A Double Blind Randomized Placebo controlled Trial Comparing Memantine and Antipsychotics for the long term treatment of Neuropsychiatric symptoms in people with Alzheimer's disease (MAIN AD)

Final study Report 30th April 2013 - Ballard C, Thomas A, Khan Z, Hanney M, Yu L M, Merrick C, Ferreira, N, Creese B, Bannister C, Burns A, Walker Z

Abstract

Background: Neuropsychiatric symptoms in people with Alzheimer's Disease cause significant distress to individuals and their carers, and present a complex clinical challenge for treatment. Current pharmacological treatment options are limited to antipsychotic medications which carry extensive safety issues. There is emerging evidence to support the potential benefits of memantine, currently licensed for treatment of moderate to severe AD, in the prophylaxis of agitation, aggression and psychosis over longer term treatment.

Method: The MAIN-AD study is a double-blind double dummy randomised placebo-controlled trial comparing memantine with antipsychotics for the treatment of neuropsychiatric symptoms over 24 weeks. 199 people with probable AD living in care homes and already receiving an antipsychotic were randomised to receive either memantine or antipsychotic. The primary outcome was The Bristol Activities of Daily Living Scale (BADLS) in addition to key secondary outcomes including Neuropsychiatric Inventory (NPI), Mini-Mental State Examination (MMSE) and mortality.

Results: There was no significant difference between the two treatment groups on the BADLS. Although there were no significant differences in total NPI scores between treatment groups at six, 12 or 24 weeks, there was a 5.01 (95% confidence intervals -1.68, 11.70, p=0.05) point advantage favouring antipsychotics at 12 weeks and a 3.63 (95% Confidence intervals -1.40, 8.67, p=0.16) point advantage favouring antipsychotics at 24 weeks., and the individuals allocated to antipsychotics were significantly less likely to experience a relapse of their neuropsychiatric symptoms at 6 week, 12 week and 24 week follow-up. The group receiving memantine had a non-significant 1.3 point advantage on the MMSE at 24 weeks. There were 9 deaths in the primary analysis population in participants receiving antipsychotics compared to 4 in those treated with memantine.

Discussion: The results indicate that there is no role for memantine in the long term treatment and prophylaxis of neuropsychiatric symptoms. The current results do indicate that antipsychotic medications did reduce the risk of relapse of neuropsychiatric symptoms, but this has to be balanced against a continued significant mortality risk. Effective and safe alternative pharmacological treatment options to antipsychotic medications are urgently needed.

Introduction

Worldwide there are 35 million people with dementia [1], the majority of whom have Alzheimer's disease (AD). It is a devastating illness, which results in a progressive decline in cognition and functional capacity, leading to eventual loss of independence and death. Neuropsychiatric symptoms such as aggression, agitation and psychosis, are very common, affecting up to 90% of people with dementia at some point over the course of their condition [2]. These symptoms lead to significant distress and risk to the person and those caring for them. In addition to the impact on individuals, neuropsychiatric symptoms also contribute significantly to the economic cost of dementia to healthcare services. These factors mean that management of neuropsychiatric symptoms is an urgent priority to enable effective and cost-effective treatment for people with AD.

Best practice guidelines addressing the management of neuropsychiatric symptoms in AD all emphasise the importance of identifying and addressing medical co-morbidities and pain, as well as highlighting the value of non-pharmacological treatment approaches to be used prior to resorting to pharmacological intervention [3, 4, 5]. The element of the guidelines addressing pharmacological management is more challenging. Atypical antipsychotics are the only class of drug for which there is robust evidence of efficacy in acute treatment (up to 12 weeks) of aggression. 18 randomised controlled trials (RCTs) have shown a significant but modest improvement in aggression with risperidone, olanzapine and aripiprazole and a smaller but still significant for the treatment of psychosis for the same agents (effect size 0.18). In contrast quetiapine appears ineffective [6, 7]. Adverse effects related to antipsychotics in the same RCTs included sedation, gait disturbances, peripheral oedema, chest infections, pneumonia, thrombo-embolic events, stroke and death [8]. Balancing modest benefits and the potential for serious harm, most best practice guidelines recommend judicious short term use of antipsychotics for severe or intractable symptoms causing significant risk or marked distress where non-pharmacological treatments have been unsuccessful. However, this raises a critical clinical dilemma as there is limited evidence to inform the longer term treatment of aggression or psychosis in people with AD, and audit studies indicate that antipsychotics are usually prescribed for longer than 6 months [9].

Only a handful of studies have investigated the effect of antipsychotics over six months or longer in people with AD. The AGIT study indicated that quetiapine was not beneficial for the treatment of agitation in AD over 26 weeks compared to placebo, and resulted in significant acceleration of cognitive decline [10]. The CATIE study indicated some benefits for risperidone and olanzapine compared to placebo at 12 weeks, but at nine month follow-up

there was no significant difference in the primary outcome [11]. Other longer term treatment studies have focussed on people with AD who have already been prescribed an antipsychotic. Randomized discontinuation with follow-up periods of three months or less have not demonstrated benefits from continued antipsychotics [12, 13]. Similarly studies replacing antipsychotics with person-centred care training or specific non-pharmacological interventions have not demonstrated greater efficacy for antipsychotics, and one study indicated a better quality of life in people where antipsychotics are discontinued [14, 15, 16]. However, three placebo-controlled antipsychotic withdrawal trials of six months or longer in duration which have not included a non-pharmacological treatment have indicated ongoing modest but significant benefits for antipsychotic drugs with respect to the treatment and prophylaxis of agitation and aggression. A six month pilot RCT of a discontinuation protocol demonstrated that relapse rates were halved in people continuing to receive haloperidol [17]. A further larger trial reported that continuing risperidone halved the relapse rate at 16 weeks and had an even more substantial benefit at 32 weeks in AD patients who initially responded to risperidone therapy [18]. Finally, a recent 12 month randomized withdrawal trial reported a non significant two-point advantage on the total Neuropsychiatric inventory (NPI) for antipsychotics compared to placebo over six months, which increased to a significant eight point advantage over 12 months [19]. However, there was a 1.8 fold increased mortality risk in the patients continuing to receive antipsychotics [20].

Despite several of the studies indicating that antipsychotics confer modest symptomatic benefits over longer term periods of treatment, the mortality attributed to antipsychotics becomes very substantial over longer term periods of treatment. For example, in the DART study at 36 months 59% of people were alive in the placebo group compared to only 30% in those assigned to antipsychotics [20]. In addition, the acceleration of cognitive decline becomes a major consideration over longer periods of treatment [7, 10]. A safe and effective pharmacological alternative to antipsychotics for the long term treatment and prophylaxis of neuropsychiatric symptoms is urgently needed.

Memantine is licensed for the treatment of moderate to severe AD and is a good candidate for treatment of neuropsychiatric symptoms. It has a good tolerability profile and confers significant benefits in cognition and function in severe AD. Although the only RCT examining mematine for the acute treatment of agitation in people with clinically significant agitation did not indicate significant improvement in agitation or aggression [21], there is emerging evidence to support the potential benefits of memantine in the prophylaxis of agitation, aggression and psychosis over longer term treatment. A meta-analysis has reported a significant, if modest, improvement in neuropsychiatric symptoms as measured by the NPI in

people treated with memantine compared to placebo over six months (2.76 points on the NPI, 95% CI 0.88 to 4.63, P=0.004) [22]. A subsequent post-hoc analysis focussing on people with agitation, aggression or psychosis in three of these trials indicated significant benefit following treatment with memantine after 24 or 28 weeks (-0.7 points vs 0.7 points; p=0.0004), particularly in agitation and aggression (response rates 61.0% vs 45.0%; p<0.001) [23]. The more recent DOMINO study showed a benefit of 4.0 [99% CI 0.6 to 7.4; p=0.002] NPI points in the memantine treatment group compared to those receiving placebo over 12 months [24]. The emerging evidence therefore suggests potential value of memantine in the longer term treatment and prophylaxis of neuropsychiatric symptoms, with likely safety advantages over antipsychotic treatment.

Objectives

The primary objective of this discontinuation trial was to evaluate the efficacy of 24 weeks' treatment with memantine in comparison to antipsychotics for the treatment and prophylaxis of neuropsychiatric symptoms in patients with AD already receiving antipsychotics for more than three months.

The primary hypothesis was that patients treated with memantine would have significant benefits with respect to daily activities. The secondary hypothesis was that memantine would have comparable efficacy in the treatment and prophylaxis of neuropsychiatric symptoms and with additional benefits in terms of safety and cognition compared to antipsychotic treatment.

Methods

This trial is registered with the National Research Register (ISRCTN68407918). The study EudraCT Number is 2007-00-4897-26. This study was approved by a human research ethics committee under the rules of the UK National Research Ethics Service.

Study design

MAIN-AD was a prospective, twenty-four week, multicentre, randomized, double-blind, double-dummy, placebo-controlled parallel group clinical trial in people with probable or possible AD according to the NINCDS ADRDA criteria [25], residing in care facilities and prescribed an antipsychotic for more than three months.

Eligibility criteria

Full eligibility criteria are reported in Table 1. Key inclusion criteria included participants living in a nursing or social care facility, to fulfil the NINCDS/ADRDA criteria for possible or probable AD and to be taking at least 0.5mg daily of haloperidol, 0.5mg daily of risperidone, 5mg daily of olanzapine or 25mg daily of quetiapine (or another antipsychotic, which in the opinion of the responsible clinician, could be safely switched to one of these antipsychotics) for a minimum of three months prior to entry into the study. Further pharmacological prescriptions were considered based on the criteria in Table 1. Patients were excluded if existing medical conditions, including mental health conditions, were deemed to confer unacceptable risk (Table 1), if they had a diagnosis of another primary neurodegenerative disorder or if a clinician considered current conditions likely to make participation in the trial distressing or to increase suffering**.** Participants with known sensitivity to memantine, amantadine, rimantidine or lactose were excluded. People who were unable to swallow tablets or capsules, or for whom it was deemed there was low probability of treatment compliance were also excluded. Written informed consent was provided by the participant where possible. If participants did not have adequate capacity, then written assent from the next of kin.

Intervention

The two study treatments were memantine (titrated to 20 mg) and antipsychotic. The study used a double-dummy design with each individual allocated active memantine and placebo antipsychotic or placebo memantine and active antipsychotic. The memantine, placebo memantine, antipsychotic and placebo antipsychotic were packed in boxes, clearly marked with name of drug, strength and expiry date. Memantine treatment was titrated to a dose of 20mg (10mg bd). Antipsychotic treatment was with one of the four antipsychotics most commonly prescribed to people with AD (risperidone, olanzapine, quetiapine, haloperidol). The capsules contained risperidone 0.5mg, Olanzapine 5mg, Quetiapine 50mg, haloperidol 0.5mg or placebo. Patients were allocated moderate (one capsule bd) or low (one capsule daily) dose to best match their pre-study dosage. The design used a fixed dose regime, increasing memantine to 20mg per day over four weeks. The incremental increases and target dose of memantine administered in this study have been shown to be well tolerated and effective in patients with AD in clinical studies. Antipsychotic dose also remained fixed throughout study participation. Treatment compliance was measured using tablet counting.

In cases of exacerbation of neuropsychiatric symptoms, a planned treatment with trazodone or carbamazepine was permitted, using clinical judgement to determine the dose within the BNF permitted dose range. Individuals receiving rescue therapy were assessed weekly and rescue medication was permitted for a maximum duration of four weeks.

Outcome measures

The primary outcome measure was the Bristol Activities of Daily Living Scale (BADLS), a 60-item informant interview covering a broad range of activities of daily living [26]. Other key outcomes were Neuropsychiatric symptoms (Neuropsychiatric Inventory –NPI) [27], agitation (Cohen-Mansfield Agitation Inventory; CMAI) [28], cognition (MMSE and Severe Impairment Battery [29]; SIB [30], global clinical outcome (Clinician's Global Impression of Change; CGIC) [31], severity of dementia (Functional Assessment Staging; FAST) [32], parkinsonism (modified Unified Parkinson's disease Rating Scale; M-UPDRS) [33] and adverse events. Assessments were completed at baseline and weeks six, 12 and 24. Each SAE was reported to the chair of the trial Data Monitoring Committee within 24 hours of learning of its occurrence and additional reports were generated for the MHRA and ethics committees to meet regulatory requirements. For scales requiring an informant, information was provided by a nurse or professional caregiver who had regular contact with the individual. As far as possible, the same informant provided information for subsequent assessments.

Sample size

The power calculation for the study was focused upon activities of daily living. The sample size calculation is based on a two-sided, two-sample t-test using the estimated standard deviation of the treatment difference measured on the ADL scale between memantine and placebo in the DART-AD study [19, 20]. In order to detect a clinically relevant difference of 2.1 on the Bristol ADL scale with 80% power, a conventional 5% significance level, and a drop-out of a maximum of ten patients per treatment arm, a total sample size of 320 patients was needed.

Blinding

Memantine and placebo memantine were provided as identical scored tablets to ensure that the active treatment and placebo could not be distinguished and to guarantee the double blind design. Memantine was supplied in wallet cards containing sufficient study drug for 28 days plus reserve study medication for seven additional days. Placebo antipsychotic capsules were identical to the over-encapsulated antipsychotics but contained inert filler. Capsules were dispensed in bottles with 28 days medication and sufficient reserve for seven days additional medication with each prescription. The clinicians, those administering the trial medication, the caregivers, the relatives, the patients themselves, and those assessing the outcomes were all blinded to treatment allocation.

Randomisation and treatment allocation

Initial randomisation was performed centrally at the Centre for Statistics in Medicine in Oxford, by use of dedicated computer software (MINIM, version 1.5 [a randomisation program for allocating patients to treatment in clinical trials]), with participants randomized in equal numbers to receive either memantine and placebo antipsychotic or placebo memantine and antipsychotic. The minimisation algorithm ensured balanced allocation of patients across the two treatment groups for the following factors: centre, type of antipsychotic (anti-muscarinic or not), dose of antipsychotic (low or moderate), presence or absence of visual hallucinations or delusions, spontaneous extra-pyramidal symptoms, MMSE score and taking cholinesterase inhibitors. The clinician responsible for randomisation of a patient faxed a randomisation form to the CSMO (or sent e-mail in exceptional circumstances) and provided details appropriate and sufficient for establishing eligibility. If a patient was eligible and informed consent/assent had been obtained and baseline assessments had been completed, the patient was randomised by the statistician either to continue taking medication or to discontinue (placebo group). The statistician directly communicated the allocation to the relevant trial pharmacy, ensuring concealment. In practice, the randomization method used in the MAIN AD study was a randomized block design. The kit numbers for memantine were randomized into two treatments (active or placebo) in blocks of size two. There was no stratification for centre or any other factors.

Role of the funding source

The funding source contributed to the initial design of the protocol for the trial, and received annual progress reports. The funder had no direct role in the clinical trial and did not contribute to the interpretation of the results or the writing of the manuscript.

Statistical Analysis

All analyses were conducted as far as consistent with missing data, on the principle of intention to treat for efficacy outcomes. The primary analysis were based upon a modified intent to treat population (ITT) comprising of all participants who were randomized and who received study medication and from whom at least one efficacy measurement was obtained after first treatment with study medication. In these individuals, multiple imputation was used to estimate projected values at the final assessment based upon the profile of values in a particular participant and the overall behaviour of the data. In additional analyses, the primary outcome measures were also evaluated using Observed Cases (OC) to enable a thorough understanding of the dataset. Analysis of safety was conducted including all participants who have received at least one dose of study medication.

The primary statistical analysis assessed the performance of memantine compared to continued antipsychotic treatment for change from baseline on the primary outcomes at the 24 week assessment point by modified intention to treat, using a mixed model with imputation of uncompleted assessments. The primary outcome was activities of daily living (Bristol ADL score). The primary analysis will utilize analysis of covariance (ANCOVA) with adjustment for baseline value of the Bristol ADL score. Further exploration of the outcomes was undertaken using ANCOVA with adjustment for the minimisation (design) factors. The assumption of equal variances was assessed using Levene's test (optimal adjusted analysis). Continuous secondary outcomes were analysed following the same strategy adopted for the primary outcome (i.e. ANCOVA).

Study Governance

An independent data-monitoring committee (DMC) was charged with overseeing patient safety. Its remit included prompt review of serious adverse events and a comprehensive review of all adverse events based upon interim data reports. The group also advised on any new or emerging information on the safety of the study treatments. If required, the DMC would make recommendations to the trial steering group and the sponsor about the safe continuation of the trial and any issues of concern. These decisions relied upon the independence and expertise of the DMC and did not follow any strict “stopping rules.”

Results

Cohort characteristics

The first patient was randomised on 18/03/209 and the last on 02/06/2011. 200 patients were identified as eligible. One person died before randomization. The remaining 199 individuals were randomized (99 to continue antipsychotic and 100 to memantine), of whom 166 (83%) commenced treatment and had at least one follow-up assessment (81 continue antipsychotic / 85 memantine), and were therefore eligible for the mITT analysis. Of those, 156 were eligible for the per protocol analysis (75 continue antipsychotic / 81 memantine). The full course of participants through the study is shown in the CONSORT diagram (Figure 1). Baseline demographic and clinical characteristics were evenly balanced across the two groups (Table 2).

Outcome measures

On the primary outcome measure of Activities of Daily Living measured by the BADLS, there was no significant difference between patients receiving memantine and those continuing antipsychotic at any of the follow-up timepoints.

Analysis of key secondary outcomes showed no statistically significant differences in agitation between treatment groups at any timepoint as measured by total CMAI scores, although there was a 4.09 (95% confidence intervals -0.35, 8.53, p=0.07) point advantage favouring antipsychotic treatment at 24 weeks. Similarly, there were no significant differences in total NPI scores between treatment groups at six, 12 or 24 weeks, although there was a 5.01 (95% confidence intervals -1.68, 11.70, p=0.05) point advantage favouring antipsychotics at 12 weeks and a 3.63 (95% Confidence intervals -1.40, 8.67, p=0.16) point advantage favouring antipsychotics at 24 weeks. Of particular note, by following the standard definition of relapse in neuropsychiatric symptoms as a 30% worsening of symptoms on the NPI, analysis indicated a higher rate of relapse at six (40% v 28.8%), 12 (44.4% v 28%) and 24 (39.2% v 29.6%) weeks in the memantine treated group compared to those receiving antipsychotic (Odds Ratio 1.99, 95% confidence intervals 1.17, 3.4, p=0.01).

On the MMSE the memantine group showed a 1.40 (95% confidence intervals -0.55, 3.35, p=0.06) point advantage at 12 weeks and a 1.29 (95% confidence intervals -0.21, 2.79, p=0.09) point advantage at 24 weeks compared to the antipsychotic group. On the SIB there was a non-significant 3.42 (95% confidence intervals -2.00, 8.84 p=0.21) point advantage favouring memantine at the 24 week timepoint. There was also a non-significant -0.95 (95% confidence intervals -2.31, 0.42, p=0.18) point advantage favouring the memantine group at 24 weeks on the measure of parkinsonism, the modified UPDRS. Clinical Global impression of change was similar in the two treatment groups at all outcome points. The results are shown in more detail in table 3.

In view of previous literature indicating that quetiapine is less efficacious than other antipsychotics in the treatment of BPSD, a post-hoc analysis was undertaken by individual antipsychotic. The analysis did not indicate significant advantages for any antipsychotic compared to memantine for the treatment of agitation as measured by the NPI (figure 2).

A range of sensitivity analyses were undertaken including controlling for all baseline covariates, a full ITT analysis and a per protocol analysis, all with similar findings and none demonstrating any significant advantage for memantine on any outcomes.

Safety

193 adverse events and 25 serious adverse events occurred in people taking antipsychotics compare to 167 adverse events and 18 serious adverse events in people taking memantine. In the primary analysis population there were 9 deaths in people taking antipsychotic and 4 deaths in people taking memantine.

Discussion

We conducted a six month randomized controlled trial comparing memantine with antipsychotic for the treatment and prophylaxis of agitation and aggression in people with AD who had already been treated with an antipsychotic for at least three months. Contrary to our hypothesis, the patients allocated to memantine did not benefit significantly compared to antipsychotic treatment with respect to activities of daily living. However, patients allocated to memantine were significantly more likely to experience a relapse in neuropsychiatric symptoms over the 24 weeks compared with those receiving an antipsychotic, with higher relapse rates at six, 12 and 24 weeks.

With respect to other outcomes, it is surprising that memantine did not confer significant benefits compared to antipsychotics in the treatment of cognition, although there was a numerical advantage of 1.4 and 1.3 point advantage with respect to the MMSE at 12 weeks and 24 weeks respectively. The substantial increase in risk of mortality with antipsychotic treatment (9 deaths v 4 deaths) is consistent with previous studies.

RCTs of six months duration or longer have indicated that antipsychotics confer a modest but significant benefit in the prophylaxis and treatment of neuropsychiatric symptoms consistent with the current findings [17, 18, 19]. The results of the present study are however surprising as 6 to 12- month trials of memantine have also suggested significant benefit in the treatment of neuropsychiatric symptoms [22, 23, 24]. Our data indicate that antipsychotics achieved numerically greater reductions in NPI and CMAI scores and significantly reduced relapse rates of neuropsychiatric symptoms compared to memantine, indicating that antipsychotics are more efficacious in the long term treatment of neuropsychiatric symptoms than another treatment which has previously demonstrated some established long term efficacy against placebo in previous trials. The lower efficacy with respect to the treatment of neuropsychiatric symptoms and the absence of significant cognitive and functional advantages clearly indicate that memantine should not be used specifically for the long term treatment or prophylaxis of neuropsychiatric symptoms.

The results do indicate that antipsychotics may have some role in the long term treatment of neuropsychiatric symptoms in people with AD. However, given the marked mortality risk, careful clinical judgement is required to balance the risk of symptom relapse against the increased health and mortality risks of long term treatment. Judicious use and regular review of prescriptions is essential. There is also a body of evidence indicating that the worsening of neuropsychiatric symptoms after the withdrawal of antipsychotics can be mitigated by non-

pharmacological interventions. Further work is now needed to build on initial studies to determine the most effective way to utilize non-pharmacological treatments in clinical practice to improve outcomes and reduce the need for continued antipsychotic treatment in people with dementia. The identification of a safe and effective pharmacological treatment for neuropsychiatric symptoms also remains an urgent priority.

Limitations and strengths

This trial did not accomplish the recruitment of the 320 participants stipulated by the original power calculation, although 199 people were randomized to treatment, which still makes the trial the largest RCT of antipsychotic discontinuation in AD patients. Sufficient data for the mITT analysis was collected on more than 80% of participants, a good completion rate given the duration of the study and the frailty of this population.

Summary

This withdrawal study found that treatment with memantine did not confer any significant benefit in activities of daily living or cognition compared with antipsychotics in people with dementia who were already prescribed an antipsychotic. Surprisingly, it also showed increased relapse of neuropsychiatric symptoms in people treated with memantine. These outcomes indicate a continued role for antipsychotics in treatment of neuropsychiatric symptoms and do not support the use of memantine for this purpose. Serious attention must now be turned to the safety implications of this outcome, and future research should focus on identifying effective alternative treatment options to antipsychotic medications.

Table 1: Eligibility criteria for participants in MAIN-AD

Criteria	**Eligibility conditions**
Existing prescription of cholinesterase inhibitor	Included if prescribed for at least six months before the date of assessment, with a stable dose for at least three months.
Existing prescription of anticonvulsants	Only included if carbamazepine or sodium valproate with stable dose for at least four weeks
Existing prescription of other psychotropic drug (eg antidepressants, benzodiazepines, chlormethiazole)	Included if dose had been stable for at least four weeks prior to randomisation
Existing prescription of memantine	Excluded if taking memantine within six weeks prior to assessment
Existing prescription of medications contra-indicated in combination with memantine as defined by the BNF including ketamine, dextromethorphan, amantidine,	Excluded
Receiving an investigational drug	Excluded if during the four weeks prior to randomisation
Receiving a drug known to cause major organ toxicity	Excluded if taken within four weeks prior to randomisation
Existing prescription of baclofen, dantrolene, dextromethorphan or antimuscarinics	Excluded
Blood pressure	Excluded if systolic blood pressure whilst sitting was greater than 180 mm/Hg or less than 90 mm/Hg, or if diastolic blood pressure whilst sitting was greater than 100 mm/Hg or less than 50 mm/Hg at the screening visits or baseline.
Untreated B12 or folate deficiency	Excluded if within three months of screening
Untreated clinically significant hypothyroidism or hyperthyroidism	Excluded except patients with thyroid disease if they were euthyroid and stable
Severe aggression	Excluded if ≥8 on item three of the NPI scale with aggression as the predominant symptom

Psychotic DSM IV Axis 1 disorder including schizophrenia, schizoaffective disorder and bipolar disorder.	Excluded if other than in the context of AD
Diagnosis of primary neurodegenerative disorders other than AD (Huntington's disease, Parkinson's disease)	Excluded
Uncontrolled epilepsy	Excluded
Delirium	Excluded if detected at time of assessment
Severe renal impairment	Excluded if estimated creatinine clearance of < 5 mL/min/1.73m2
Severe hepatic impairment	Excluded

Table 2: Demographic and Clinical Characteristics and Assessments at Baseline (All Patients Randomized)

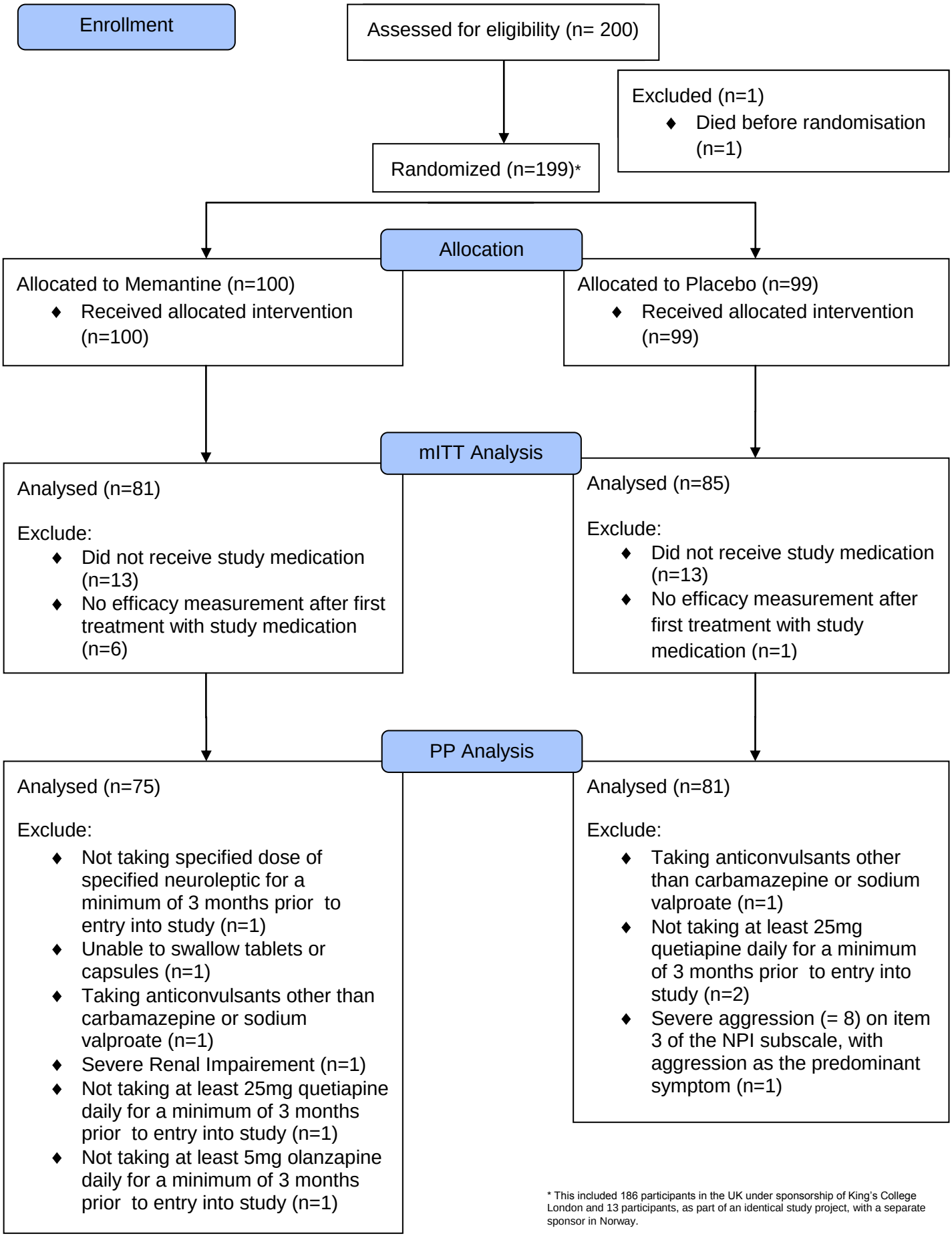
Baseline Characteristics or Assessment	Statistics	Memantine (N=100)	Placebo (N=99)
Age (years)	Mean (SD) [range]	83.1 (9.4) [57,99]	83.4 (6.6) [63,97]
Sex (female)	No. (%)	67 (67)	71 (71.7)
BADLS	Mean (SD) (no. of patients)	34.0 (10.2) (n=90)	32.6 (10.8) (n=90)
	Median (IQR) [range]	35 (25, 41) [14, 58]	33 (24, 40) [7, 57]
CMAI	Mean (SD) (no. of patients)	52.7 (18.7) (n=90)	50.1 (16.2) (n=88)
	Median (IQR) [range]	50 (37, 60) [29, 123]	46 (38, 60) 29, 110]
SIB	Mean (SD) (no. of patients)	49.5 (31.5) (n=70)	65.0 (33.0) (n=63)
	Median (IQR) [range]	77 (37, 88) [0, 98]	49 (19, 79) [0, 143]
NPI	Mean (SD) (no. of patients)	17.8 (15.8) (n=90)	17.3 (16.1) (n=87)
	Median (IQR) [range]	14 (5, 26) [0, 68]	13 (6, 25) [0, 97]
MMSE	Mean (SD) (no. of patients)	6.7 (6.0) (n=63)	10.2 (6.8) (n=67)
	Median (IQR) [range]	1 (5, 11) [0, 24]	4 (11, 15) [0, 25]
FAST	Mean (SD) (no. of patients)	6.2 (0.6) (n=91)	6.1 (0.6) (n=91)
	Median (IQR) [range]	6 (6, 7) [4, 7]	6 (6, 6) [4, 7]
M-UPDRS	Mean (SD) (no. of patients)	7.1 (5.4) (n=90)	6.9 (5.5) (n=90)
	Median (IQR) [range]	2 (7,10) [0, 19]	2 (7,10) [0, 25]
Dose of neuroleptic (high)	No. (%)	26 (26.0)	27 (27.3)

Table 3:

Week	BADL Score*		Difference (95% Confidence Interval)	p-value
	Memantine (n=81)	Placebo (n=83)		
6	31.99	32.39	-0.40 (-3.04, 2.24)†	0.6923
12	32.72	33.02	-0.29 (-2.99, 2.40) †	0.7786
24	33.90	33.67	0.23 (-1.80, 2.27)	0.8204
Week	Mean CMAI Score*		Difference (95% Confidence Interval)	p-value
	Memantine (n=81)	Placebo (n=83)		
6	49.94	49.53	0.41 (-5.37, 6.19)†	0.8553
12	48.77	47.63	1.13 (-4.77, 7.03) †	0.6192
24	51.84	47.75	4.09 (-0.35, 8.53)	0.0711
Week	BADL Score*		Difference (95% Confidence Interval)	p-value
	Memantine (n=81)	Placebo (n=82)		
6	18.41	16.15	2.27 (-4.27, 8.81)†	0.3699
12	18.38	13.36	5.01 (-1.68, 11.70) †	0.0531
24	18.04	14.41	3.63 (-1.40, 8.67)	0.1570
Week	Mean SIB Score*		Difference (95% Confidence Interval)	p-value
	Memantine (n=58)	Placebo (n=59)		
6	56.26	57.34	-1.08 (-7.90, 5.73)†	0.6791
12	59.11	58.02	1.09 (-5.93, 8.11)†	0.6855
24	56.68	53.26	3.42 (-2.00, 8.84)	0.2144
Week	Mean MMSE Score*		Difference (95% Confidence Interval)	p-value
	Memantine (n=53)	Placebo (n=60)		
6	8.79	8.27	0.52 (-1.36, 2.40)†	0.4745
12	8.97	7.57	1.40 (-0.55, 3.35) †	0.0641
24	8.55	7.26	1.29 (-0.21, 2.79)	0.0905
Week	Mean MUPDRS Score*		Difference (95% Confidence Interval)	p-value
	Memantine (n=70)	Placebo (n=70)		
24	7.28	8.22	-0.95 (-2.31,0.42)	0.1728

Week	CGIC Odds ratio (95% C.I)	p-value
6	0.942 (0.462, 1.921)	0.8688
24	0.765 (0.355, 1.651)	0.4941
Overall	0.849 (0.489, 1.474)	0.5588

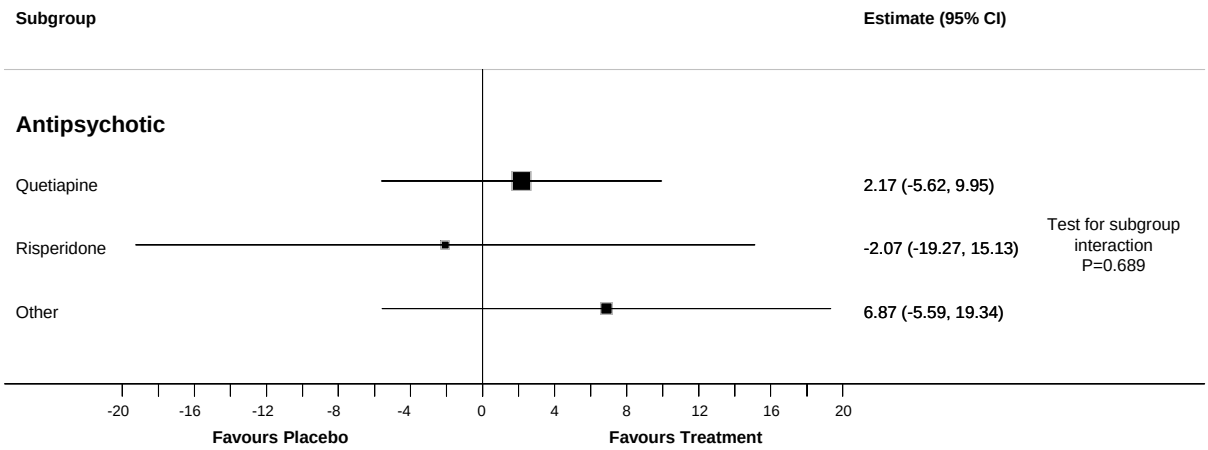
Figure 1: Consort Flow Chart



* This included 186 participants in the UK under sponsorship of King's College London and 13 participants, as part of an identical study project, with a separate sponsor in Norway.

Figure 2

Subgroup analysis of change in NPI score from baseline to 24 weeks



For antipsychotic medication the test for subgroup interaction yields a P-value of 0.689, so there is no observable subgroup effect.

References

1 Alzheimer's Disease Internationall (ADL). *World Alzheimer Report 2012: Overcoming the stigma of dementia. ADL,* 2009. http://www.alz.co.uk/research/files/WorldAlzheimerReport.pdf.

2 Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: Cache County Study. *Int J Geriatr Psychiatry* 2008; 23: 170–177.

3 National Institute for Health and Clinical Excellence (NICE). *Dementia: Supporting people with dementia and their carers in health and social care*. NICE, 2006. http://publications.nice.org.uk/dementia-cg42

4 Lyketsos CG, Colenda CC, Beck C, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia due to Alzheimer disease. Am J Geriatr Psych 2006; 14: 561–72.

5 Alzheimer's Society. *Optimising treatment and care for behavioural and psychological symptoms of dementia.* Alzheimer's Society, 2013. www.alzheimers.org.uk/bpsdguide

6 Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci* 2006; 7(6): 492-500.

7 Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006; 14(3): 191-210.

8 Ballard CG, Gauthier S, Cummings JL et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurosci* 2009; 5: 245–55.

9 Barnes TR, Banerjee S, Collins N, et al. Antipsychotics in dementia: prevalence and quality of antipsychotic drug prescribing in UK mental health services. *Br J Psychiatry* 2012; 201(3): 221-6.

10 Ballard C, Margallo-Lana M, Juszczak E, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ* 16 2005; 330(7496): 874.

11 Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 12 2006; 355(15): 1525-1538.

12 Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study. *J Geriatr Psychiatry Neurol* 1997; 10(3): 119-126.

13 Ballard CG, Thomas A, Fossey J, et al. A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. *J Clin Psychiatry* 2004; 65(1): 114-119.

14 Fossey J, Ballard C, Juszczak E, et al. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. *BMJ* 2006; 332(7544): 756-761.

15 Cohen-Mansfield J, Lipson S, Werner P, et al. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. *Arch Intern Med* 1999; 159(15): 1733-1740.

16 Ballard C, Margallo-Lana M, O'Brien JT, et al. Top cited papers in International Psychogeriatrics: 6a. Quality of life for people with dementia living in residential and nursing home care: the impact of performance on activities of daily living, behavioral and psychological symptoms, language skills, and psychotropic drugs. Int Psychogeriatr 2009; 21(6): 1026-30.

17 Devanand DP, Pelton GH, Cunqueiro K, et al. A 6-month, randomized, double-blind, placebo-controlled pilot discontinuation trial following response to haloperidol treatment of psychosis and agitation in Alzheimer's disease. *Int J Geriatr Psychiatry* 2011; 26(9): 937-943.

18 Devanand DP, Mintzer J, Schultz SK, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med* 2012; 367(16): 1497-1507.

19 Ballard C, Lana MM, Theodoulou M, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). *PLoS Med* 2008; 5(4): e76.

20 Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol* 2009; 8(2): 151-157.

21 Fox C, Crugel M, Maidment I, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PloS One* 2012; 7(5): e35185.

22 McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev* 2006; (2): CD003154.

23 Wilcock GK, Ballard CG, Cooper JA, et al. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry* 2008; 69(3): 341-348.

24 Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012; 366: 893-903.

25 McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34: 939–944.

26 Byrne LM, Wilson PM, Bucks RS, et al. The sensitivity to change over time of the Bristol Activities of Daily Living Scale in Alzheimer's disease. *Int J Geriatr Psyc* 2000; 15: 656–61.

27 Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44: 2308-2314.

28 Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol* 1989; 44(3): M77–84.

29 Folstein M, Folstein S, McHugh P. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *J Psych Res* 1975; 12(3): 189–198.

30 Schmitt FA, Ashford W, Ernesto C, et al. The severe impairment battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. The Alzheimer's disease cooperative study. *Alzheimer Dis Assoc Disord* 1997; 11: 51–56.

31 Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Co-operative Study-Clinical Global Impression of Change. The Alzheimer's Disease Co-operative Study. *Alzheimer Dis Assoc Disord* 1997; 11: 22–32.

32 Auer S, Reisberg B. The GDS/FAST staging system. *Int Psychogeriatr* 1997; 9 Suppl 1:167-71.

33 Ballard C, McKeith I, Burn D, et al. The UPDRS scale as a means of identifying extrapyramidal signs in patients suffering from dementia with Lewy bodies. *Acta Neurol Scand* 1997; 96: 366–371.