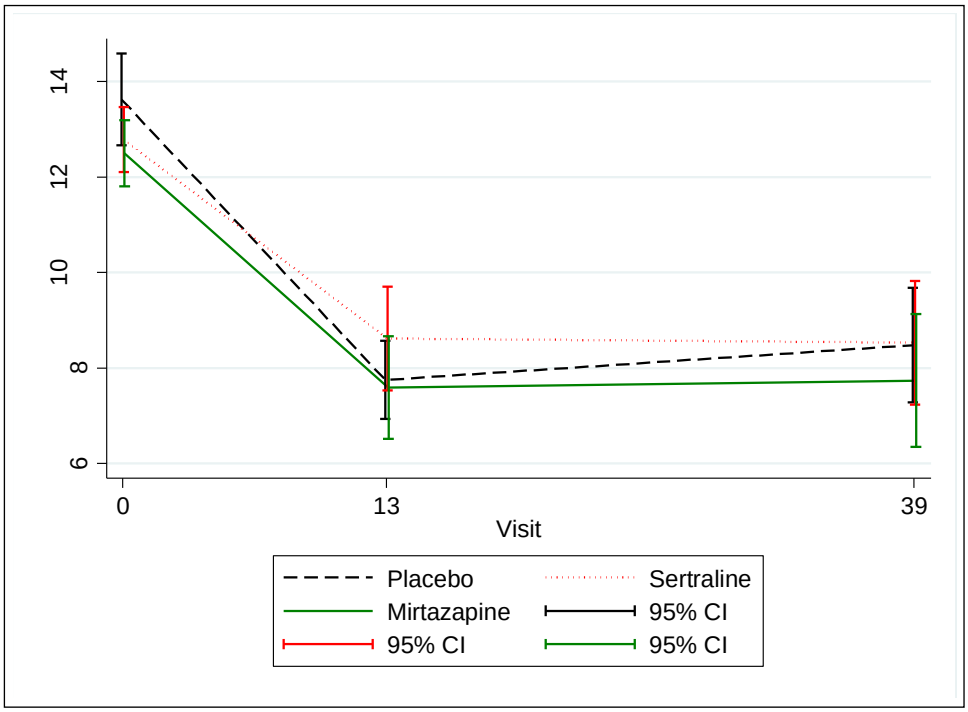
Outcomes and estimation

Primary outcome: CSDD

In total, 258 participants completed the research worker rated CSDD at 13 weeks post randomisation, with 226 participants going on to completed the measure at 39 weeks. As measured by the CSDD severity of depression was shown to decrease in all three intervention groups, compared with baseline. The results of which can be seen in Figure 3. The absolute change from baseline at 13 weeks was greatest for

placebo -5.6 (SD 4.7), compared to -3.9 (5.1) for sertraline and -5.0 (4.9) for mirtazapine. This was difference was maintained through to 39 weeks, change scores of -4.8 (5.5) for placebo, -4.0 (5.2) for sertraline and -5.0 (6.1) for mirtazapine.

Figure 4: CSDD scores by treatment group, unadjusted means with 95% CI (a lower CSDD score means less depressive symptoms).



The results from the linear mixed modelling, Table 4, after adjusting for baseline depression and the stratification factor centre highlighted 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.

On exploratory analysis of the primary outcome measure, we classified the participants as suffering from depression based on the CSDD, a score of 8 or higher is threshold for depression, Table 5. As part of our eligibility criteria all participants at baseline had depression. This criteria was examined at 13 and 39 weeks. By 13 weeks the same proportion of participants in all treatment arms had moved to the no depression classification (49%), the main deviation from this trend was seen at 39 weeks where Mirtazapine showed the largest percentage of non-depressive arm (55%). On evaluation with from a generalised linear mixed model (using the a logit link for the dichotomous data) adjusting for baseline depression and the stratification factor centre, there was no evidence for a difference in the proportion of participants

classified with depression by the CSDD at 13 or 39 weeks, between treatment arms, table 6.

Table 5: Primary outcomes of research worker rated CSDD score

	CSDD Score		
	Placebo	**Sertraline**	**Mirtazapine**
Baseline mean (sd)	13.6 (5.2); n=111	12.8 (3.6); n =107	12.5 (3.7):n=108
Week 13 mean (sd)	7.8 (4.1): n= 95	8.6 (4.9): n=78	7.9 (5.0): n= 85
Week 39 mean (sd)	8.5 (5.5): n=82	8.6 (5.5): n=68	7.7 (6.2): n= 76
Mean difference from placebo(SE) (95% CI) P-value; n			
13 weeks	-	1.17 (0.72) (-0.23 to 2.78) 0.10; n=173	0.01 (0.70) (-1.37 to 1.38) 0.99; n=180
39 weeks	-	0.38 (0.76) (-1.12 to 1.87) 0.63; n=150	-0.67 (0.74) (-2.12 to 0.79) 0.37; n=158)
Mean difference From mirtazapine (95% CI) P-value; n			
13 weeks	-	1.16 (0.72) (-0.25 to 2.57) 0.11; n=163	-
39 weeks	-	1.04 (0.76) (-0.48 to 2.56) 0.18; n=144	-

Table 6: proportion of participants with depression

Visit	**Baseline**		**Week 13**		**Week 39**	
Treatment	**Depression**		**Depression**		**Depression**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
Placebo		111	47 (49%)	48	40 (49%)	42
Sertraline		107	38 (49%)	40	33 (47%)	37
Mirtazapine		108	42 (49%)	43	42 (55%)	34
Total		326	127	131	115	111

Number (%) of cases of depression

Table 7: Generalised linear mixed modelling of depression classification

	Odds Ratio	**Std. Err.**	**P-value**	**(95% Conf.**	**Interval)**
Week 13 sertraline vs. placebo	1.050	0.349	0.883	0.547	2.016
Week 13 mirtazapine vs. placebo	1.008	0.327	0.979	0.534	1.906
Week 13 sertraline vs. mirtazapine	1.042	0.351	0.904	0.538	2.018

Week 39 sertraline vs. placebo	1.077	0.408	0.845	0.512	2.263
Week 39 mirtazapine vs. placebo	0.692	0.256	0.319	0.335	1.428
Week 39 sertraline vs. mirtazapine	1.557	0.596	0.247	0.736	3.296

Adjusted logistic Model for depression status at 13 and 39 weeks, full adjusted model.

Secondary outcomes

Table 8 shows the effectiveness of the medications compared with placebo and between each other on secondary outcomes in participants and carers. Again, few differences can be attributed to the antidepressants. However, there were fewer neuropsychiatric symptoms and higher carer-rated participant scores for health related quality of life (DEMQOL-proxy) in participants given mirtazapine compared with sertraline, but these differences did not persist to 39 weeks (table 4).

Our findings did not differ in subgroup analyses examining outcomes by baseline depression severity (CSDD score 8–11 vs ≥12). All but eight participants (one in the placebo group, three in the sertraline group, and four in the mirtazapine group) met criteria for categorical diagnosis of depression in Alzheimer's disease as per Olin criteria.[49] Sensitivity analyses with the Olin criteria as a moderator were not appropriate because of the low frequency of participants who did not meet Olin criteria. However, this gives reassurance of the clinical significance of the depression in dementia investigated here.

Carers whose relatives were receiving placebo had higher quality of life scores at 13 weeks (SF-12 mental component score) and higher mental health scores (GHQ-12) than did those on sertraline (table 8). Finally, carers of participants in the mirtazapine group had higher quality of life scores (SF-12 mental component score) at 13 weeks than did the carers of participants in the sertraline group. However, these differences did not persist at 39 weeks.

Table 8: Comparisons of secondary participant carer outcome (including depression severity)

		Week 13			Week 39		
		Sertraline v Placebo	**Mirtazapine v Placebo**	**Sertraline v mirtazapine**	**Sertraline v Placebo**	**Mirtazapine v Placebo**	**Sertraline v mirtazapine**
Cognition MMSE	Coeff (SE) 95% CI (p value)	-0.22 (0.65) -1.50 to 1.05 (0.73)	-0.27 (0.61) -1.48 to 0.94 (0.66)	0.05 (0.64) -1.21 to 1.31 (0.94)	-0.55 (0.68) -1.89 to 0.79 (0.42)	-1.71 (0.67) -2.48 to 0.14 (0.08)	0.62 (0.69) -0.73 to 1.97 (0.37)
Activity limitation BADL	Coeff (SE) 95% CI (p value)	1.40 (1.26) -1.07 to 3.88 (0.27)	-0.04 (1.23) -2.44 to 2.36) (0.97)	1.44 (1.30) -1.10 to 3.99 (0.27)	1.63 (1.35) -1.01 to 4.27 (0.26)	1.19 (1.30) -1.37 to 3.75 (0.36)	0.44 (1.38) -2.26 to 3.14 (0.75)
Behaviour Problems NPI	Coeff (SE) 95% CI (p value)	2.72 (2.41) -2.01 to 7.45 (0.26)	-3.56 (2.30) -8.07 to 0.96 (0.12)	6.28 (2.42) 1.53 to 11.03 **(0.010)**	2.02 (2.53) -2.94 to 6.97 (0.43)	-1.51 (2.42) -6.25 to 3.24 (0.53)	3.53 (2.53) -1.44 to 8.49 (0.164)
Depression severity							
low CSDD score 8-11	Coeff (SE) 95% CI (p value	1.12 (1.01) -0.85 to 3.10 (0.26)	-0.30 (0.98) -2.21 to 1.61 (0.76)	1.43 (0.99) -0.51 to 3.36 (0.15)	0.33 (1.04) -1.72 to 2.37 (0.76)	-0.99 (1.02) -2.98 to 1.00 (0.33)	1.31 (1.04) -0.72 to 3.34 (0.20)
high CSDD score 12+	Coeff (SE) 95% CI (p value	1.18 (0.91) -0.60 to 2.96 (0.34)	0.27 (0.89) -1.47 to 2.01 (0.76)	0.91 (0.91) -0.95 to 2.77 (0.34)	0.38 (0.94) -1.47 to 2.23 0.69	-0.41 (0.91) -2..20 to 1.37 0.65	0.0.80 (0.97) -1.10 to 2.69 0.41
Life quality DEMQOL	Coeff (SE) 95% CI (p value)	0.30 (1.89) -3.40 to 4.01 (0.87)	-0.06 (1.76) -3.52 to 3.39 (0.97)	0.37 (1.89) -3.52 to 3.39 (0.85)	-1.76 (2.04) -5.75 to 2.23 (0.39)	-0.03 (1.92) -3.80 to 3.75 (0.99)	-1.74 (2.07) -5.79 to 2.32 (0.40)
Life quality DEMQOL-Proxy	Coeff (SE) 95% CI (p value)	-1.98 (2.14) -6.16 to 2.21 (0.36)	3.13 (2.15) -1.09 to 7.35 (0.15)	-5.11 (2.22) -9.45 to -0.76 **(0.021)**	2.69 (2.28) -1.77 to 7.15 (0.24)	3.69 (2.28) -0.77 to 8.16 (0.11)	-1.00 (2.35) -5.61 to 3.60 (0.67)
Life quality Self-rated EQ5D	Coeff (SE) 95% CI (p value)	-3.44 (3.78) -10.86 to 3.98 (0.36)	2.00 (3.67) -5.18 to 9.19 (0.59)	-5.44 (3.72) -5.18 to 9.19 (0.14)	-4.34 (4.19) -12.56 to 3.88 (0.30)	-1.18 (4.12) -9.25 to 6.89 (0.78)	-3.16 (4.21) -9.25 to 6.89 (0.45)
Life quality Carer-rated EQ5D	Coeff (SE) 95% CI (p value)	0.61 (3.05) -5.38 to 6.59 (0.84)	3.62 (3.03) -2.31 to 9.55 (0.23)	-3.02 (3.17) -9.23 to 3.20 (0.34)	-0.27 (3.32) -6.77 to 6.24 (0.94)	-1.11 (3.23) -7.44 to 5.21 (0.73)	0.85 (3.42) -5.86 to 7.56 (0.80)
Carer burden Zarit	Coeff (SE) 95% CI (p value)	-0.50 (1.93) -4.28 to 3.27 (0.80)	-1.14 (1.83) -4.93 to 0.65 (0.56)	0.64 (1.98) -3.23 to 4.51 (0.75)	-0.09 (2.07) -4.15 to 3.98 (0.97)	-2.80 (2.14) -6.99 to 1.38 (0.19)	2.71 (2.13) -1.45 to 6.88 (0.20)
Carer mental health GHQ	Coeff (SE) 95% CI (p value)	1.47 (0.72) 0.06 to 2.89 **(0.042)**	-0.57 (1.23) -0.84 to 1.98 (0.43)	0.90 (0.75) -0.56 to 2.37 (0.23)	0.43 (0.77) -1.09 to 1.95 (0.58)	-0.61 (0.77) -2.12 to 0.90 (0.43)	1.04 (0.80) -0.53 to 2.61 (0.20)
Life quality SF-12 PCS physical	Coeff (SE) 95% CI (p value)	1.28 (1.40) -1.48 to 4.03 (0.36)	-0.53 (1.39) -2.20 to 3.26 (0.70)	0.75 (1.45) -2.10 to 3.59 (0.61)	-1.68 (1.48) -4.58 to 1.22 (0.26)	0.02 (1.46) -2.84 to 2.88 (0.99)	-1.70 (1.53) -2.84 to 2.88 (0.27)
Life quality SF-12 MCS Mental	Coeff (SE) 95% CI (p value)	-2.99 (1.47) -5.87 to -0.11 **(0.042)**	0.52 (1.45) -2.31 to 3.36 (0.72)	-3.52 (1.52) -6.50 to -0.54 **(0.021)**	0.09 (1.54) -2.94 to 3.11 (0.96)	-0.31 (1.51) -3.28 to 2.66 (0.84)	0.40 (1.60) -2.74 to 3.54 (0.80)

NPI

The distributional assumptions of the regression model were improved by specifying a negative binomial distribution for the NPI data. The data was examined cross sectionally, thus missing data was accounted for by inverse probability weighting. The subscales of the NPI can be combined to yield four factors: Factor 1 Agitation, Disinhibition and Irritability; Factor 2 Delusions, Depression and Anxiety; Factor 3: Hallucinations, Aberrant motor behaviour and Sleep; Factor 4 Elation, Apathy: Appetite. The summaries for the factors came be seen in table 9. Under the new regression model, there is evidence for a beneficial effect of mirtazapine in comparison to sertraline. The difference in odds between sertraline and placebo, although non-significant, trends towards a better outcome in placebo. These differences are seen at 13 weeks, table 10.

The significant odds seen for the total score (OR 1.39; 95% CI 1.08-1.78, P=0.009), is supported by factors 2 and 3. These effects are not continued into week 39.

Table 9: mean (SD) of the NPI factors

Baseline	**Placebo**	**Sertraline**	**Mirtazapine**
Data available Mean (sd)			
Baseline			
Factor1	110 6.89 (6.44)	107 5.87 (5.53)	108 6.5 (6.67)
Factor2	111 9.18 (6.65)	105 8.76 (6.33)	108 9.42 (7.55)
Factor3	111 6.41 (6.73)	106 5.71 (5.57)	108 6.36 (7.21)
Factor4	107 7.43 (6.25)	105 6.62 (5.18)	108 7.58 (6.44)
Week 13			
Factor1	97 4.30 (4.65)	79 4.58 (5.32)	88 4.28 (5.68)
Factor2	96 5.21 (5.59)	79 5.85 (6.62)	88 4.17 (5.54)
Factor3	97 4.41 (5.14)	79 5.43 (6.02)	88 4.02 (5.74)
Factor4	93 5.53 (5.56)	75 5.25 (5.65)	88 4.42 (4.73)
Week 39			
Factor1	84 5.08 (5.58)	70 4.91 (6.03)	78 4.36 (5.88)
Factor2	84 5.37 (5.48)	69 5.61 (6.44)	78 5.32 (7.08)
Factor3	83 3.39 (4.83)	70 4.46 (5.35)	78 4.34 (6.22)
Factor4	81 5.59 (5.57)	68 5.68 (5.38)	78 5.19 (6.45)

Table 10: Odds ratio, the NPI and derived factor scores. Fully adjusted modelling

		Week 13			Week 39		
		Sertraline v Placebo	**Mirtazapine v Placebo**	**Sertraline v Mirtazapine**	**Sertraline v Placebo**	**Mirtazapine v Placebo**	**Sertraline v mirtazapine**
Total Score	Odds Ratio (SE) 95% CI (p value)	1.098 (0.12) 0.884 to 1.363 0.397	0.790 (0.10) 0.618 to 1.009 0.059	1.390 (0.18) 1.084 to 1.782 **0.009**	1.150 (0.15) 0.884 to 1.495 0.298	0.933 (0.14) 0.693 to 1.256 0.647	1.232 (0.18) 0.926 to 1.640 0.151
Factor 1	Odds Ratio (SE) 95% CI (p value)	1.104 (0.19) 0.782 to 1.558 0.573	1.013 (0.21) 0.678 to 1.516 0.948	1.090 (0.24) 0.706 to 1.681 0.698	1.101 (0.233) 0.728 to 1.666 0.649	0.913 (0.19) 0.608 to 1.372 0.663	1.206 (0.28) 0.760 to 1.911 0.427
Factor 2	Odds Ratio (SE) 95% CI (p value)	1.203 (0.22) 0.840 to 1.723 0.313	0.738 (0.13) 0.516 to 1.054 0.095	1.631 (0.30) 1.141 to 2.331 **0.007**	0.996 (0.18) 0.697 to 1.425 0.984	0.886 (0.17) 0.609 to 1.287 0.524	1.125 (0.21) 0.775 to 1.634 0.536
Factor 3	Odds Ratio (SE) 95% CI (p value)	1.395 (0.26) 0.964 to 2.018 0.078	0.716 (0.17) 0.451 to 1.138 0.158	1.946 (0.45) 1.239 to 3.056 **0.004**	1.663 (0.42) 1.020 to 2.713 **0.042**	1.398 (0.35) 0.856 to 2.283 0.181	1.190 (0.26) 0.779 to 1.819 0.422
Factor 4	Odds Ratio (SE) 95% CI (p value)	1.064 (0.18) 0.762 to 1.486 0.715	0.853 (0.13) 0.633 to 1.148 0.294	1.248 (0.22) 0.887 to 1.755 0.204	1.141 (0.21) 0.786 to 1.656 0.488	0.842 (0.17) 0.570 to 1.244 0.387	1.355 (0.27) 0.912 to 2.015 0.133

Safety data

In total, 119 participants reported 240 adverse reactions. Table 11 shows adverse reactions by week 39. 29 of 111 participants (26%) in the placebo group had adverse reactions, compared with 46 of 107 (43%) in the sertraline group (p=0·010) and 44 of 108 (41%) in the mirtazapine group (p=0·031; overall p value for placebo vs either drug 0·017). Gastrointestinal reactions were most common with sertraline (usually nausea) and psychological reactions were most common with mirtazapine (usually drowsiness and sedation). At 13 weeks, there were 15 serious adverse events in the placebo group of which three (20%) were rated severe, compared with 12 in the sertraline group (eight severe [67%]) and 14 (10 severe [71%]) in the mirtazapine group. 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).

Table 11: Adverse reactions definite, probable, and possibly related top study intervention by week 39.

Classification	Treatment Group			Total Events
	placebo (events)	sertraline (events)	mirtazapine (events)	
Psychological	10 (22)	9 (18)	24 (44)	53 (84)
Neurological	8 (9)	16 (25)	18 (21)	42 (55)
Gastrointestinal	7 (7)	20 (24)	11 (13)	38 (44)
Other	2 (2)	5 (5)	3 (3)	10 (10)
Genitourinary	4 (4)	3 (3)	2 (3)	9 (10)
Musculoskeletal	2 (3)	3 (3)	3 (3)	8 (9)
Dermatological	3 (4)	3 (3)	2 (2)	8 (9)
Respiratory	2 (2)	1 (1)	2 (2)	5 (5)
Cardiovascular	1 (1)	0 (0)	2 (4)	3 (5)
Infection	1 (1)	1 (1)	1 (1)	3 (3)
ENT	2 (2)	1 (1)	0 (0)	3 (3)
Haematological	1 (1)	1 (1)	0 (0)	2 (2)
Endocrine	0 (0)	1 (1)	0 (0)	1 (1)
Total**	29 (58)	46 (86)	44 (96)	119 (240)

Data are number of participants (number of events)

Health Economic Results

Baseline comparisons

At baseline, full service use data were available for 326 participants (111 placebo, 107 sertraline, 108 mirtazapine). At 13 weeks economic data were available for 97 participants in the placebo group, 78 in the sertraline group and 88 in the mirtazapine group. By 39 weeks there were 84 participants in the placebo group, 69 in the sertraline group and 77 in the mirtazapine group.

Service use and support

Contacts made by patients with services and support over weeks 0-13 and 0-39 are shown in Table 12. There were few differences between the three patient groups in either time period, except when mirtazapine and sertraline were compared with placebo and mirtazapine was compared with sertraline. There were no statistically significant differences between the groups in the number of contacts with any services.

Table 12 Service use

	Placebo		Sertraline		Mirtazapine	
Week 0-13	**n=97**		**n=78**		**n=88**	
	No. using	**Mean [a] (SD)**	**No. using**	**Mean [a] (SD)**	**No. using**	**Mean [a] (SD)**
Hospital-based care						
Inpatient (bed day) [b]	8	1.65 (7.98)	5	1.58 (6.82)	5	0.49 (2.19)
Outpatient (attendance)	33	0.53 (1.08)	25	0.60 (1.10)	26	0.53 (1.10)
Accident and emergency (Attendance)	8	0.12(0.48)	5	0.08 (0.27)	4	0.57 (0.28)
Day hospital (contact)	3	0.23 (1.44)	6	0.83 (4.11)	4	0.32 (1.66)
Community-based care						
GP (contact)	57	1.36 (2.36)	44	1.09 (1.44)	49	1.22 (2.84)
Geriatrician (contact)	3	0.03 (0.17)	0	0	88	0.03 (0.18)
Nurse* (contact)	41	0.87 (1.49)	29	2.50 (10.83)	43	1.56 (3.71)
Occupational therapist (contact)	11	0.21 (0.66)	7	0.35 (1.70)	5	0.08 (0.38)
Community psychiatrist (contact)	21	0.26 (0.54)	14	0.24 (0.63)	19	0.27 (0.58)
Psychologist (contact)	2	0.82 (0.64)	3	0.06 (0.37)	2	0.09 (0.62)
Counsellor (contact)	1	0.01 (0.10)	3	0.36 (2.94)	2	0.17 (1.32)
Care manager (contact)	7	0.10 (0.42)	1	0.01 (0.11)	4	0.05 (0.21)
Social worker (contact)	15	0.21 (0.69)	10	0.19 (0.58)	12	0.28 (0.87)
Home care worker/care attendant (contact)	19	18.57 (60.57)	17	21.92 (72.77)	22	28.33 (72.19)
Chiropodist (contact)	33	0.43 (0.710	16	0.26 (0.57)	23	0.40 (0.88)
Sitting scheme (contact)	5	1.21 (6.71)	5	0.68 (4.29)	3	0.59 (3.75)
Self-help group (contact)	0	0	0	0	1	0.03 (0.32)
Meals on wheels (contact)	3	0.30 (1.77)	3	5.82 (33.95)	4	2.32 (12.74)
Dentist (contact)	10	0.13 (0.49)	10	0.15 (0.43)	15	0.23 (0.58)
Optician (contact)	10	0.12 (0.39)	13	0.19 (0.46)	12	0.15 (0.39)
Day services						
Day services (day)	15	4.15 (11.95)	17	6.50 (15.64)	16	5.47 (13.33)
Lunch club (visit)	3	1.88 (15.92)	0	0	3	1.18 (8.51)
Social club (visit)	2	0.27 (1.86)	4	0.67 (2.89)	2	0.44 (3.08)
Informal care						
Care giving (hours/week)	45	10.05 (17.65)	37	11.63 (21.59)	42	9.84 (23.85)
	Placebo		**Sertraline**		**Mirtazapine**	
Week 0-39	**n=84**		**n=69**		**n=78**	
Inpatient (bed day) [b]	9	3.05 (10.48)	11	2.55 (9.26)	14	4.54 (15.08)
Outpatient (attendance)	44	0.83 (1.15)	33	0.90 (1.41)	29	0.69 (1.15)
Accident and emergency (attendance)	13	0.17 (0.41)	8	0.25 (0.86)	7	0.10 (0.35)
Day hospital (contact)	1	0.01 (0.11)	8	2.61 (9.42)	3	0.56 (3.30)
Community based care						
GP (contact)	57	1.51 (1.83)	40	1.52 (2.15)	55	1.88 (2.40)
Geriatrician (contact)	4	0.05 (0.21)	0	0	2	0.03 (0.16)
Nurse* (contact)	37	1.24 (2.34)	33	5.84 (29.57)	34	1.46 (3.53)

Occupational therapist (contact)	9	0.17 (0.53)	8	0.45 (2.23)	5	0.10 (0.44)
Community psychiatrist (contact)	22	0.33 (0.67)	15	0.26 (0.53)	29	0.60 (1.48)
Psychologist (contact)	5	0.21 (1.34)	2	0.03 (0.17)	1	0.01 (0.11)
Counsellor (contact)						
Care manager (contact)	6	0.52 (2.87)	3	0.04 (0.21)	5	0.10 (0.44)
Social worker (contact)	12	0.58 (2.98)	15	0.42 (0.98)	17	0.44 (1.47)
Home care worker/care attendant (contact)	16	33.56 (107.73)	19	38.07 (95.60)	17	38.95 (110.10)
Chiropodist (contact)	35	0.88 (1.37)	20	0.53 (1.52)	32	1.11 (1.89)
Sitting scheme (contact)	0	0	5	1.23 (5.49)	4	0.76 (3.69)
Meals on wheels (contact)	2	0.63 (5.67)	2	3.77 (21.70)	2	3.14 (19.49)
Dentist (contact)	18	0.33 (0.96)	18	0.47 (1.25)	19	0.34 (0.81)
Dietician (contact)	0	0	0	0	1	0.01 (0.11)
Day services						
Day services (day)	16	5.57 (14.31)	18	7.26 (15.13)	16	5.17 (12.63)
Lunch club (visit)	1	0.31 (2.84)	1	0.38 (3.15)	3	0.83 (4.84)
Social club (visit)	2	0.62 (4.47)	3	0.57 (2.69)	1	0.33 (2.94)
Informal care						
Care giving (hours per week)	40	12.27 (21.24)	34	12.32 (24.07)	33	6.74 (11.82)

[a]across full sample
[b] psychiatric and non-psychiatric inpatient bed days
*****practice nurse, district nurse health visitor, community psychiatric, cardiac nurse, incontinence nurse

Costs

Daily medication costs for sertraline 50mg of £0.05 and mirtazapine 15mg of £0.23 were applied. Mean cost of medication per person was estimated to be £7 (CI 6 to 9) and £37 (CI 32 to 41).

Mean total costs over 0-13-weeks and 0-39 weeks are detailed in Table 13. Pairwise comparisons were made between the two antidepressants and placebo using regression analysis and bootstrapping. There were no statistically significant differences between the groups in either of the time periods, either when health and social care service costs only were included, or when health and social care services and informal care costs are summed.

After adjustment for baseline costs, CSDD score at baseline and site, there were no statistically significant differences in health and social care costs – or in health, social care and informal care costs – in any pairwise comparison in either time period.

In terms of observed mean *differences*, aggregated health and social care service costs per patient over 0-13 weeks were £3 between sertraline and placebo, £307 between placebo and mirtazapine and £310 between sertraline and mirtazapine. In

each case, the first named treatment was the more costly. In the 6 months leading up to 39 weeks, mean difference in health and social care costs was £693 between sertraline and placebo, £404 between mirtazapine and placebo, and £289 between sertraline and mirtazapine. Again, in each case the first-named treatment was more costly.

Informal care costs exceeded health and social care costs by a factor of 1.2 to 1.7. Including informal care costs results in a change in the ranking of total costs, with mirtazapine being the least expensive of all treatments in both periods.

Table 13 Health, social care and informal care costs and outcome

		Placebo		Sertraline		Mirtazapine	Bootstrapped mean difference (95% CI)		
	N	Mean (sd), £	n	Mean (sd), £	n	Mean (sd), £	Sertraline - Placebo	Mirtazapine - Placebo	Mirtazapine - Sertraline
(a) Medication costs									
0-13 weeks	97	0	78	7 (5)	88	37 (22)	7 (6 to 8)	37 (32 to 41)	30 (25 to 34)
0-39 weeks	84	0	69	7 (5)	78	37 (22)	7 (6 to 8)	37 (32 to 41)	30 (25 to 34)
(b) Health and social care costs									
0-13 weeks	97	1438 (3339)	78	1434 (2326)	88	1094 (1871)	-4 (-900 to 798)	-344 (-1207 to 322)	-340 (-1049 to 283)
0-39 weeks	84	2146 (4402)	69	2832 (4111)	78	2513 (4290)	686 (-630 to 1973)	367 (-977 to 1596)	-319 (-1643 to 1023)
(c) Informal care cost									
0-13 weeks	97	2744 (4819)	78	3175 (5897)	88	2687 (6511)	431 (-1000 to 2242)	-57 (-1686 to 1537)	-488 (-2380 to 1470)
0-39 weeks	84	3351 (5799)	69	3363 (6573)	78	1841 (3228)	12 (-1940 to 2256)	-1510 (-3088 to -136)	-1522 (-3398 to -72)
Total costs *excluding* informal care inputs (a+b)									
0-13 weeks	97	1438 (3339)	78	1441 (2327)	88	1131 (1869)	3 (-893 to 806)	-307 (-1172 to 358)	-310 (-910 to 299)
0-39 weeks	84	2146 (4402)	69	2839 (4112)	78	2550 (4289)	693 (-622 to 1980)	404 (-972 to 1626)	-289 (-1545 to 1151)
Total costs *including* informal care inputs (a+b+c)									
0-13 weeks	97	4182 (5821)	78	4616 (6488)	88	3818 (7060)	434 (-1340 to 2356)	-365 (-2212 to 1560)	-798 (-2754 to 1498)
0-39 weeks	84	5497 (7922)	69	6202 (8241)	78	4391 (5285)	705 (-1855 to 3234)	-1106 (-3137 to 970)	-1811 (-4048 to 543)
Depression score (CSDD)									
13 weeks	95	7.8 (4.1)	78	8.6 (4.9)	85	7.9 (5.0)	0.84 (-0.60 to 2.14)	0.16 (-1.53 to 1.11)	-0.7 (-0.57 to 2.52)
39 weeks	82	8.5 (5.5)	68	8.6 (5.5)	76	7.7 (6.2)	0.05 (-1.83 to 1.67)	-0.80 (-2.55 to 1.21)	-0.9 (-1.10 to 2.73)
QALY 39 weeks (EQ-5D)	57	0.55 (0.17)	53	0.57 (0.14)	52	0.60 (0.13)	0.03 (-0.09 to 0.03)	0.05 (-0.10 to 0.01)	0.02 (-.03 to 0.07)

Table 14 Differences in incremental cost, effect, and cost-effectiveness

	Sertraline – placebo		Mirtazapine – placebo		Mirtazapine - Sertraline	
	0-13 weeks	**0-39 weeks**	**0-13 weeks**	**0-39 weeks**	**0-13 weeks**	**0-39 weeks**
Incremental cost (£, 2009/2010)						
Health and social care; mean [95% CI]	3 (-893 to 806)	693 (-622 to 1980)	-307 (-1172 to 358)	404 (-972 to 1626)	-310 (-910 to 299)	-289 (-1545 to 1151)
Health and social care and Informal care; mean [95% CI]	434 (-1340 to 2356)	705 (-1855 to 3234)	-365 (-2212 to 970)	-1106 (-3137 to 970)	-798 (-2754 to 1498)	-1811 (-4048 to 543)
Incremental effect:						
CSDD score; mean [95% CI]*	0.84 (-0.60 to 2.14)	0.05 (-1.83 to 1.67)	0.16 (-1.53 to 1.11)	-0.80 (-2.55 to 1.21)	-0.7 (-0.57 to 2.52)	-0.9 (-1.10 to 2.73)
QALY (EQ-5D); mean [95% CI]**	-	0.03 (-0.09 to 0.03)	-	0.05 (-0.10 to 0.01)	-	0.02 (-.03 to 0.07)
Incremental cost-effectiveness (£) - Health and social care and:						
(a) CSDD score	4	13860	1919	-505	443	321
	(Dominated)	(Dominated)	(Lower costs; worse outcome)	(Higher costs; better outcome)	(Mirtazapine dominant)	(Mirtazapine dominant)
(b) QALY (EQ-5D)	-	23100	-	8080	-	-14450
	-	(Higher costs; better outcome)	-	(Higher costs; better outcome)	-	(Mirtazapine dominant)
Incremental cost-effectiveness (£) - Health and social care and informal care costs and :						
(a) CSDD score	517	14100	2281	1382	1140	2012
	(Dominated)	(Dominated)	(Lower costs; worse outcome)	(Mirtazapine dominant)	(Mirtazapine dominant)	(Mirtazapine dominant)
(b) QALY (EQ-5D) **	-	23500	-	-22120	-	-90550
	-	(Higher costs; better outcome)	-	(Mirtazapine dominant)	-	(Mirtazapine dominant)

Dominated = active treatment has higher costs and worse outcome; Dominant = active treatment has lower costs and better outcome; *On CSDD higher scores worse outcome; therefore negative incremental CSDD scores indicate better outcome for active treatment. In case of the comparison between mirtazapine and sertraline this is mirtazapine; **patient rated

Cost-effectiveness

As noted earlier, the primary economic evaluation was a cost-effectiveness analysis with CSDD as the outcome over, first, the period 0-13 weeks after randomisation, and second the period 0-39 weeks after randomisation. A secondary analysis was a cost-utility analysis using QALYs computed from the EQ-5D and societal weights over the same periods. Data used in the estimation of the ICERs are shown in Table 14. An ICER was calculated for each analysis comparing sertraline and mirtazapine against placebo and comparing mirtazapine against sertraline.

As reported previously, there were no significant differences in CSDD scores or QALYs in any of the pairwise comparisons between sertraline, mirtazapine and placebo. There were also no significant pairwise differences in costs from either perspective between the treatment groups.

Given uncertainty surrounding the choice of treatment when incremental costs are higher and incremental outcome better (or when incremental costs are lower and incremental outcome also lower), CEACs were used to aid decision-making. Probability estimates were plotted for a range of implicit monetary values attached to improvements in depression score and QALY gain. We are not aware of any studies that have attached monetary values to incremental changes in CSDD.

In Figure 5, we see that mirtazapine has a low probability (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. The probability rose to 80% if society was willing to pay £5,000 for a unit improvement in CSDD score, and stays at 80% over values of willingness to pay for an improvement in CSDD score up to £30,000. Sertraline had a less than 20% chance of being cost-effective compared to placebo, with the probability increasing moderately to about 42% if society was willing to pay £5,000 for each point improvement in CSDD score; and stayed below 50% for willingness to pay values greater than £5000 and up to £30,000 for a point improvement in CSDD score.

When both active treatments – sertraline and mirtazapine - were compared against each other the likelihood that treatment with mirtazapine would be seen as more cost-effective than sertraline would be over 60% from a health and social care perspective (and over 90% from a health, social care and informal care costs perspective).

Figures 5 and 6 show the CEACs from the secondary economic evaluation, where costs were considered alongside QALYs. Although we found no significant differences in QALY gain in any of the pairwise comparisons between sertraline, mirtazapine and placebo, we see a trend towards marginally higher QALY gains (using the EQ-5D measured directly from patients) for the active treatments.

Figure 7 suggests that the probability that mirtazapine is more cost-effective than placebo was 89% and increased to over 90% for a willingness to pay of £30,000 for a QALY. The likelihood of sertraline being more cost-effective than placebo was just over 50% and rose to just over 70% over higher values of willingness to pay for a QALY. Figure 8 shows mirtazapine had a higher probability of being more cost-effective than sertraline (over a range of willingness to pay values from £0 to £30,000) when health and social care costs are considered on their own, and also when considering health, social care and informal care costs.

In addition to assessing the uncertainty surrounding the cost-effectiveness of the antidepressants, we also assessed uncertainty around parameter estimates included in the cost analysis. For the main analyses, informal care costs were based on hourly cost of a home care worker. This hourly value for the care-giving inputs by friends and family was replaced in sensitivity analysis by an opportunity cost estimate, calculated as the gross hourly wage of a carer in paid employment and zero for a carer not in paid employment. Using alternative values of caregiver time inputs did not alter the findings (Table 15).

Figure 5 Probability treatment is cost effective – 0-39 week: Health, social care costs and depression score (CSDD)

Figure 6 Probability Mirtazapine is cost effective relative to Sertraline at 0-39 weeks: Costs and depression score (CSDD)

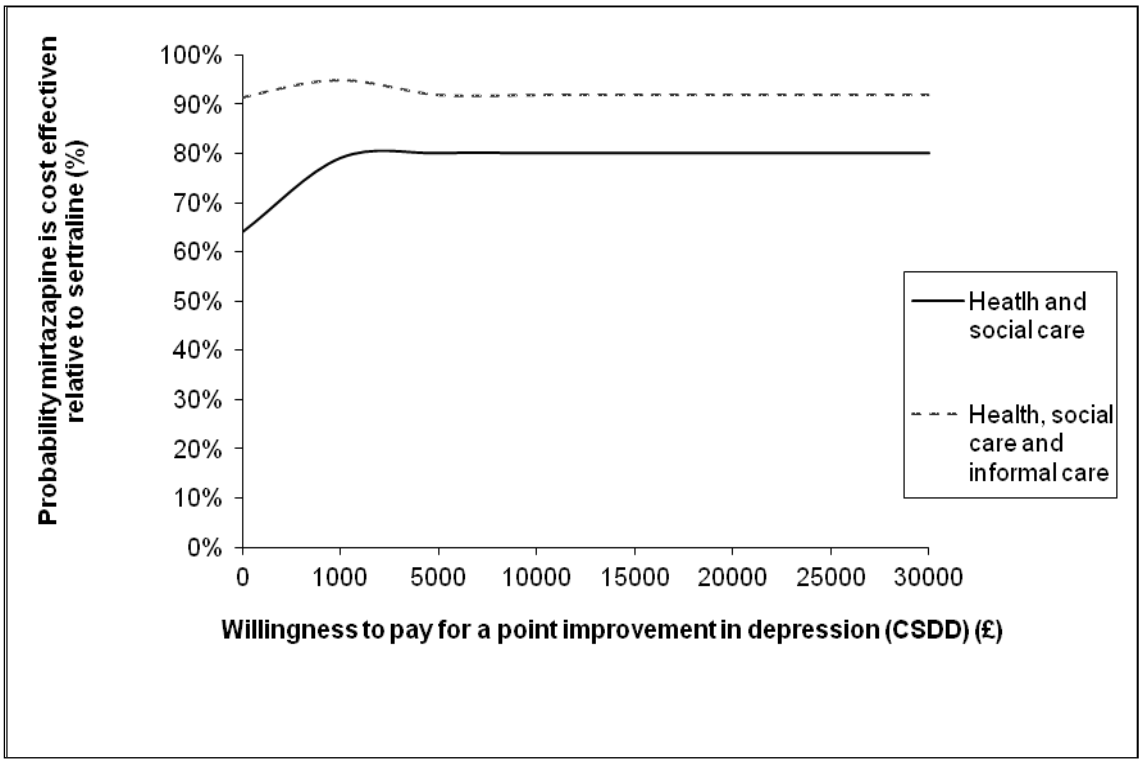


Figure 7 Probability treatment is cost effective relative to placebo: Health, social care and informal care costs and QALYs

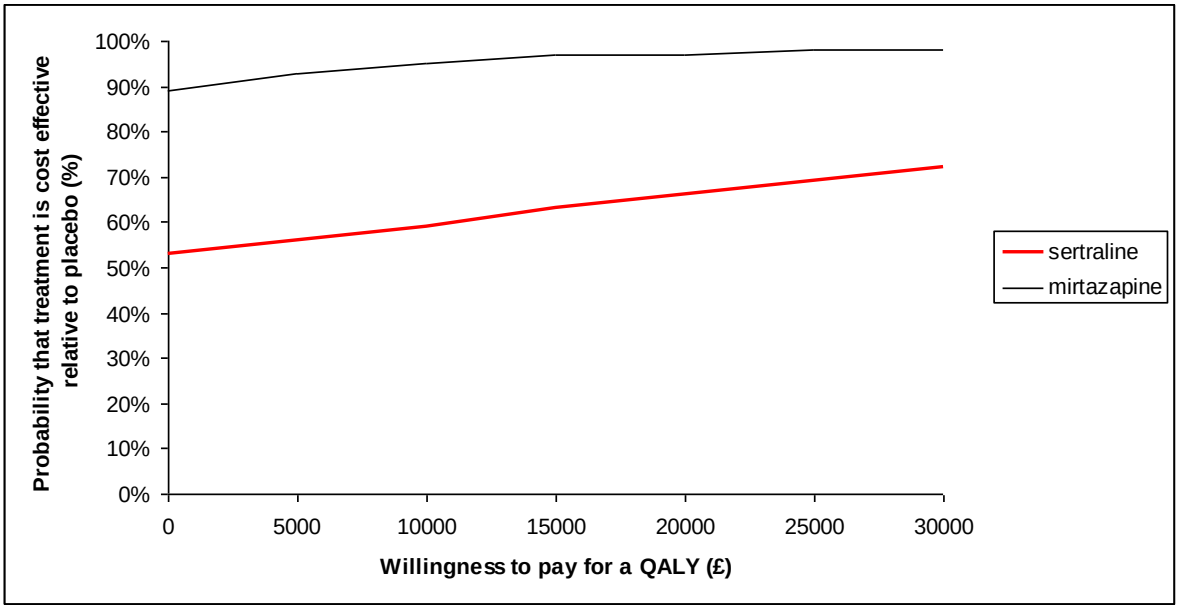


Figure 8 Probability Mirtazapine is cost effective relative to Sertraline: Costs and QALYs

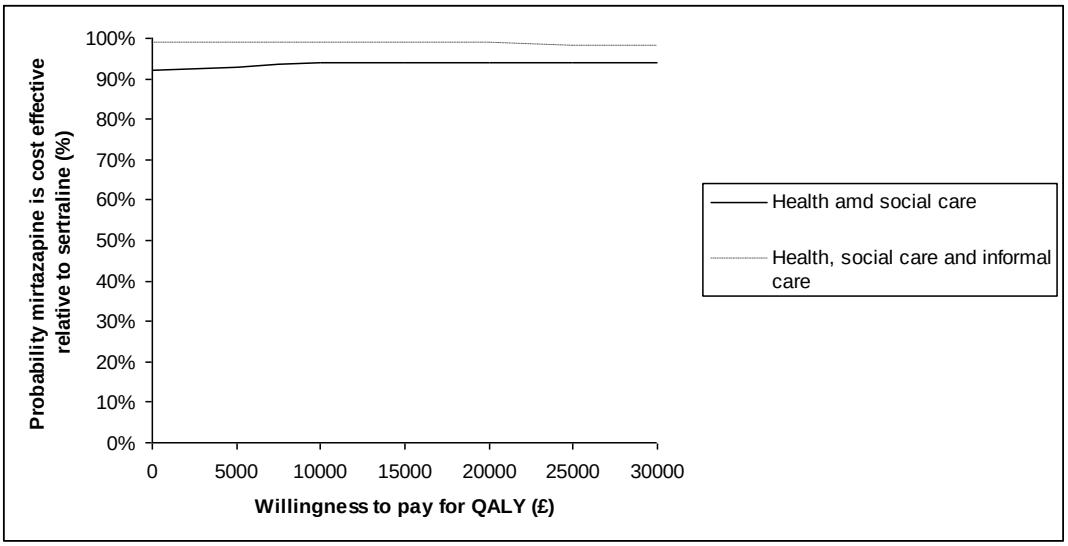


Table 16 Sensitivity analysis

	Placebo Mean (sd)	Sertraline Mean (sd)	Mirtazapine Mean (sd)	Mean difference (Sertraline – Placebo) (95% CI)	Mean difference (Mirtazapine – Placebo) (95% CI)	Mean difference (Mirtazapine – Sertraline) (95% CI)
Main analysis – 0-13 weeks (total cost including informal care)	4182 (5821)	4616 (6488)	3818 (7060)	434 (-1340 to 2356)	-365 (-2212 to 1560)	-798 (-2754 to 1498)
(a) Applying gross wage for informal care inputs	3368 (4769)	3663 (5008)	3592 (5461)	322 (-1081 to 1797)	-353 (-1778 to 1087)	-71 (-1588 to 1588)
Main analysis – 0-39 weeks (total cost including informal care)	5497 (7922)	6202 (8241)	4391 (5285)	705 (-1855 to 3234)	-1106 (-3137 to 970)	-1811 (-4048 to 543)
(a) Applying gross wage for informal care inputs	4476 (6512)	5177 (6574)	3830 (4777)	702 (-1313 to 2751)	-645 (-2415 to 986)	-1347 (-3368 to 280)

CHAPTER 4: DISCUSSION

This is a trial with negative findings but important clinical implications. The data suggest clearly that antidepressants, given with normal care, are not clinically effective when compared with placebo for the treatment of clinically significant depression in dementia. This implies a need to change the current clinical practice of prescribing antidepressants as the first line treatment of depression in dementia due to Alzheimer's disease.

Limitations

First, the drop out will have introduced bias if those dropping out had a different response to the trial interventions or placebo compared with those completing the trial. However this was designed as a pragmatic trial with few exclusions to mirror closely real clinical populations, and the levels of disengagement are similar to those experienced in clinical settings. Strenuous efforts were made to follow up and obtain outcome data on all those randomised but who defaulted from either the trial compound or clinical services.

A second putative limitation is the revision during the trial of the target sample size. Because of slower than forecast recruitment, we sought an extension and therefore further funding. The funder ordered interim analyses to determine the numbers needed using the data available on 75 cases followed up at 13 weeks. The new target set was 339. We recruited 326, falling short of the new target by 13. Nevertheless, this is the largest ever RCT of depression in dementia with unequivocal findings showing no effect of either antidepressant compared with placebo. Had the pattern of change seen in those recruited been continued, the extra precision in estimates that would have come from either another 13 cases, or even achieving the original trial target of 507, would not have generated a statistically significant positive result for either antidepressant.

Third, measurement error caused by the effect of cognitive impairment on domains such as memory, language, and reasoning is a potential limitation. However the study included only those measures best validated for use in dementia. Our primary outcome, the CSDD, is the most robust available measure of depression in dementia[60] incorporating data from the carer, the person with dementia, and the rater. Finally, we did not capture elements of intervention by the clinical teams other than the group to which they were randomised. Had we been able to characterise these non-drug elements of treatment then we might have been able to investigate their role in patient recovery. However there is no suggestion that

these would have varied across the three groups, so again the results would not have changed.

Finally it might be considered a limitation that we did not adjust the results for the multiple comparisons made in the secondary analyses. The data are presented as they are so that the reader can interpret the actual findings as they find best. The work should be reviewed considering a 1% significance level for all secondaries.

Generalisability

This study was designed to reflect real clinical populations and interventions as closely as possible. To this end we minimised exclusions and had permissive inclusion criteria. However the findings may not generalise to those too critically ill to risk randomisation (chiefly those with high suicide risk). Only three potential participants were excluded on this criterion but there will have been more not referred into the trial. Equally, outcomes of those with depression but a CSDD score under 8 would not be covered by this study. In practice however very few people with a CSDD score at this level would be considered to have clinically significant depression, so the effect on generalisability will be limited.

One of the strengths of this study is its size and the broad nature of the study group, both by the range of depressive symptoms and the severity of dementia, neither of which appeared to influence outcomes. We included not only those with narrowly defined Alzheimer's disease but also those with probable and possible Alzheimer's disease. This is closer to the population encountered in clinical practice where there is often mixed dementia (ie those with a vascular component to their dementia). However prudence would limit generalisability to Alzheimer's disease and mixed dementia only and not to other subtypes such as vascular dementia, dementia with Lewy bodies or fronto-temporal dementia.

The one major limit to generalisability comes from all cases being drawn from referrals to old age psychiatry services. Such services are designed to deal with complex clinical situations, but there will be instances where people with depression in dementia are not referred to specialist services but remain either treated or untreated in primary care. Possibly, such cases would respond differently to antidepressants. However, finding unrecognised and untreated cases in primary care is difficult and referral of such cases to specialist services is good practice. Given the participants were not drawn from specialist research clinics or tertiary care, but from nine geographically diverse areas and a large number of clinicians representative of services in general (please see acknowledgements), the external validity of the results reported here will be maximised.

The drugs used in this study represent the two most used classes of antidepressants but the extent to whether other classes (eg dual-acting antidepressants like venlafaxine) might have an effect is unclear; it would however be reasonable to expect broadly similar responses in drugs of the same general class.

Interpretation

The main message from this study is that the drugs from the two classes of antidepressants most likely to be prescribed for depression in Alzheimer's disease appear to be no more effective than placebo. This negative finding does not seem attributable to the type or the severity of depression in dementia included, or to the severity and vascularity of the dementia included. In this our results are in line with those of the DIADS-II study.[28,29] It is however encouraging for people with depression in dementia that there was a strong consistent pattern of improvement in the depression at three and nine month follow up for this group of people referred to old age psychiatric services. This study gives strong evidence that this improvement is not attributable to antidepressants. What this study cannot tell us is if this improvement is a function of the non-drug "treatment as usual" by these old age psychiatric services, or due to artefact such as regression to the mean, the Hawthorne effect, or part of the natural history of depression in dementia. The last is perhaps made less likely by the finding that 221/326 (68%) had been depressed for more than six months prior to randomisation.

In terms of harms from medication, there were more adverse reactions in those treated with antidepressants compared with placebo as in other studies.[28,29] It is important to be cautious about drawing conclusions from the analyses of secondary outcomes; the key message remains that there is no positive effect of the antidepressants on any of the pre-specified comparisons compared with placebo. There is however a signal in the data consistent with the pattern of adverse reactions observed. There were fewer neuropsychiatric symptoms, higher carer-rated participant quality of life, and higher carer quality of life in those treated with mirtazapine compared with sertraline. Also, carers of those receiving placebo had higher quality of life themselves and better mental health compared with those caring for people on sertraline. Taken together, even though these differences did not persist at 39 week follow-up, they may suggest that sertraline has more negative impacts than mirtazapine. This is of clinical importance since it is common clinical practice to use sertraline following the positive results of the first DIADS study.[26]

One of the unique elements of this study is the simultaneous evaluation of cost effectiveness as well as clinical effectiveness. As far as we are aware, this is the first randomised controlled trial with an economic evaluation of the use of pharmacotherapy for older people with dementia and depression. Because of the lack of significant pairwise differences in costs or outcomes (CSDD score) between sertraline, mirtazapine and placebo, the active treatments mirtazapine and sertraline have a low probability of being cost-effective compared to placebo. However it is interesting that when both active treatments are compared against each other, treatment with mirtazapine has a high probability of being cost effective compared with sertraline.

Care professionals, policy makers and people with dementia and their families are primarily interested in quality of life, and so a secondary cost-effectiveness analysis examined pairwise cost differences between the three treatments relative to the incremental difference in QALY gain. There were non-significant pairwise differences in costs or outcomes (QALY gains) between sertraline, mirtazapine and placebo. Sertraline had a low probability of being cost-effective compared to placebo. However; treatment with mirtazapine had a high probability of being cost-effective compared to placebo or when compared against sertraline.

This seems counter-intuitive given the lack of clinical effectiveness demonstrated in the primary analyses. We considered possible reasons for this finding: first, there was a trend towards lower incremental costs and higher incremental QALY gains for mirtazapine when compared to sertraline and placebo in turn. The trends observed towards lower costs were due to the significantly lower informal care inputs when with patients treated with mirtazapine compared with those treated with placebo or sertraline. The differences in improvements in quality of life could perhaps be explained in part by the effects of treatment with mirtazapine such as amelioration of sleep disturbances or anxiety state not explored in this study.[61,62] Improvements in sleep could potentially enhance mood not captured by the CSDD and mood has been shown to be correlated with patient-reported EQ-5D scores.[63] In this way mirtazapine might have a more general effect that was beneficial for both the patient and the carer.

When looking at our secondary outcomes (such as quality of life and NPI) it may well be that the amendments to protocol in terms of sample size resulted in a loss of power for secondary analyses. As discussed above, during the study, the protocol needed to be amended after slower than expected recruitment. An interim analysis was completed of the primary outcome and the sample size was recalculated based on the estimates from the interim analysis. The variance in these CSDD scores was smaller than previously expected.

So under the new calculation (of a smaller sample size), there was enough power to show the potential differences in the CSDD, but there was no such analyses for the secondary outcomes. The study may therefore not have been sufficiently powered to test the patterns of response observed in the secondary outcomes.

In any case it is striking that in the long run those randomised to mirtazapine appear to use half as much carer time as those randomised to sertraline or placebo. Likewise the pattern of dominance of mirtazapine over sertraline is maintained in these analyses. All providing further evidence that sertraline may not be a good choice for the treatment of depression in dementia. The extent to which this is generalizable to other SSRIs is not clear from our study. The potential positive effects of mirtazapine seem more general than specific and may act more in the realm of general behavioural and psychological symptoms in dementia (BPSD) than depression per se. It is possible for example that a positive effect on sleep or agitation in the person with dementia may result in relief, not only for the person with dementia but also the carer in terms of hours of care needed.

The development of BPSD (eg agitation, aggression, wandering, shouting, repeated questioning, depression and sleep disturbance) is common in dementia occurring at some stage in up to 90% of cases. They cause problems in themselves, which complicate care, and they can occur at any stage of the illness. They are a legitimate object for intervention to decrease distress and harm, and increase quality of life for the person with dementia and their carers. One area for concern is the reflexive use of antipsychotics to treat these symptoms. A ministerial enquiry into the use of antipsychotic drugs in dementia concluded that "…current systems appear to deliver a largely antipsychotic-based response".[64] It is clear that these medications are being prescribed to deal with behavioural and psychological symptoms in dementia rather than just for psychosis.

The evidence includes gaps, contradictions and complexity but there is emerging consensus with respect to the level of use and risk of antipsychotic drugs for people with dementia. Reviewing the evidence, these drugs appear to have only a limited positive effect in treating these symptoms but can cause significant harm to people with dementia. On balance, it appears that around 180,000 people with dementia are treated with antipsychotic medication across the country per year. Of these, up to 36,000 may derive some benefit from the treatment. In terms of negative effects that are directly attributable to the use of antipsychotic medication, use at this level equates to an additional 1,800 deaths, and an additional 1,620 cerebrovascular adverse events, around half of which may be severe, per year.[64]

Despite the limited evidence base, the use of non-pharmacological interventions as the first-line treatment for BPSD reflects 'best practice' when taking into account safety considerations and the high rates of resolution of symptoms with placebo in pharmacological trials.[34] The main reason for the widespread use of antipsychotics is the limited evidence for alternative treatments. Other pharmacological treatments used include anticonvulsants (carbamazepine and sodium valproate), and antidepressants (trazadone and citalopram). The best evidence is for carbamazepine, which has been shown to be better than placebo for agitation in several small placebo-controlled trials,[65] but there is limited information about long-term safety in people with dementia. A recent meta-analysis concluded that sodium valproate was only effective at high doses that were associated with unacceptable side effects.[66] The results of double-blind placebo-controlled trials of trazadone have been disappointing.[67]

In a double-blind placebo-controlled trial of people with AD that predominantly focused on depression, citalopram was also associated with improvement in a number of other behavioural and psychiatric symptoms, including irritability and restlessness.[68] However, as neuropsychiatric symptoms were not the main focus of the study, only a modest proportion of participants had clinically significant behavioural and psychiatric symptoms at baseline so the results are difficult to interpret. In a definitive trial of a cholinesterase inhibitor for the treatment of clinically significant agitation in people with AD, donepezil showed no advantage over placebo.[69] One recent re-analysis of a placebo-controlled trial of memantine in people with moderate to severe AD suggested that patients with neuropsychiatric symptoms benefited from treatment.[70]

The data presented here suggest that there may well be value in conducting an RCT of mirtazapine for the treatment of BPSD; no such trial has ever been completed. One small scale open label pilot studies gives supportive evidence for the potential of a trial in this area (those on mirtazapine did better).[71] Given the paucity of alternatives and the priority of finding safe and effective treatments for BPSD, these data suggest that a placebo-controlled trial of mirtazapine would be of value.

CHAPTER 5: CONCLUSIONS

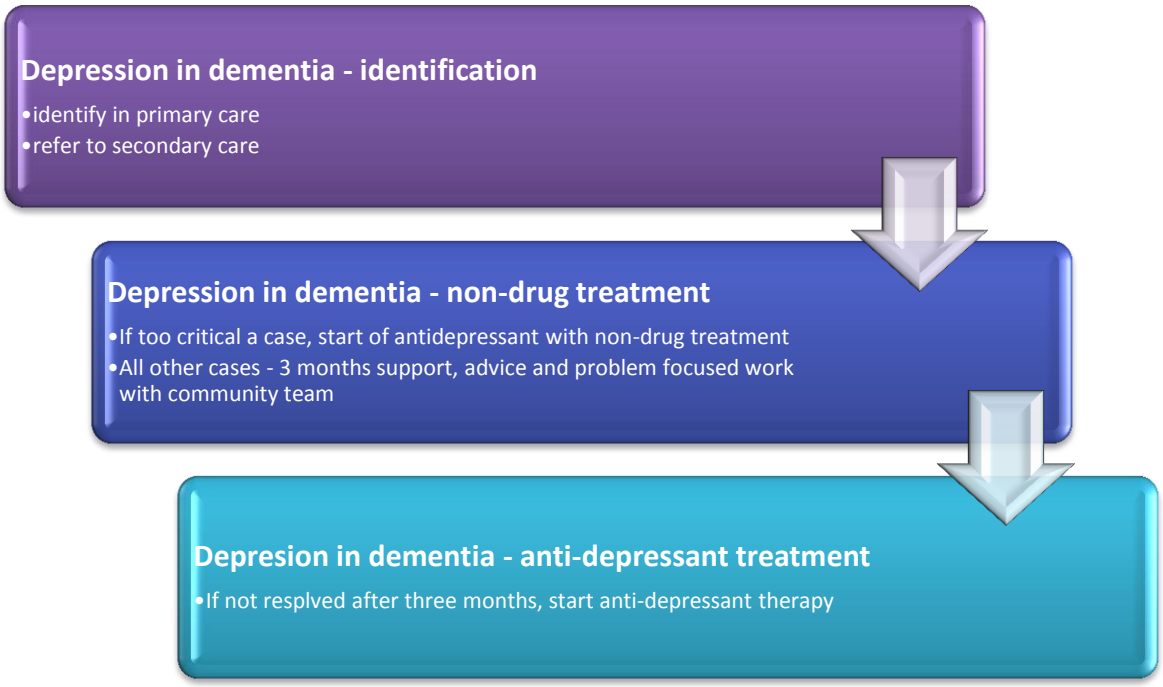
Implications for health care

So what can be concluded? This study finds no evidence to support the use of antidepressants as as a first line treatment for people with depression in Alzheimer's disease who are referred to old age psychiatry services as many cases will resolve with usual care and without sertraline or mirtazapine. An important exclusion to this are the most critical of cases (by reason for example of self-harm or other risk) which were not included in this study.

Stepped care, with 'watchful waiting' is advocated currently 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 an alternative to antidepressants at the next stage of severity.[72] 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 focussed on problems encountered by the person with dementia and the carer, covering aspects of dementia as well 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. Compared with this personalised care the Hawthorne effect of the study assessments is likely to have had only a minor impact. These data suggest that having depression in dementia may be an appropriate trigger for referral to specialist services where non-drug treatments can be deployed, perhaps avoiding the use of medication with potential for adverse reactions.

In summary, the practical implications of this study are that we should reframe the way we think about the treatment of people with dementia who are depressed, the evidence does not support the routine prescription of antidepressants for depression in dementia. As we find no evidence to support use of antidepressants, it suggests that potential cases might be more appropriately managed by specialist services that are able to offer non-drug interventions for depression and case management that may not be available in primary care. Based on the data (a decrease at 13 weeks and this then maintained), save for those in whom medication is indicated by risk or extreme severity, In the absence of evidence to the contrary it might be appropriate to reconsider antidepressant prescribing for those who have not responded within a three month period (Figure 9).

Figure 9: management of depression in dementia



Recommendations for research

1. The secondary analyses presented here suggest that there would be value in carrying out a placebo controlled trial of the clinical and cost effectiveness of mirtazapine in the management of BPSD.

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 anti-dementia medication (eg 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.

5. Further work is needed to investigate the cost modelling results in this rich dataset, investigating carer burden and possible moderators to the treatment effects.

6. There is scope for re-analysis of the primary outcome in terms of carer and participant CSDD results.

CHAPTER 6: ACKNOWLEDGEMENTS

Contributors

SB was the chief investigator for the study and designed and managed the study with input from the group. JH and MD did the statistical analyses. All authors participated in data interpretation. SB drafted the first and subsequent versions of this report with input and key revisions by all authors, who reviewed and approved the final submitted report.

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Conflicts of interest

SB, MD, CB, RB, PB, CF, CH, CK, MK, CL, JL, GL, EM-C, JM, MO, JO'B, AT, KW, and AB have received consultancy fees, speakers' fees, research funding, or educational support to attend conferences from pharmaceutical companies involved in the manufacture of antidepressants and anti-dementia drugs. SB and AB have been employed by the Department of Health for England and CB has been employed by the Alzheimer's Society. JH, RR, NMcC, SN, MP, and RW declare that they have no conflicts of interest.

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CHAPTER 7: REFERENCES

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Appendix – Trial protocol