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 effectiveness of sertraline and mirtazapine

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Abstract

Background

Depression is common in dementia causing considerable distress, and other negative impacts. Treating it is a clinical priority but the evidence base is sparse and equivocal.

Methods

The HTA-SADD (study of the use of antidepressants for depression in dementia) trial was a multi-centre parallel group double-blind placebo-controlled pragmatic RCT of the clinical effectiveness of sertraline and mirtazapine (primary outcome 13 weeks; long term 39 weeks). Eligibility: probable or possible Alzheimer's Disease, depression (4+ weeks), and Cornell Scale for Depression in Dementia (CSDD) score of 8+, from 9 English old age psychiatry services. Exclusions: clinically too critical (eg suicide risk); contra-indication to medication; taking antidepressants; in another trial; and having no carer. Interventions: (1) sertraline, (2) mirtazapine, and (3) placebo, all with normal care. Target doses: 150mg sertraline or 45mg mirtazapine daily. The objective was to determine clinical effectiveness of sertraline and mirtazapine in reducing depression 13 weeks post-randomisation compared with placebo. The main outcome was CSDD score. Randomisation: 1:1:1 allocation with stratified computer-generated block randomisation by centre with randomly varying block sizes by a Trials Unit, independent of trial team. Medication and placebo were identical for each antidepressant. Referring clinicians, research workers, participants, pharmacies and statisticians were blinded until analyses were completed.

Findings

326 participants were randomised (111 placebo, 107 sertraline, 108 mirtazapine). The main outcome, mean differences (95%CI) in CSDD at 13 weeks from an adjusted linear mixed model were: placebo/sertraline 1.17 (-0.23 to 2.58, p=0.10); placebo/mirtazapine 0.01 (-1.37 to 1.38, p=0.99); and mirtazapine/sertraline 1.16 (-0.25 to 2.57, p=0.11). There were no statistically significant differences in depression score between groups at 13 or 39 weeks. The placebo group had fewer adverse reactions (29/111, 26%) than sertraline (46/107, 43%) or mirtazapine (44/108, 41%; p=0.017) and fewer serious adverse events rated as severe (p=0.003). 39 week mortality was equal with five deaths in each group.

Interpretation

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 and there are harms associated with their use. This implies a need to change current practice of antidepressants being the first line treatment of depression in Alzheimer's disease. *EudraCT Number* - 2006-000105-38

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Introduction

Background

Dementia is a severe and challenging public health issue, affecting 35 million worldwide (trebling by 2050);[1] costing $600 billion annually; 1% of world GDP.[2] Dementia has a devastating impact on those affected and their family carers across culture, gender, ethnicity and class. Depression is common in dementia with prevalence over 20%,[3,4] causing distress, reducing quality of life,[5] exacerbating cognitive and functional impairment,[6] increasing mortality,[3] and increasing carer stress and depression.[7]

Treating depression in people with dementia is a clinical priority but the evidence base is sparse and equivocal. The most recent Cochrane review[8] identified six relevant studies; only three could be meta-analysed. The first two studied the tricyclic antidepressants (TCAs) clomipramine[9] (n=24) and imipramine[10] (n=61), and the third, DIADS[11,12] (n=44,) sertraline a specific serotonin reuptake inhibitor (SSRI).[13] Findings of the first were balanced, the second negative and the third positive. The review concluded there was only weak evidence of the effectiveness of antidepressants in dementia. Two studies used TCAs “drugs not commonly used in this population” due to anticholinergic side effects; only one used the most commonly used class (SSRIs). None covered newer classes of antidepressants and all were of short duration. One further relevant randomised controlled trial (RCT) has been published since. DIADS-2, compared 67 people prescribed sertraline with 64 given placebo; in contrast to DIADS, they found no benefit of sertraline at 12 or 24 weeks.[14,15] A recent systematic review and meta-analysis including these data (total n=330)[16] confirmed the evidence base as equivocal with larger definitive trials needed.

Despite this, 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[17] concluded “SSRIs may offer some benefit”. A UK guideline suggests antidepressants as the only form of management for depression in dementia[18] and the UK NICE/SCIE Clinical Guideline on Dementia[19] advocates their use. Given uncertainty in this clinically important area, the UK NIHR commissioned this study to fill gaps in the evidence base definitively..

Objectives To determine the clinical 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 harm; other outcomes (quality of life, cognition, carer burden, carer quality of life, death); and the influence of clinical characteristics (dementia severity, dementia type, depression type, depression severity, and neuropsychiatric symptoms). Cost data and analyses will be presented elsewhere.

Methods

Trial design

Multi-centre parallel group double-blind placebo-controlled RCT of the clinical effectiveness of two antidepressants with 13 and 39 week follow up (1:1:1 allocation). Ethical approval: North West 7 (Greater Manchester) Ethics Committee. Full trial protocol:http://www.iop.kcl.ac.uk/projects/?id=10287.

Participants

Eligibility - A pragmatic trial, with inclusion criteria mirroring clinical practice. All met NINCDS/ADRDA criteria for probable or possible Alzheimer's Disease[20] (ascertained by referring psychiatrist) and co-existing depression (4+ weeks duration) assessed as potentially needing antidepressants. A research worker then assessed depression severity using the CSDD,[13] those scoring 8+ were eligible. All research workers were trained in the assessments including the CSDD in group sessions at seven meetings through the trial plus individual training sessions with the trial manager. All recruited between the meetings were trained by the trial manager and local top-up training was provided whenever necessary. As well as initial CSDD training sessions, meetings featured refreshers, with scoring exercises showing good reliability between raters. 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 informant. Participants were recruited from old age psychiatry services in nine English centres (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, North London, Southampton, and South London & Kent).

Interventions

Three groups: (1) sertraline, (2) mirtazapine, and (3) placebo, all with normal clinical care. The target doses were 150mg sertraline or 45mg mirtazapine daily. 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). The participants started on one of each tablet. They were told to increase the dose to two of each at two weeks. At four weeks the research worker telephoned and completed a CSDD. If the score was 4 or more then the dose was increased to the target dose of three of each tablet. If the score was below 4 at week 4 they stayed on two of each and were contacted at week 8 when, if their CSDD was 4 or more the dose was increased to three of each tablet. Thereafter it was open to clinicians to adjust the dose.

Outcomes

Co-primary outcomes – Depression in dementia, CSDD,[13] and costs Client Service Receipt Inventory (CSRI)[21] at 13 weeks. Cost data will be reported elsewhere.

Secondary outcomes and moderators - disease-specific health related quality of life (DEMQOL and DEMQOL-Proxy);[22] generic quality of life (EQ-5D interview administered to carer);[23] withdrawal from treatment; cognition (Mini Mental State Examination MMSE);[24] depression severity (CSDD score low 8-11, high 12+); depression type (depression in Alzheimer's disease by Olin criteria[25]); medication adherence; adverse events; carer mental health (General Health Questionnaire GHQ-12)[26]; carer quality of life (SF-12v2);[27] carer burden (Zarit);[28] behavioural disorder (Neuropsychiatric Inventory NPI);[29] and baseline dementia vascularity index (modified Hachinski).[30]

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; Standardised Effect Size [SES] 0.4) for 13 week sertraline/placebo and mirtazapine/placebo comparisons, and 86% power at 39 weeks. This allowed 20% loss to follow-up and CSDD baseline/outcome correlation $\geq$ 0.6 using analysis of covariance with two sided 5% significance levels and two sided 95% confidence intervals (95%CI) for a (clinically significant) 10% difference in adverse events between groups.

Change to protocol – Due to a call for extra funding following slower recruitment than predicted, the sample size needed for the trial was statistically reviewed by the Data Monitoring and Ethics committee when there were 75 subjects with 13 week follow-up data. The parameters of the sample size calculation were not changed (sd 5; SES 0.4). The new target was based on observed values which gave greater precision than the pre-study assumptions. An extended recruitment period was agreed with a revised target of 339 for the sample (113 in each group). This involved unblinding a statistician to the identity of the placebo group; that statistician was not involved in the final analyses.

Randomisation

Participants were allocated to placebo, sertraline or mirtazapine (1:1:1) through the Clinical Trials Unit (CTU) after baseline assessment and consent. The CTU independently undertook treatment allocation. Allocation was by centre using stratified block randomisation with randomly varying block sizes and computer-generated randomisation. Allocation was 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 analyses were complete.

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. Continuous variables were summarised with mean and sd, categorical variables were summarised using frequency and percentages. The primary analyses, CSDD differences between treatment groups (sertraline/placebo and mirtazapine/placebo), were estimated with mixed linear regression models[31]. Covariates were treatment, baseline CSDD, 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 using diagnostic plots. Modelling was based on the

assumption that data were missing at random and predictors of missing data (treatment group and centre) were included in the modelling. A logistic model was used to assess predictors of missing data (examining all baseline clinical and demographic variables). Categorical variables were compared using Fisher's Exact test. Secondary outcomes were analysed using 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 centre. Results from all analyses were summarised at 13 and 39 weeks with 2 sided 95%CIs.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All named authors had access to data, commented on drafts, and approved the final report. SB had final responsibility for the decision to submit for publication.

Results

Participant flow

Participant flow is presented in Figure 1. By week 39, 27 (24%) had withdrawn from placebo, 37 (35%) from sertraline and 31 (29%) from mirtazapine. Dropouts were not statistically significantly different between groups (Fisher's exact test, p=0.26).

Recruitment

326 participants were recruited into the study between January 2007 and December 2009; follow-up interviews were completed by October 2010.

Baseline data

Baseline demographic and clinical characteristics by group are presented for participants and carers in Tables 1 and 2 respectively. There were no differences between the randomisation groups.

Numbers analyzed

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. The

overall mean dosages (including those who withdrew from medication) taken were 70mg of sertraline and 24mg of mirtazapine. For those who remained on prescribed medication the mean dosage was 95mg sertraline and 30mg of mirtazapine.

Outcomes and estimation

Severity of depression (CSDD score), decreased in all three intervention groups compared with baseline. The greatest absolute improvement at the primary endpoint (13 weeks) was with placebo -5.6 (sd 4.7) compared to -3.9 (sd 5.1) with sertraline and -5.0 (sd 4.9) with mirtazapine. At 39 weeks recovery from baseline was sustained in all groups with change score of -4.8 (sd 5.5) for placebo, -4.0 (sd 5.2) for sertraline and -5.0 (sd 6.1) for mirtazapine. Changes in CSDD score over the trial period are summarised in Figure 2.

The result of the linear mixed modelling, adjusting for baseline depression severity and centre are presented in Table 3. In terms of the primary outcome, there were no statistically significant differences between either sertraline or mirtazapine and placebo or between sertraline and mirtazapine. These analyses provide robust evidence of a lack of clinical effectiveness of the antidepressants tested here compared with placebo.

The effectiveness of the medications compared with placebo and between themselves on secondary participant outcomes are presented in Table 4. Again there is little change attributable to the antidepressants. The only statistically significant associations observed were at week 13 where fewer neuropsychiatric symptoms and higher carer-rated participant health related quality of life (DEMQOL-Proxy) were observed in the mirtazapine group compared with sertraline. These differences did not persist at 39 weeks .

There was no change in the findings when subgroup analyses were completed examining outcomes by different baseline depression severity (CSDD score 8-11 v 12+). All but 8 participants (1 placebo, 3 sertraline, 4 mirtazapine) met criteria for categorical diagnosis of depression in Alzheimer's disease using "Olin criteria" Sensitivity analyses with the Olin criteria as a moderator were not appropriate, due to the very low frequency of Olin criteria non-caseness. However this gives reassurance of the clinical significance of the depression in dementia investigated here.

Examining carer outcomes at 13 weeks, those whose relative was receiving placebo had higher quality of life (SF-12 Mental Component Score) and better mental health (GHQ-12) than those on sertraline. Finally there was higher quality of life (SF-12 Mental Component Score) at 13 weeks in the carers of the mirtazapine group compared with the carers of the sertraline group. These differences did not persist at 39 weeks .

Harms

Adverse reactions to week 39 are presented in Table 5. The placebo group had a lower overall rate of adverse reactions (29/111, 26%) compared with sertraline (46/107, 43%) and mirtazapine (44/108, 41%); this difference was statistically significant (Fisher's Exact test, p=0.017). The pattern was different between groups with gastrointestinal reactions more common with sertraline (most commonly nausea) and psychological reactions more common with mirtazapine (most commonly drowsiness and sedation). Examining severity, at 13 weeks, there were 15 serious adverse events in the placebo group of which 3 (20%) were rated severe; 12 in the sertraline group (8 [67%] severe) and 14 (10 [71%]) severe) in the mirtazapine group. Overall there was no statistically significant difference in the number of serious adverse events reported but more of these were severe in those on antidepressants compared with placebo (Fisher's Exact test, p=0.003). There was no difference in mortality between the three groups with five deaths in each at 39 weeks.

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, drop out will introduce bias if those lost have a different response to the interventions or placebo compared with those completing the trial. However this was a pragmatic trial with few exclusions to mirror real clinical populations and levels of disengagement similar to those in clinical settings. Strenuous efforts were made to follow

up and obtain outcome data on all randomised who defaulted from either the trial compound or services.

A second possible limitation is the revision during the trial of the target sample size. However, the new target was set using the same parameters as the pre-study calculations. We recruited 326/339, falling short 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 from either another 13 cases, or even achieving the original 507, would not have generated a statistically significant positive result for either antidepressant.

Third, measurement error caused by cognitive impairment is a potential limitation. However the study included only measures well validated for use in dementia. Our primary outcome, the CSDD, is the most robust available measure of depression in dementia,[32] incorporating data from the carer, the person with dementia, and the rater.

Finally, we did not capture elements of intervention by clinical teams. Had we been able to characterise non-drug elements of treatment, we might have been able to investigate their role in patient recovery. However randomisation means these were distributed equally across the three groups, so results would not have changed.

Generalisability

This study was designed to reflect real clinical populations and interventions closely. We minimised exclusions and had permissive inclusion criteria. However the findings will not apply 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. However very few people with a CSDD score at this level would have clinically significant depression, so impact on generalisability will be limited.

Study strengths include its size and the broad nature of the study group, both by severity of depression and dementia, neither of which appeared to influence outcomes. We included not just narrowly defined Alzheimer's disease but also those with probable and

possible Alzheimer's. This is closer to populations encountered in clinical practice where there is often mixed dementia (with a vascular component to dementia). However prudence would limit generalisation to Alzheimer's disease and mixed dementia and not other subtypes (vascular dementia, dementia with Lewy bodies or fronto-temporal dementia).

One limit to generalisability comes from cases being drawn from old age psychiatry services. Such services are designed to deal with complex clinical situations, however some 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, untreated cases in primary care is difficult and referral of such cases to specialist services is good practice. Since participants were not drawn from specialist research clinics or tertiary care, but from nine geographically diverse areas with a large number of clinicians representative of services in general (please see acknowledgements), the external validity of the results here will be maximised.

The drugs used in this study represent the two most used classes of antidepressants but 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 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. 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 on antidepressants compared with placebo as in other studies.[14,15] It is important to be cautious about conclusions from analyses of secondary outcomes; the key message remains that there is no positive effect of the antidepressants on any pre-specified comparison 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 has become common clinical practice to use sertraline following the positive results of the first DIADS study.[12]

So what can be concluded? The data suggest that antidepressants should not be prescribed 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, without sertraline or mirtazapine. Stepped care, with 'watchful waiting' is advocated for the community treatment of depression (without dementia). The first step being "low-intensity psychosocial interventions" with more complex psychosocial interventions an alternative to antidepressants at the next stage of severity.[33] Those recruited into the trial benefitted from the 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.

As in the DIADS-2 study, the lack of response of depression to antidepressants observed here do not seem to be attributable to low depression severity, the type of depression recruited or to low medication compliance.. This suggests that depression in dementia may be different in terms of neurobiology than depression occurring in those without dementia. Diagnosing depression in dementia can be complicated. This study provides support for the need for accurate specialist diagnosis and management of dementia and co-morbidities[34] given that establishing such services has been shown to be feasibile[35] and cost effective.[36]

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, with the routine prescription of antidepressants reconsidered. Where potential cases are recognised these should be referred to local specialist services. Based on the data (a decrease in depression at 13 weeks with this then maintained), the use of antidepressants might be reserved for those whose depression has not resolved within three months of referral, except for those in whom medication is indicated by risk or extreme severity.

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

Conflicts of interest
All authors except JH, RR, NMcC, SN, MP and RW have received consultancy fees, speaker fees, research funding and/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 UK Alzheimer's Society. JH, RR, NMcC, SN, MP and RW reported no such potential conflicts of interest. All authors reported no actual conflicts of interest in their work on this project.

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Panel

Research in context

Systematic review

We searched PubMed and Cochrane Library databases up to 1 March 2011, without language restrictions for full papers 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 of where there was no recognised depression outcome measure, where there was no placebo, and where no threshold for depressive disorder was specified. We identified the most recent Cochrane Review[8] and three further more recent systematic reviews.[16,37,38] In terms of meta-analysis, the Cochrane review identified three studies (107 subjects) where data that could be combined. Results were negative for Hamilton scores (4 studies, n=128) mean effect size -0.93 [95%CI -3.27, 1.41], but positive for CSDD (1 study n=44) -6.7 [-11.5 to -1.90], though this was from just one study. They concluded that there was only weak evidence available of the effectiveness of antidepressants in dementia. The 2007 study,[35] using different quality assessment, included data from 5 studies (165 subjects) and concluded that antidepressants were superior to placebo for both treatment response (odds ratio [OR] 2.32; 95% confidence interval [CI], 1.04 to 5.16) and remission of depression (OR 2.75; 95% CI, 1.13 to 6.65) with rates of discontinuation comparable to placebo. One subsequent trial[14,15] found no positive effect of sertraline at 3 and six months. The meta-analysis of the 2010 systematic review[34] is questionable because, although it includes this most recent trial, it appears that it might count the data from the first DIADS trial twice, using both the interim and the final trial data. Finally the 2011 study concluded that the efficacy of antidepressants in people with depression and dementia is not established. The reviews and meta-analyses taken together are non-conclusive but all reported that limitations of previous trials included small size, few using drugs that were used in clinical practice and short term follow-up.

Interpretation

The two classes of antidepressants most likely to be prescribed for depression in Alzheimer’s disease appear to be no more effective than placebo. In terms of harms from medication, there were more adverse reactions in those treated with antidepressants compared with placebo. The practical implications of this study are that we should reframe the way we think about the treatment of people with Alzheimer’s disease who are depressed, with the routine prescription of antidepressants reconsidered.

Ethics

This study was approved by the North West 7 (Greater Manchester) Ethics Committee.

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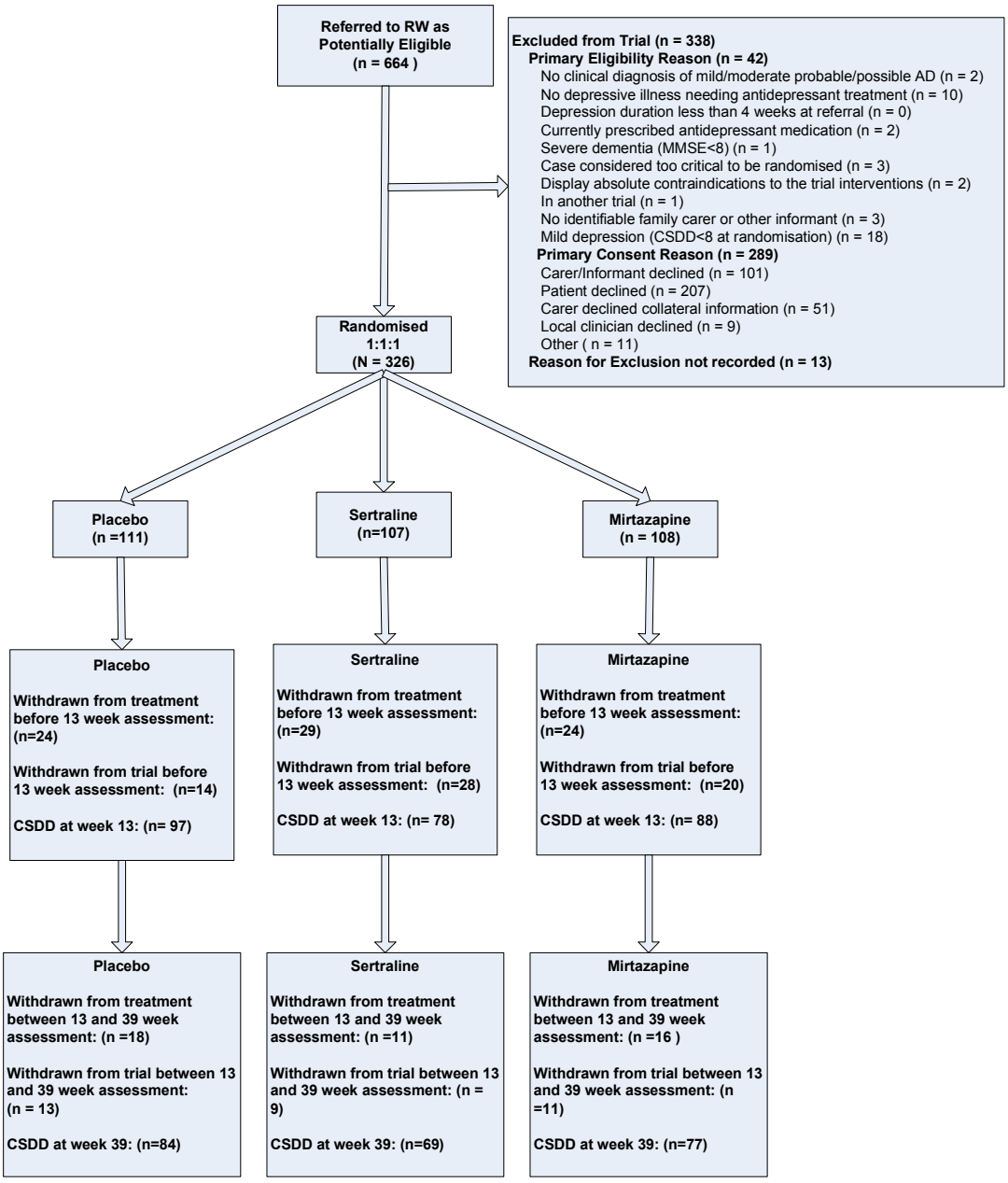
Figure1: Trial participant flow (Consort diagram)



Notes:
Withdrawal from treatment implies the participant remains in the trial.
Withdrawal from the trial implies the participant withdraws from the trial and from treatment.
These two categories of withdrawal are mutually exclusive.

Table 1: Summary of participant and carer demographics and characteristics at baseline

	Placebo N= 111	Sertraline N= 107	Mirtazapine N= 108
Participant			
Age (years)	79 (8.8)	80 (8.4)	79 (8.4)
Sex (Male)	40 (36%)	34 (32%)	31 (29%)
Ethnicity (White)	104 (93%)	98 (92%)	101 (94%)
Marital status (Married)	48 (43%)	51 (48%)	60 (56%)
Residence (lives in care home)	20 (18%)	13 (13%)	17 (16%)
Carer	N= 151	N=123	N=139
Age (years)	59 (14.8)	61 (13.9)	61 (17.1)
Sex (male)	46 (31%)	37 (30%)	48 (35%)
Ethnicity (White)	119 (79%)	109 (90%)	119 (86%)
Martial status (married)	93 (61%)	82 (77%)	85 (79%)
Relationship to participant (paid carer)	40 (26%)	19 (16%)	34 (25%)

Data are mean (sd) or number (%) unless stated otherwise

Table 2: Summary of clinical characteristics at baseline for participants and carers

		Placebo N=111	**Sertraline N= 107**	**Mirtazapine N=108**
Duration of depression	<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)	62 (58)	54 (50)
Dementia vascularity[a]		2.1 (1.3)	2.2 (1.3)	2.2 (1.3)
Carer rated ***Higher scores indicate a better outcome***				
Participant SF-12 Physical component (0-100) Mental Health (0-100)		103 43.2 (10.6) 50.1 (11.8)	101 45.2 (11.2) 47.9 (11.1)	96 44.9 (12.4) 46.1 (12.5)
Participant generic quality of life EuroQOL VAS (0-100)		109 52.3 (21.1)	106 53.8 (19.6)	105 51.9 (22.4)
Lower scores indicate a better outcome				
Participant depression CSDD (0-38)		111 13.6 (5.2)	107 12.8 (3.6)	108 12.5 (3.7)
Participant activity limitation BADL (0-60)		111 18.2 (11.1)	106 16.6 (11.2)	107 18.4 (10.9)
Participant quality of life DEMQOL Proxy (31-124)		91 88.4 (15.3)	97 86.5 (15.6)	91 86.9 (13.1)
Carer mental health GHQ-12 (0-36)		105 12.6 (5.1)	103 12.5 (4.9)	98 13.0 (5.9)
Carer burden Zarit (0-88)		87 27.2 (16.6)	93 27.8 (14.7)	91 26.1 (16.0)
Participant Neuropsychiatric symptoms NPI (0-144)		106 30.2 (17.6)	104 26.9 (16.8)	108 29.9 (20.9)
Participant rated ***Higher scores indicate a better outcome***				
Participant cognition Standardised MMSE (0-30)		82 18.2 (7.4)	79 18.5 (6.7)	90 17.6 (6.0)
Participant generic quality of life EuroQOL VAS (0-100)		92 60.3 (24.1)	86 66.6 (17.8)	91 66.9 (18.5)
Lower scores indicate a better outcome				
Participant generic quality of life DEMQOL (28-112)		87 83.7 (17.2)	82 82.5 (14.3)	91 85.1 (12.8)

Data are mean (sd) or number (%) unless stated otherwise
Frequencies given above summary statistics
[a]modified Hachinski index

Table 3: 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 2.58) 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	-

Data are mean scores (sd) or n (%), unless otherwise stated. Comparisons of the differences are made at 13 and 39 weeks from the final adjusted linear mixed model.

Figure 2: CSDD scores by treatment group, unadjusted means with 95% CI (a lower CSDD score means less depressive symptoms).

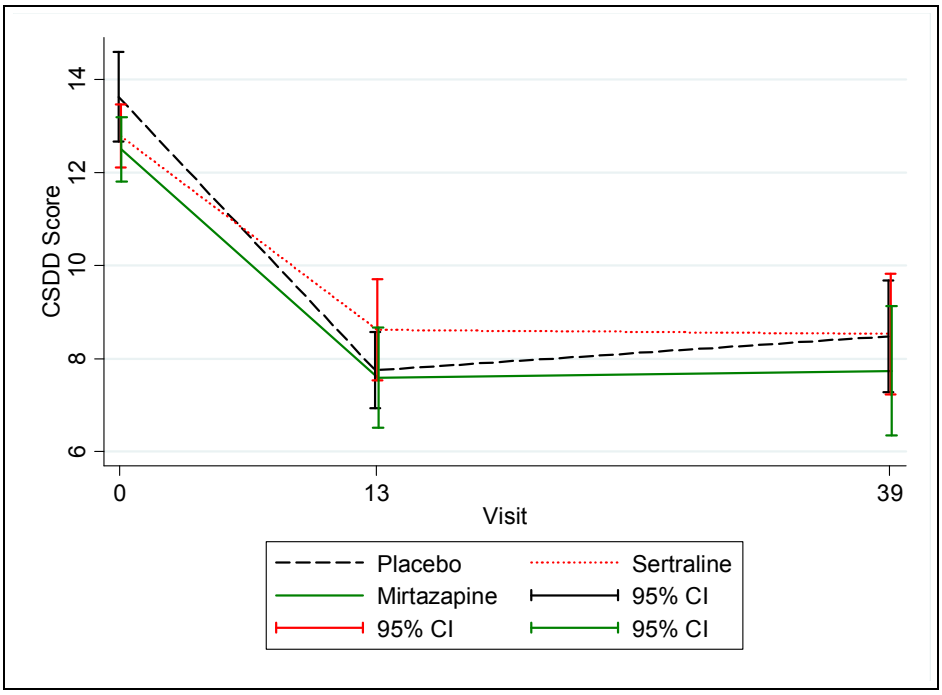


Table 4: Effect of the medications compared with placebo and between themselves on secondary participant outcomes and depression severity

		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)

Table 4: Effect of the medications compared with placebo and between themselves on secondary carer outcomes

		Week 13			**Week 39**		
		Sertraline v Placebo	**Mirtazapine v Placebo**	**Sertraline v mirtazapine**	**Sertraline v Placebo**	**Mirtazapine v Placebo**	**Sertraline v mirtazapine**
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)

Table 5: Adverse reactions (definite, probable, and possibly related) by study group

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)**

**Total number of participants reporting events (note possible to report more than one category of events)