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## A pragmatic, multicentre, double-blind, placebo-controlled randomised trial to assess the safety, clinical and cost-effectiveness of mirtazapine and carbamazepine in people with Alzheimer's disease and agitated behaviours: the HTA-SYMBAD trial

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# Abstract

## A pragmatic, multicentre, double-blind, placebo-controlled randomised trial to assess the safety, clinical and cost-effectiveness of mirtazapine and carbamazepine in people with Alzheimer's disease and agitated behaviours: the HTA-SYMBAD trial

Sube Banerjee<sup>1\*</sup>, Nicolas Farina<sup>2</sup>, Catherine Henderson<sup>3</sup>, Juliet High<sup>4</sup>, Susan Stirling<sup>4</sup>, Lee Shepstone<sup>4</sup>, Julia Fountain<sup>5</sup>, Clive Ballard<sup>6</sup>, Peter Bentham<sup>7</sup>, Alistair Burns<sup>8</sup>, Chris Fox<sup>4</sup>, Paul Francis<sup>6</sup>, Robert Howard<sup>9</sup>, Martin Knapp<sup>3</sup>, Iracema Leroi<sup>10</sup>, Gill Livingston<sup>9</sup>, Ramin Nilforooshan<sup>11</sup>, Shirley Nurock<sup>12</sup>, John O'Brien<sup>13</sup>, Annabel Price<sup>14</sup>, Alan J Thomas<sup>15</sup>, Ann Marie Swart<sup>4</sup>, Tanya Telling<sup>16</sup> and Naji Tabet<sup>2</sup>

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**Background:** Agitation is common and impacts negatively on people with dementia and carers. Non-drug patient-centred care is first-line treatment, but we need other treatment when this fails. Current evidence is sparse on safer and effective alternatives to antipsychotics.

**Objectives:** To assess clinical and cost-effectiveness and safety of mirtazapine and carbamazepine in treating agitation in dementia.

**Design:** Pragmatic, phase III, multicentre, double-blind, superiority, randomised, placebo-controlled trial of the clinical effectiveness of mirtazapine over 12 weeks (carbamazepine arm discontinued).

**Setting:** Twenty-six UK secondary care centres.

**Participants:** *Eligibility:* probable or possible Alzheimer's disease, agitation unresponsive to non-drug treatment, Cohen-Mansfield Agitation Inventory score  $\geq 45$ .

**Interventions:** Mirtazapine (target 45 mg), carbamazepine (target 300 mg) and placebo.

**Outcome measures:** *Primary:* Cohen-Mansfield Agitation Inventory score 12 weeks post randomisation. *Main economic outcome evaluation:* incremental cost per six-point difference in Cohen-Mansfield Agitation Inventory score at 12 weeks, from health and social care system perspective. Data from participants and informants at baseline, 6 and 12 weeks. Long-term follow-up Cohen-Mansfield Agitation Inventory data collected by telephone from informants at 6 and 12 months.

**Randomisation and blinding:** Participants allocated 1 : 1 : 1 ratio (to discontinuation of the carbamazepine arm, 1 : 1 thereafter) to receive placebo or carbamazepine or mirtazapine, with treatment as usual. Random allocation was block stratified by centre and residence type with random block lengths of three or six (after discontinuation of carbamazepine, two or four). Double-blind, with drug and placebo identically encapsulated. Referring clinicians, participants, trial management team and research workers who did assessments were masked to group allocation.

**Results:** Two hundred and forty-four participants recruited and randomised (102 mirtazapine, 102 placebo, 40 carbamazepine). The carbamazepine arm was discontinued due to slow overall recruitment; carbamazepine/placebo analyses are therefore statistically underpowered and not detailed in the abstract. *Mean difference* placebo-mirtazapine (-1.74, 95% confidence interval -7.17 to 3.69;  $p = 0.53$ ). *Harms:* The number of controls with adverse events (65/102, 64%) was similar to the mirtazapine group (67/102, 66%). However, there were more deaths in the mirtazapine group ( $n = 7$ ) by week 16 than in the control group ( $n = 1$ ). Post hoc analysis suggests this was of marginal statistical significance ( $p = 0.065$ ); this difference did not persist at 6- and 12-month assessments. At 12 weeks, the costs of unpaid care by the dyadic carer were significantly higher in the mirtazapine than placebo group [difference: £1120 (95% confidence interval £56 to £2184)]. In the cost-effectiveness analyses, mean raw and adjusted outcome scores and costs of the complete cases samples showed no differences between groups.

**Limitations:** Our study has four important potential limitations: (1) we dropped the proposed carbamazepine group; (2) the trial was not powered to investigate a mortality difference between the groups; (3) recruitment beyond February 2020, was constrained by the COVID-19 pandemic; and (4) generalisability is limited by recruitment of participants from old-age psychiatry services and care homes.

**Conclusions:** The data suggest mirtazapine is not clinically or cost-effective (compared to placebo) for agitation in dementia. There is little reason to recommend mirtazapine for people with dementia with agitation.

**Future work:** Effective and cost-effective management strategies for agitation in dementia are needed where non-pharmacological approaches are unsuccessful.

**Study registration:** This trial is registered as ISRCTN17411897/NCT03031184.

**Funding:** This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 27, No. 23. See the NIHR Journals Library website for further project information.

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## List of abbreviations

AD	Alzheimer's disease	MHRA	Medicines and Healthcare Products Regulatory Agency
AE	adverse event		
BPSD	Behavioural and Psychological Symptoms in Dementia	MLM	Multilevel models
CI	confidence interval	NASSA	noradrenergic and specific serotonergic antidepressant
CMAI	Cohen-Mansfield Agitation Inventory	NCTU	Norwich Clinical Trials Unit
CRF	Case Report Form	NICE	National Institute for Health and Care Excellence
CSRI	Client Service Receipt Inventory	NMB	net monetary benefit
CTCAE	Common Terminology Criteria for Adverse Events	NPI	Neuropsychiatric Inventory
DEMQOL	Dementia-Specific Quality of Life	PI	principal investigator
DMC	Data Monitoring Committee	PIC	Participant Identification Centre
ECG	electrocardiogram	PIN	Participant Identification Number
eCRF	Electronic Case Report Form	PPI	patient and public involvement
EU	European Union	QALYs	quality-adjusted life-years
GCP	Good Clinical Practice	RCT	randomised controlled trial
GDPR	General Data Protection Regulation	SAE	serious adverse event
GHQ-12	General Health Questionnaire	SAR	serious adverse reaction
ICH	International Conference on Harmonisation	SD	standard deviation
IMP	Investigational Medicinal Product	SDV	Source Data Verification
LEAP	Lived Experience Advisory Panel	SmPC	Summary of Product Characteristics
		SPFT	Sussex Partnership Foundation Trust
		SUSAR	suspected unexpected serious adverse reaction
		TMG	Trial Management Group
		TSC	Trial Steering Committee
		UEA	University of East Anglia



## Plain language summary

It is common for people with Alzheimer's disease to experience agitation, for example feeling restless or unsettled. If left untreated, agitation can lead to poorer quality of life and increased hospitalisation and strain for family carers. Often these symptoms are treated with medications that are usually used to manage psychosis (antipsychotic drugs), but such medication has limited effectiveness and can cause serious adverse effects to patients, including risk of increased death. Two medications that are already commonly prescribed for other health issues, mirtazapine (an antidepressant) and carbamazepine (a drug used to treat epilepsy), had been identified as a possible alternative way of treating agitation in Alzheimer's disease that might not have the harms associated with antipsychotic medication.

In this study, we compared the effects of giving mirtazapine or carbamazepine with a dummy drug (placebo) in people with Alzheimer's disease who were experiencing agitation. The results of the study showed that neither medication was any more effective than the placebo in reducing agitation over 12 weeks in terms of improving symptoms, or in economic terms. Mirtazapine may lead to additional carer costs as compared to placebo. The study findings are stronger for mirtazapine than carbamazepine because the carbamazepine arm was stopped when it had recruited less than half the numbers needed. That was done because the study was not recruiting quickly enough to support both the mirtazapine and the carbamazepine arms.

The findings from this study show that mirtazapine should not be recommended to treat agitation in Alzheimer's disease. More work is needed to formulate effective ways and to test new drug and non-drug treatments for agitation in dementia.





# Scientific summary

## Background

Agitation is common in people with dementia and impacts negatively on the quality of life of both people with dementia and carers. Non-drug patient-centred care is the first-line treatment, but there is a need for other treatment when this fails. Current evidence is sparse on safer and effective alternatives to antipsychotics. We assessed efficacy and safety of mirtazapine (an antidepressant) and carbamazepine (an anticonvulsant) prescribed for agitation in dementia.

## Aim

To assess the safety, clinical and cost-effectiveness of mirtazapine and carbamazepine in the treatment of agitation in dementia.

## Primary objectives

1. To determine if mirtazapine is more clinically effective in reducing agitated behaviours in dementia than placebo, measured by Cohen-Mansfield Agitation Inventory (CMAI) score 12 weeks post randomisation.
2. To determine if carbamazepine is more clinically effective in reducing agitated behaviours in dementia than placebo measured by CMAI score 12 weeks post randomisation.

## Methods

### Design

Pragmatic, phase III, multicentre, double-blind, superiority, randomised, placebo-controlled trial of the clinical effectiveness of mirtazapine and carbamazepine over 12 weeks.

### Intervention

(1) Mirtazapine, (2) carbamazepine and (3) placebo. Target dose: 45 mg of mirtazapine or 300 mg of carbamazepine.

### Inclusion and exclusion criteria

Patients were eligible if the following criteria were met:

1. a clinical diagnosis of probable or possible Alzheimer's disease
2. a diagnosis of co-existing agitated behaviours
3. evidence that the agitated behaviours have not responded to management
4. an assessment of CMAI (Long Form) score of 45 or greater
5. written informed consent to enter and be randomised into the trial
6. availability of a suitable informant.

Exclusion criteria included:

1. current treatment with antidepressants [including Monoamine Oxidase Inhibitors (MAOIs)], anticonvulsants or antipsychotics
2. contraindications to the administration of mirtazapine or carbamazepine

3. patients with second-degree atrioventricular block
4. patients with a history of bone marrow depression or history of hepatic porphyrias
5. cases too critical for randomisation (i.e. where there is a suicide risk or where the patient presents a risk of harm to others)
6. female subjects under the age of 55 years of childbearing potential.

### **Setting**

Participants were drawn from existing patients and new patient referrals to old age psychiatric services, memory clinics, specific Participant Identification Centres, primary care centres and those in care homes in 26 UK sites.

### **Consent**

Capacity to consent was assessed before proceeding with the consent process and included consideration of the provision of assent by the patient and consent on their behalf by their legal representative. If the patient had capacity to consent, the carer consented to the provision of information on data for measures on the patient (e.g. CMAI) and also on themselves in terms of impact.

### **Randomisation and blinding**

Participants were allocated in a 1 : 1 : 1 ratio (up to the discontinuation of the carbamazepine arm and 1 : 1 thereafter) to receive placebo or carbamazepine or mirtazapine, together with treatment as usual. Random allocation was block stratified by centre and type of residence (care home vs. own household) with random block lengths of three or six up to the discontinuation of the carbamazepine arm and thereafter of two or four. The trial was double-blind, with drug and placebo identically encapsulated. Referring clinicians, participants, the trial management team and the research workers who did baseline and follow-up assessments were masked to group allocation.

### **Outcomes**

#### **Primary outcome**

CMAI score (Long Form) at 12 weeks.

#### **Secondary outcomes**

1. Costs derived from Client Service Receipt Inventory, and quality-adjusted life-years from cost data alongside supplemented information from Dementia-Specific Quality of Life and EuroQol-5 Dimensions, five-level version interviews 12 weeks post randomisation.
2. CMAI score and cost at 6 weeks post randomisation.
3. Patient and carer quality of life, and carer outcomes at 6 and 12 weeks post randomisation.
4. Adverse events from week 0 to week 16 and adherence at 6 and 12 weeks post randomisation.
5. CMAI score, adverse events and adherence at 6 and 12 weeks, conditional on evidence of effectiveness of Investigational Medicinal Product over placebo.
6. Longer-term follow-up: CMAI score, institutionalisation, death and clinical management at 26 and 52 weeks post randomisation.

### **Sample size and statistical analysis**

An initial calculated sample size of 400 (randomised 1 : 1 : 1) provided 90% power using two-sided 5% significance tests to detect a drug versus placebo mean difference in CMAI score at 12 weeks of 6 points. This equated to an effect size of  $d = 0.4$  (assuming a common standard deviation of 15) or a clinically significant 30% decrease in CMAI from placebo to active drug. With a realistic 15% attrition, a sample of 471 (157 per arm) was aimed for. Mid-trial, with the discontinuation of the carbamazepine arm, the sample size calculation was revisited with emerging data and it was adjusted so that the aim (excluding those randomised to carbamazepine) was for an overall sample of 222 (randomised 1 : 1) to

provide 80% power using two-sided 5% significance tests to detect a mirtazapine versus placebo mean difference in CMAI score at 12 weeks of six points, assuming attrition of no more than 10%.

Analyses were based on intention-to-treat (all participants were analysed according to the group to which they were randomised, irrespective of the treatment or dose received). The primary outcome (CMAI at 12 weeks) was analysed using a general linear regression model including baseline CMAI score as a covariate. General linear regression models were created for secondary outcomes.

### **Economic evaluation**

The primary outcome for the economic evaluation was the incremental cost per six-point difference in CMAI score at 12 weeks, from a health and social care system perspective.

### **Patient and public involvement**

Ensuring the involvement of people living with dementia and their family carers was integral to the Study of Mirtazapine for Agitated Behaviours in Dementia (SYMBAD) trial from the application for funding and trial design stage through to its conduct, analysis and communication. SN was a co-applicant and led on public/carer involvement in the trial throughout, and she was supported by a Lived Experience Advisory Panel (LEAP) group hosted by Sussex Partnership Foundation Trust (SPFT) co-ordinated by JF and the NIHR DeNDRoN (Dementias and Neurodegenerative Diseases Research Network) group.

### **Protocol change**

Due to slower than expected recruitment the carbamazepine arm was discontinued in August 2018 when 40 people had been randomised to it. This summary therefore focusses on the mirtazapine versus placebo comparisons.

## **Results**

Between January 2017 and February 2020, 204 participants were recruited and randomised to either the mirtazapine ( $n = 102$ ) or placebo arm ( $n = 102$ ). Mean CMAI scores at 12 weeks were not significantly different between participants allocated to receive mirtazapine and placebo [adjusted mean difference  $-1.74$ , 95% confidence interval (CI)  $-7.17$  to  $3.69$ ;  $p = 0.53$ , direction of change in favour of mirtazapine but not statistically significant]. The number of controls with adverse events [65/102 (64%)] was similar to that in the mirtazapine group [67/102 (66%)]. There were more deaths in the mirtazapine group ( $n = 7$ ) by week 16 than in the control group ( $n = 1$ ), with post hoc analysis suggesting this was of marginal statistical significance ( $p = 0.065$ ), but this difference did not persist at 6- and 12-month follow-ups. The cost-effectiveness analyses similarly showed no evidence of benefit of mirtazapine over placebo, and no difference in costs between groups at 12 weeks. The carbamazepine arm closed in August 2018 when there had been 40 randomisations to that group, we therefore do not have statistical power for comparisons with placebo. However, exploratory analyses using the same modelling as for mirtazapine versus placebo showed there was also little evidence of any benefits compared to placebo (adjusted mean difference 2.46, 95% CI  $-5.01$  to  $9.93$ ;  $p = 0.52$ ), with similar levels of adverse events reported [27/40 (68%)].

## **Conclusions**

This is a trial with negative findings but important clinical implications. The data suggest that mirtazapine is not clinically effective or cost-effective (compared to placebo) for clinically significant agitation in dementia. Our findings suggest that there is little reason to recommend the use of mirtazapine for people with dementia who experience agitation. Effective and cost-effective management strategies for agitation in dementia are needed, particularly where non-pharmacological approaches have been unsuccessful, and for people with dementia and their carers living in community settings.

### **Trial registration**

This trial is registered as ISRCTN17411897 and ClinicalTrials.gov as NCT03031184.

### **Funding**

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*, Vol. 27, No. 23. See the NIHR Journals Library website for further project information.

# Chapter 1 Introduction

## Scientific background

Dementia is one of the most common and serious public health issues of our time.<sup>1</sup> Over 46 million people have dementia worldwide, a figure set to double in the next 20 years.<sup>2</sup> The commonest cause of dementia is Alzheimer's disease (AD), which causes irreversible and progressive decline in memory, reasoning, communication skills and the ability to carry out daily activities. Alongside this cognitive and functional decline, individuals may develop neuropsychiatric symptoms (NPS) such as agitation, sleep disturbance, depression and psychosis.<sup>3</sup> These are common, occurring in up to 90% of people with dementia, with agitation as one of the most persistent symptoms.<sup>4</sup> Agitation is defined as inappropriate verbal, vocal or motor activity that is not thought to be caused by unmet need; it encompasses physical and verbal aggression and is particularly problematic.<sup>5</sup> It affects nearly half of people with AD over a month<sup>6</sup> and 80% of those with clinically significant symptoms will have them 6 months later.<sup>7</sup> Agitation is associated with deteriorating relationships with family and professional carers, care home admission, increased costs of care, carer burden and burnout and decreased quality of life.<sup>5,7,8</sup>

Agitation in dementia has substantial economic consequences, accounting for between 12% and 44% of dementia care costs annually<sup>9,10</sup> and imposing significant costs on unpaid carers.<sup>11</sup> Costs rise as the severity of agitation increases.<sup>10,12</sup> The annual excess health and social care cost of agitation in AD in the UK has been estimated at £2B.<sup>9</sup>

Agitation in dementia is therefore a legitimate target for therapeutic intervention, but it is a symptom with a number of possible causes, including pain, physical or psychological distress, misperception of threat (e.g. when receiving personal care), and response to hallucinations or delusions. Using non-pharmacological interventions that investigate aetiology and provide a tailored response as a first-line treatment for agitation in dementia, such as the DICE approach (Describe the problem, Investigate the cause, Create a plan, Evaluate its effectiveness), is recommended as best practice.<sup>1,13</sup> However, given the clinical significance of agitation, there is a need for second-line treatments when no underlying causes are found or when correction of these has not resulted in improvement. The mainstay of drug treatment is the use of antipsychotic medication. These drugs, however, have low efficacy, with the American Psychiatric Association guideline group reporting that they 'demonstrate minimal or no efficacy with strong placebo effects'<sup>14</sup> and have been shown to cause particular harms in those with dementia, including excess dementia-specific mortality. In 2009, around 180,000 people with dementia were prescribed antipsychotic medication across the UK per year and this equated to an additional 1800 deaths and an additional 1620 cerebrovascular adverse events (AEs) attributable to the use of antipsychotics in dementia.<sup>15</sup> While their rate of prescription to people with dementia has decreased,<sup>16</sup> they are still commonly used and such treatment is largely unlicensed. In most countries, few or no treatments have been given regulatory approval for such use. In the UK, the only drugs with a relevant license are risperidone and haloperidol and these are highly restrictive. Risperidone is indicated for the 'short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others' and haloperidol for 'persistent aggression and psychotic symptoms in moderate to severe Alzheimer's dementia and vascular dementia [when non-pharmacological treatment is ineffective and there is a risk of harm to self or others]'.<sup>1</sup>

Other drug treatments have been suggested for agitation in dementia but trials of antidementia medication, the acetylcholinesterase donepezil<sup>17</sup> and the N-Methyl-D-Aspartate (NMDA) inhibitor memantine,<sup>18</sup> have been tested in randomised controlled trials (RCTs) and not demonstrated efficacy. In a large multicentre trial, the anticonvulsant sodium valproate did not delay or prevent NPS in dementia.<sup>19</sup>

Benzodiazepines are used short-term clinically but there are no trials and adverse effects such as falls are common and of concern.<sup>20</sup> Antidepressants have also been investigated as an alternative to antipsychotics. The CitAD trial of citalopram for agitated behaviours provided evidence that a target dose of citalopram 30mg per day had a small positive effect on agitation in dementia<sup>21</sup> in those who were less agitated and less cognitively impaired.<sup>22</sup> Adverse cardiac and cognitive effects identified in the trial limit its use in clinical practice.<sup>21</sup> Antidepressants are not mentioned as a potential treatment for agitation in the English National Institute for Health and Care Excellence (NICE) guideline on dementia assessment and management<sup>23</sup> but they are increasingly used as a treatment of agitation in dementia. This substitution strategy to seek to avoid the prescription of antipsychotics has been reported in a large study of US nursing homes where the prescription rates of mood stabilisers such as sodium valproate, carbamazepine and particularly gabapentin increased as those for antipsychotics decreased.<sup>24,25</sup> Such prescribing of antidepressants is part of the common polypharmacy seen among people with dementia in the community.<sup>26</sup>

## Mirtazapine for agitated behaviours in dementia

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NASSA), is widely used in older people; from 2009 to 2014, in a study of 4.8 million antidepressant initiations in Europe, it was the antidepressant that was most commonly prescribed for older people and also to those with dementia.<sup>27</sup> A centrally active presynaptic  $\alpha_2$ -antagonist, it stimulates both noradrenergic and serotonergic systems mediated via 5-HT<sub>1</sub> receptors, with 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors blocked by mirtazapine. Histamine H<sub>1</sub>-antagonistic activity is thought to cause its sedative properties. It has little anticholinergic activity, unlike citalopram, and, at therapeutic doses, has few cardiovascular effects. Mirtazapine is a relatively potent antagonist/inverse agonist at key receptors likely to be pivotal in target symptoms including antagonism of  $\alpha_2$ -adrenergic, 5-HT<sub>1A</sub> and histamine H<sub>1</sub> receptors. The overall effects are to increase noradrenergic and serotonergic neurotransmission which may explain its use in depression while the H<sub>1</sub> antagonism is associated with useful acute sedative benefits. The pharmacological profile of mirtazapine is such that at higher dosages, the sedative effect decreases due to noradrenaline stimulation. It is a well-established treatment for depression and is well tolerated by older people and so a popular choice by psychiatrists which will encourage recruitment. It is available generically at low cost in the NHS. Cost implications, were it found to be effective, would be therefore minimal.

In pre-specified secondary analyses of the HTA-SADD data set, reported in the HTA-SADD final report,<sup>28</sup> we have found a positive effect of mirtazapine on decreasing Behavioural and Psychological Symptoms in Dementia (BPSD) [as measured by Neuropsychiatric Inventory (NPI) score] at 13 weeks. Taking the top 50% of raw NPI scores (i.e. those with appreciable BPSD), there was a 7.1-point difference in NPI score [95% confidence interval (CI) -0.50 to 14.68;  $p = 0.067$ ] between mirtazapine and placebo and a 13.2-point difference between mirtazapine and sertraline (95% CI 4.47 to 21.95;  $p = 0.003$ ). An additional surprising but encouraging positive finding was from the cost-effectiveness analyses. Over the course of the trial, the time spent by unpaid carers caring for participants in the mirtazapine group was almost half that for patients in the placebo group (6.74 vs. 12.27 hours per week) and sertraline group (6.74 vs. 12.32 hours per week). Informal care costs were £1510 (95% CI -3088 to -136) and £1522 (95% CI -3398 to -72) less for the mirtazapine-treated group when compared with placebo and sertraline respectively. In the secondary outcome evaluation, looking at quality-of-life gains and costs, treatment with mirtazapine had a high likelihood of cost-effectiveness compared to placebo or sertraline.<sup>28,29</sup> The improvements in quality of life for mirtazapine relative to the other treatments contributed to the cost-effectiveness result, and there is a plausibility that comes from the putative ability of mirtazapine to ameliorate sleep disturbances and anxiety.<sup>30,31</sup> Improvements in sleep could potentially improve life quality and therefore patient-reported EuroQol-5 Dimension (EQ-5D) scores; they could also release carer time directly and also ameliorate an important source of carer distress.<sup>32</sup> In this way, mirtazapine might have a general effect, beneficial

for both the patient and the carer, even without exerting an antidepressant effect. Two small-scale open-label pilot studies give supportive evidence for the potential of a trial in this area [Cakir and Kulaksizoglu<sup>33</sup> (those on mirtazapine did better); Reichman *et al.*<sup>34</sup> (NPI decreased by 5.8 points)]. This would be the first placebo-controlled RCT of mirtazapine for agitation in dementia. 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.

## Carbamazepine for agitated behaviours in dementia

Carbamazepine stabilises the inactivated state of voltage-gated sodium channels and potentiates GABA receptors. It is recommended in the BNF for epilepsy, prophylaxis of bipolar disorder and trigeminal neuralgia. It is generally safe within the proposed dose ranges; there are few data on people with AD, but it seems that there is no increase in mortality as in antipsychotics for AD.<sup>35</sup> Carbamazepine has been widely used in psychiatric disorders and AD, off licence, to treat symptoms including agitation, aggression, irritability and impulsivity. Open-label studies and case reports have indicated promise in agitation in AD.<sup>36</sup> Two small 6-week parallel-group RCTs of carbamazepine for BPSD have been published.<sup>37,38</sup> The first in 55 patients (modal dose 300 mg) showed significant symptom decrease. It was well tolerated with no decrease in cognition, function or increased side effects relative to placebo. The second (400 mg in 21 patients not responding to antipsychotics) showed a trend but not a significant advantage over placebo. Meta-analysis indicated significant benefit compared with placebo treatment on the Brief Psychiatric Rating Scale (mean difference -5.5 points, 95% CI -8.5 to -2.5 points) and on the Clinical Global Impression Scale [odds ratio (OR) 10.2, 95% CI 3.1 to 33.1].<sup>39</sup> A third small trial of the similar compound oxcarbazepine ( $n = 103$ ) indicated a trend towards benefit ( $p = 0.07$ ) with active drug performing better than placebo in all analyses.<sup>40</sup>

## Why is the study needed?

Agitated behaviours drive poor quality of life in dementia and poor outcomes including hospitalisation and care home placement and high cost. They have profound negative effects on people with dementia themselves, their family carers, services and society. They are a major issue in care homes, in general hospitals and in people's own homes. The non-drug treatments we have are not always successful and the antipsychotic drugs that we use are associated with unacceptable increases in mortality and morbidity and low clinical effectiveness. There is a pressing need nationally and internationally for safe alternative pharmacological treatments. Research into better treatments for agitated behaviours in dementia was identified as a top 10 research priority by the Alzheimer's Society and the James Lind Alliance.<sup>41</sup> This involved extensive engagement with people with dementia, carers, health and social care practitioners and organisations that represent these groups. Over 4000 questions on prevention, diagnosis, treatment and care of dementia were considered and the top 10 identified, including: 'What non-pharmacological and/or pharmacological (drug) interventions are most effective for managing challenging behaviour in people with dementia?' The need for better research into pharmacological treatments for agitation and aggression is also articulated in the National Dementia Strategy,<sup>42</sup> the outputs of the 2010 Ministerial Dementia Research Summit and 2011 NIHR Dementia Research Workshop summarised in the Ministerial Advisory Group for Dementia Research (MAGDR) final report 'Priority Topics in Dementia Research' published by the MRC in February 2011.<sup>43</sup> MAGDR concluded 'further research into behavioural and psychological symptoms in order to provide more effective management of challenging behaviour and improved quality of life' was one of the top six headline priorities for research.

In this study, we therefore aimed to establish the clinical and cost-effectiveness and safety profile of carbamazepine (discontinued when 40 people had been randomised into this arm due to slower than projected recruitment) or mirtazapine in reducing agitation in AD relative to placebo.





# Chapter 2 Methods

## Study design

This is a pragmatic, multicentre, double-blind, placebo-controlled superiority RCT of safety, clinical and cost-effectiveness of mirtazapine (with usual care) at 6 and 12 weeks on agitated behaviours in dementia. We included a long-term follow-up period to allow limited assessment of longer-term outcomes at 26 and 52 weeks. An internal pilot phase assessed trial recruitment, with progression to a full trial dependent on the number of patients recruited within the pilot recruitment period.

## Important changes to methods

SYMBAD was initially designed as a three-arm trial, comparing both carbamazepine and placebo and mirtazapine and placebo for a difference in change in Cohen-Mansfield Agitation Inventory (CMAI) score at 12 weeks as the primary objective. Challenges in recruitment in this population resulted in the funder requesting that the available data be reviewed to July 2018, with the aim of dropping one arm of the trial.

The SYMBAD independent Data Monitoring Committee (DMC) reviewed available data comparing the two active arms with placebo. They were asked to consider efficacy data (the primary end point, CMAI at 12 weeks), safety data [frequency of AEs and serious adverse events (SAEs) on an individual basis] and compliance with treatment (dropouts and adherence with the prescribed amount of treatment medication). This was done subgroup blind: the DMC knew which was the placebo group but not the identity of the two active groups. Based on each set of data, the DMC were asked which arm they would recommend stopping or if they felt unable to make a recommendation. Taking all three sets together, the DMC were again asked whether they would recommend stopping one arm or were unable to make a recommendation.

The DMC could provide no recommendation on the basis of treatment compliance but recommended on the basis of efficacy and safety data the discontinuation of the carbamazepine arm. This recommendation did not provide, in any way, any indication that sufficient evidence had accrued to deem either drug to be effective or non-effective.

In August 2018, the protocol was submitted for a substantial amendment to change to a two-arm trial design, comparing mirtazapine with placebo as the primary objective. Protocol version 2.0 shows the new trial design. Up to the date of approval of this substantial amendment, 40 patients had been randomised to receive carbamazepine. These data have been analysed in the same way as the mirtazapine data. [Chapters 2–4](#) reflect the amended protocol and refer only to the mirtazapine/placebo comparisons.

See [Appendix 1](#) for summary of protocol changes.

## Aim

The overall trial aim was to assess the safety, clinical and cost-effectiveness of mirtazapine in the treatment of agitation in dementia.

The null hypothesis is that there is no difference in CMAI scores between patients treated with placebo and mirtazapine at 12 weeks.

## METHODS

The primary objective is to determine if mirtazapine is more clinically effective in reducing agitated behaviours in dementia than placebo, measured by CMAI score 12 weeks post randomisation.

The secondary objectives are:

1. to determine if mirtazapine is more cost-effective than placebo at 12 weeks post randomisation
2. to determine if mirtazapine is more clinically and cost-effective than placebo in reducing CMAI score at 6 weeks post randomisation
3. to determine differences in effectiveness between mirtazapine and placebo on carers
4. to determine whether there are differences between the groups in AEs and adherence
5. to determine long-term differences between those randomised to placebo and mirtazapine in a head-to-head comparison of agitation (measured by CMAI score), institutionalisation, death and clinical management at 26 and 52 weeks post randomisation.

## Participants

### *Inclusion criteria*

- Patients with a clinical diagnosis of probable or possible AD using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.<sup>44</sup>
- A diagnosis of co-existing agitated behaviours.
- Evidence that the agitated behaviours have not responded to management according to the AS/DH algorithm.<sup>45</sup>
- An assessment of CMAI (Long Form<sup>46</sup>) score of 45 or greater.
- Written informed consent to enter and be randomised into the trial.
- Availability of a suitable informant (consenting identifiable family carer or paid carer) to provide information on carer-completed outcome measures and who consents to take part in the trial.

### *Exclusion criteria*

- Current treatment with antidepressants (including MAOIs) or antipsychotics. Normal clinical practice should be followed, with an appropriate wash-out period before trial drug administration. For MAOIs, this should be at least 2 weeks.
- Contraindications to the administration of mirtazapine or carbamazepine as per the current Summary of Product Characteristics (SmPC).
- Patients with second-degree atrioventricular block [patients with third-degree heart block, with a pacemaker fitted, may be included at principal investigator (PI) discretion].
- Cases too critical for randomisation (i.e. where there is a suicide risk or where the patient presents a risk of harm to others).
- Female subjects under the age of 55 years of childbearing potential, defined as follows: postmenopausal females who have not had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH > 40 mIU/ml or females who have not had a hysterectomy or bilateral oophorectomy at least 6 weeks prior to enrolment.

## Setting

Participants were drawn from existing patients and new patient referrals to old age psychiatric services, memory clinics, specific Participant Identification Centres (PICs), primary care centres and those in care homes in 26 UK sites.

## Interventions

Initially there were three groups: (1) mirtazapine, (2) carbamazepine and (3) placebo. As noted above, the carbamazepine arm was dropped during the course of the study in August 2018. The target dose was 45 mg of mirtazapine or 300 mg of carbamazepine per day. Drugs and their placebos were identically presented with participants aiming to take three capsules orally once a day.

## Randomisation

Once a patient's screening CMAI score has been assessed as being  $\geq 45$ , the research worker discussed the case with the site PI who was permitted to prescribe Investigational Medicinal Product (IMP). The PI confirmed or not the patient's eligibility to join the study, and on confirmation, the research worker used an online randomisation system to randomise the patient for the trial. This system required confirmation of eligibility criteria. Details of the randomisation were confirmed by e-mail to the research worker, site PI, Chief investigator and co-ordinating team at Norwich Clinical Trials Unit (NCTU). A semi-blinded randomisation e-mail detailing IMP allocation was sent to site pharmacy contact/s only. The PI provided a signed prescription for the patient's trial medication. The research worker then collected this prescription from the central pharmacy and delivered it to the patient at a scheduled 'Week 0' IMP delivery visit. Local policies for treating patients outside of their registered NHS Trust were followed as appropriate. Random allocation was block stratified by centre and type of residence (care home vs. own household) with random block lengths of three or six before the discontinuation of the carbamazepine arm and thereafter of two or four. The trial was double-blind, with drug and placebo identically encapsulated. Referring clinicians, participants, the trial management team and the research workers who did baseline and follow-up assessments were masked to group allocation.

## Primary outcome

Cohen-Mansfield Agitation Inventory score (Long Form) at 12 weeks.

## Secondary outcomes

1. Costs derived from Client Service Receipt Inventory (CSRI), and quality-adjusted life-years (QALYs) from cost data alongside supplemented information from Dementia-Specific Quality of Life (DEMQOL) and EuroQol-5 Dimensions, five-level version (EQ-5D-5L) interviews 12 weeks post randomisation.
2. CMAI score and cost at 6 weeks post randomisation.
3. Patient and carer quality of life, and carer outcomes at 6 and 12 weeks post randomisation.
4. AEs from week 0 to week 16 and adherence at 6 and 12 weeks post randomisation.
5. CMAI score, AEs and adherence at 6 and 12 weeks, conditional on evidence of effectiveness of IMP over placebo.
6. Longer-term follow-up: CMAI score, institutionalisation, death and clinical management at 26 and 52 weeks post randomisation.

## Instruments used in the study – range and scoring

1. CMAI (agitation): score ranges from 29 (no agitated behaviour) to 203 (very agitated behaviour).
2. Mini Mental State Examination (MMSE) (cognition): score ranges from 0 (severe impairment) to 30 (normal).

3. General Health Questionnaire (GHQ-12) (mental health): score ranges from 0 (least severe problems, good) to 36 (most severe).
4. Zarit Carer Burden: range from 0 (no burden) to 88 (most severe).
5. DEMQOL (quality of life): DEMQOL range from 28 (poor) to 112 (good); DEMQOL-Proxy: range from 31 (poor) to 124 (good).
6. NPI (neuropsychiatric symptoms) total: total score range from 0 (none) to 144 (severe); NPI agitation/aggression: range from 0 (none) to 12 (severe); NPI depression/anxiety/irritation: range from 0 (none) to 36 (severe); and NPI carer distress: range 0 (none) to 60 (severe).

### Change in outcomes over the time of the trial

There were no changes to the primary outcomes of the trial following the registration of the trial.

### Sample size

An initial calculated sample size of 400 (randomised 1 : 1 : 1) provided 90% power using two-sided 5% significance tests to detect a drug versus placebo mean difference in CMAI score at 12 weeks of 6 points. This equated to an effect size of  $d = 0.4$  [assuming a common standard deviation (SD) of 15] or a clinically significant 30% decrease in CMAI from placebo to active drug. With a realistic 15% attrition, a sample of 471 (157 per arm) was aimed for. Due to slower than projected recruitment, an arm of the study (carbamazepine) was dropped and sample size was amended in consultation with the funder, DMC and TMC (see [Important changes to methods](#)). Based on the same parameters, an amended sample size target of 222 was calculated (randomised 1 : 1) allowing for a 10% attrition (111 per arm).

The primary outcome measure in this trial was the CMAI. Active drug treatment, compared with placebo, may be associated with changes in the CMAI that are much  $> 6$  points, but SYMBAD was powered to detect the smallest difference in the CMAI that could be considered clinically meaningful. This estimation was based on the changes and SD of change score seen in the CALM trial which included a similar patient population treated with donepezil where 6 CMAI points was 35% of the SD.

### Blinding and unblinding

#### Blinding

All non-statistical members of the trial team, their clinicians, participants and their carers were blinded to trial arm allocation. To maintain the blind, active medication and the placebo were identically encapsulated.

#### Unblinding

Final unblinding of all trial participants occurred following the creation of a locked analysis data set. The decision to unblind a single case was made when knowledge of an individual's allocated treatment was required:

- to enable treatment of severe AE/s, or
- in the event of an overdose.

Where possible, requests for emergency or unplanned unblinding of individuals were made via the trial manager, and in agreement of the Chief Investigator. However, in circumstances where there is insufficient time to make this request or for agreement to be sought, the treating clinician was able to make the decision to unblind immediately. This was done via the study database (local PIs and

the CI have special logins which allowed for unblinding and was closely audited within the database management system) or by contacting the CI who authorised unblinding by the Data Management Team. All instances of unblinding were recorded and reported to NCTU by the local PI, including the identity of all recipients of the unblinding information.

## Data management

### Confidentiality

Any paper copies of personal trial data were kept at the participating site in a secure location with restricted access. Only non-identifiable data were kept at the NCTU office with authorised NCTU staff members having access. Only staff working on the trial had password access to this information.

Confidentiality of patient's personal data was ensured by not collecting patient names on Case Report Forms (CRFs) that were to be sent to NCTU and storing the data in a pseudo-anonymised fashion at NCTU. At trial enrolment, the patient was issued a Participant Identification Number (PIN) and this acted as the primary identifier for the patient, with secondary identifiers of initials (and date of birth as required).

The patient and carer's consent forms carried their name and signature. These were kept at the trial site, and a copy was sent to NCTU for monitoring purposes. Consent forms were kept separate from patient data.

### Data collection tools and source document identification

Research workers completed paper CRFs during their visits to participants and their carers. They entered data onto a central database via an online system once they had internet access. Research workers received training on data collection and use of the online system. Identification logs, screening logs and enrolment logs were kept locally, either in paper or electronic form.

Source data worksheets were drafted by the trial manager with the CI, trial statistician, data management team and PIs. The database specification was prepared by the NCTU data manager and approved by the CI and trial statistician prior to the database being built. The database was prepared by the CTU data programmer and tested by the trial statistician, trial manager and study site staff for user acceptability prior to the final system being launched.

Data collection, data entry and queries raised by members of the HTA-SYMBAD trial team were conducted in line with NCTU and trial-specific Data Management Standard Operating Procedures.

Clinical trial team members received trial protocol training. All data was handled in accordance with the Data Protection Act 1998 and as updated in the 2018 Act, and the General Data Protection Regulation (GDPR) [European Union (EU)] 2016/679.

### Data handling

Within each trial site, patients were allocated a unique trial PIN. Data were entered under this PIN onto the central database stored on the servers based at University of East Anglia (UEA). The database was password protected and only accessible to members of the SYMBAD trial team at NCTU, the participating sites and external regulators (upon request). The server is in a secure room, which is protected by CCTV, where access is restricted to members of the UEA Information Systems team by security door access. The study database was built using Microsoft SQL Server tools and direct access was restricted to NCTU data management staff. Data entry was via web pages created using Microsoft.NET technology. All internet traffic was encrypted using the standard SSL (Secure Sockets Layer) methodology. The data entry system validated data on entry to ensure they were of the expected type (e.g. integers, dates, etc.) and range of values. Periodically and at database lock the data were further validated for errors and inconsistencies. The database was linked to

an audit tool where all data additions, modifications and deletions are recorded with date/time and the user ID of the person making the change. The database was designed to comply with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), within the Standard Operating Procedures for Data Management in NCTU and also where appropriate with UEA Information Technology (IT) procedures.

The database and coding values were developed by the NCTU data manager in conjunction with the Chief Investigator, study statistician and other NCTU members and the trial team. The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests and search facilities to identify validation failure/missing data. Further details can be found in the SYMBAD Trial Data Management Plan. The database will be retained on the servers of UEA for 10 years following the end of the trial.

The identification, screening and enrolment logs, linking participant identifiable data to the PIN, were held locally by the research sites and at NCTU. This was either in written form in a locked filing cabinet or electronically in password-protected form on hospital computers. After completion of the trial, the identification, screening and enrolment logs will be stored securely by the sites for a minimum of 10 years.

### Monitoring and site visits

For each site, a site initiation visit (SIV) was arranged by the trial manager with the core study team. A remote visit (teleconference or video conference call) was considered if they met predefined criteria of experience.

The minimum attendance for the SIV (in person or remotely) was the PI, lead research nurse, lead data manager (if applicable), pharmacy lead and research worker, any sub-Investigators were also encouraged to attend. All sites received a standardised copy of site initiation slides to aid the training of new staff working on the trial.

Each site was provided with a paper site file containing all the documents required to be held at site, generated at NCTU to comply with ICH GCP guidelines. A confirmation receipt was sent with the file for completion at site to confirm all documents had been received. Prior to a site being activated, the receipt was required to be received and returned to the TM or delegate at NCTU.

Before COVID-19, all sites recruiting at least five participants received one routine monitoring visit during the course of the trial. After lockdown, three sites (South West London, Central and North West London and Sheffield) that recruited more than five and were not visited, checks for these were made online. Site monitoring included the following checks:

- ensuring that key eligibility variables match source data
- blood test results and electrocardiogram (ECG) printouts
- SAE [and serious adverse reaction (SAR)/suspected unexpected serious adverse reaction (SUSAR) where applicable] reports were verified against clinical notes where possible
- clinic notes checked for unreported notable or serious events, where possible
- data from participants experiencing study drug discontinuations/dose lowering
- 50% Source Data Verification from patient packs transcribed to Electronic Case Report Forms (eCRFs) will be checked for at least 20% of patients recruited at the site at the time of the visit; if time allows, more patient packs will be checked. The CMAI questionnaire/score will always be checked for the randomly selected 20% of patients; a selection of the other questionnaires up to a minimum of 50% of the data will be checked

- sites will not be warned in advance which patient packs will be checked; the monitor will take a list with them and select the listed patient numbers from all of the available packs
- any major or critical findings should prompt the monitoring team to increase the level of monitoring to cover as many participant files as time allows
- completeness of trial drug dispensing, accountability and drug supply inventories
- documentation and procedures will be checked for protocol deviations and serious breaches
- consent forms
- delegation logs
- confirmation that safety checks had been completed and reviewed by the PI prior to randomisation
- accuracy of site file (and pharmacy file checks where relevant).

After the visit, the PI and site team were provided with a report summarising the documents that had been reviewed and the corrective actions that were required by the site team. A response was required to be provided to the TT. The Trial Manager reviewed responses and compiled them alongside the on-site monitoring findings. The final report was signed off by the TT member performing the visit and the CI (reviewer). Additional monitoring visits were conducted on a 'for cause' approach. Monitoring of data quality, recruitment rates, pharmacy, Investigator Site File documents, consent and safety also occurred centrally.

## Assessment by time point

For an overview of assessments over time, please see [Table 1](#).

## Safety assessments

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP applied to this trial: any unfavourable and intended sign, symptom or illness that developed or worsened during the period of the study was classified as an AE, whether or not it was considered to be related to the study treatment. AEs included unwanted side effects, sensitivity reactions, abnormal laboratory results, injury or intercurrent illnesses, and may be expected or unexpected. These were recorded on the CRF.

The period for SAE reporting was from the time of randomisation until 4 weeks post final trial medication administration. The participants were followed up by a telephone interview 4 weeks after the last dose of trial medication (the week 16 call). All events were followed until resolution, including if that meant beyond 4 weeks' post final trial medication implementation.

### Definitions

Definitions of AEs are presented in [Table 2](#).

### Recording and reporting adverse events

NCTU were notified of all SAEs within 24 hours of the investigator becoming aware of the event. Investigators notified NCTU of any SAEs that occurred from the time of randomisation until 4 weeks after the last protocol treatment administration. SARs and SUSARs were notified to NCTU until trial closure. Any subsequent events that could be attributed to treatment were reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) using the yellow card system (<https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/>).

The SAE form was completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care in the trial) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE

TABLE 1 Research assessment by time point

Assessment	Baseline <sup>a</sup>	Rx 'week 0' visit (0–7 days after last baseline or randomisation visit)	Week 2 (12–16 days after week 0 visit date) <sup>b</sup>	Week 4 (21–35 days after week 0 visit) <sup>b</sup>	Week 6 (35–49 days after week 0 visit) <sup>a</sup>	Week 12 (77–91 days after week 0 visit) <sup>a</sup>	Week 16 <sup>h</sup> (105–119 days after week 0 visit) <sup>b</sup>	Week 26 <sup>c,d</sup> (week 25–27)	Week 52 <sup>c,d</sup> (week 51–53)
Consent	X								
CMAI (Long Form)	X				X	X			
Safety bloods <sup>d</sup> (FBC, U&Es, LFT)	X <sup>e</sup>					X <sup>f</sup>			
ECG <sup>d</sup>	X <sup>e</sup>					X <sup>f</sup>			
CSRI <sup>g</sup>	X				X	X			
Disease-specific Quality of Life DEMQOL	X				X	X			
Carer assessed dis- ease-specific Quality of Life DEMQOL-Proxy	X				X	X			
Generic Quality of Life EQ-5D-5L (Proxy)	X				X	X			
Cognitive impairment sMMSE	X				X	X			
BPSD	X				X	X			
C-SSRS (Cognitively impaired version)	X				X	X			
Randomisation		X							
Dispensing		X							
Adherence			X			X			
AEs			X	X		X			X
Medication assessment (for dose changes)			X	X	X	X			



TABLE 1 Research assessment by time point (continued)

Assessment	Baseline <sup>a</sup>	Rx 'week 0' visit (0-7 days after last baseline or randomisation visit) <sup>b</sup>	Week 2 (12-16 days after week 0 visit date) <sup>b</sup>	Week 4 (21-35 days after week 0 visit) <sup>b</sup>	Week 6 (35-49 days after week 0 visit) <sup>a</sup>	Week 12 (77-91 days after week 0 visit) <sup>a</sup>	Week 16 <sup>h</sup> (105-119 days after week 0 visit) <sup>b</sup>	Week 26 <sup>cd</sup> (week 25-27)	Week 52 <sup>cd</sup> (week 51-53)
Use of rescue medications			X	X	X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X
Withdrawal of treatment			X	X	X	X			
Carer mental health GHQ-12 <sup>h</sup>	X				X	X			
Carer quality of life EQ-5D-5L <sup>h</sup>	X				X	X			
Carer burden Zarit CBI <sup>h</sup>	X				X	X			
Carer proxy report of CMAI score <sup>b</sup>								X	X
Carer proxy report of treatment <sup>b</sup>								X	X
Institutionalisation <sup>b</sup>								X	X
Death <sup>b</sup>								X	X

FBC, full blood count; LFT, liver function (blood) test; U&Es, urea and electrolytes blood test.

a Face-to-face visits may take place over more than one visit if required, particularly if blood/ECG tests are to be collected. Patient must be randomised no more than 28 days after consent was given.

b At weeks 2, 4, 16, 26 and 52, carers will be contacted by telephone. All other visits will take place in the patient's place of residence, unless the patient requests otherwise.

c Longer-term assessments undertaken by site research workers employed on the research grant while the research sites remain open, and by Centre of Dementia Studies staff at Brighton and Sussex Medical School when the sites closed.

d Recommended tests, a reasonable attempt should be made to collect these in all cases, but if not possible, then PI to make a decision on clinical grounds as to eligibility as would be the case in normal clinical practice.

e May utilise existing results (if available) up to 28 days prior to randomisation date.

f Ideally these tests would be done at week 12 visit, but may be done up to ±14 days after last dose of study medication if required.

g Medication and health service use may also be accessed from GP records by research workers.

h Asked of unpaid carers only.

i Week 16 call not required if patient stopped trial medication prior to week 8; AEs can be recorded at week 12 visit. If trial medication was stopped completely between weeks 8 and 12, the week 16 call must still be carried out but AEs/SAEs only need to be reported up to 4 weeks after medication was stopped.

**TABLE 2** Definitions of adverse events within the SYMBAD trial

Adverse event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product
Adverse reaction (AR)	Any untoward and unintended response to an IMP related to any dose administered
Unexpected adverse reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SmPC) for an authorised product
Serious adverse event or serious adverse reaction	Any AE or AR that at any dose: <ul style="list-style-type: none"> <li>• results in death</li> <li>• is life-threatening<sup>a</sup></li> <li>• requires hospitalisation or prolongs existing hospitalisation<sup>b</sup></li> <li>• results in persistent or significant disability or incapacity</li> <li>• is a congenital anomaly or birth defect</li> <li>• or is another important medical condition<sup>c</sup></li> </ul>

a The term life-threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction).

b Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) does not constitute an SAE.

c Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life-threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation or development of drug dependency).

form was completed and signed by a member of the site trial team and e-mailed as appropriate within the timeline. The responsible investigator checked the SAE form at the earliest opportunity, made any changes necessary, signed and then e-mailed it to NCTU. Detailed written reports were completed as appropriate. Systems were in place at each site to enable the investigator to check the form for clinical accuracy.

The minimum criteria required for reporting an SAE were the patient trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that was unavailable at the time of the first report was sent as soon as it became available. The SAE form was scanned and sent by e-mail to the trial team at NCTU.

Participants were followed up until clinical recovery was complete and laboratory results had returned to normal or baseline values, or until the event had stabilised. Follow-up visits continued after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms were completed and e-mailed to NCTU as further information became available. Additional information and/or copies of test results (etc.) could be provided separately. The participant was identified by trial number, date of birth and initials only. The participant's name was not used on any correspondence and was blacked out and replaced with trial identifiers on any test results.

### **Assessment of adverse events**

The severity of all AEs and/or ARs (serious and non-serious) in this trial was based on the Research Worker and site PI's clinical judgement. For general (e.g. non-haematological) AEs/ARs, they were graded using the following definitions:

1. mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
2. moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
3. severe: an event that prevents normal everyday activities.

For haematological (e.g. from blood test results) AEs/ARs, they were graded using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) 14 June 2010 criteria:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bed-ridden, etc.)
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE.

In addition to severity, the investigators assessed the causality of serious events or reactions in relation to the trial therapy using the definitions in [Table 3](#). SAEs that were considered related to the trial treatment were reviewed against the list of expected events in the approved version of the mirtazapine SmPC. Events that did not appear on the list or happened more frequently than listed were considered unexpected and reported as SUSARs.

## Statistical methods

### Primary outcome measures

Analyses were based on intention-to-treat (all participants were analysed according to the group to which they were randomised, irrespective of the treatment or dose received). The primary outcome (CMAI at 12 weeks) was analysed using a general linear regression model including baseline CMAI score as a covariate, place of residence as a fixed effect and recruitment centre as a random effect. Treatment group was added as a fixed effect, with two levels (placebo vs. mirtazapine). Model assumptions were checked by use of diagnostic plots. The primary analysis used complete cases (excluding those with missing values). Imputation was done under the MAR assumption. A sensitivity analysis imputed missing values using multiple imputation with chained equations approach [the *mi impute chained* command in Stata® (StataCorp LP, College Station, TX, USA)].

### Secondary outcome measures

Analysis of secondary outcomes, including long-term outcomes at 26 and 52 weeks followed an analogous approach using general linear regression models including baseline outcome, stratification variables and treatment group. We completed a post hoc analysis comparing death rates in the groups using Fisher's exact test.

## Health economics

### Economic evaluation

The primary outcome for the economic evaluation was the incremental cost per 6-point difference in CMAI score at 12 weeks, from a health and social care system perspective. A 6-point difference represents a clinically significant minimum difference, or 30% decrease on the measure from placebo to mirtazapine. In addition, we conducted a secondary cost-effectiveness analysis on this outcome measure from the societal perspective. We conducted secondary cost-utility analyses of participants' and unpaid carers' QALYs at 12 weeks, from both the health and social care and societal perspectives (encompassing health and social care, unpaid care and out-of-pocket costs of purchasing adaptive equipment). Three measures of health-related quality of life were used to derive participant utilities: informant-rated EQ-5D-5L,<sup>47,48</sup> informant-rated DEMQOL-Proxy-U and participant-rated DEMQOL-U.<sup>49,50</sup> Unpaid carers' utilities were derived from carer self-rated EQ-5D-5L. QALYs were calculated using the area under

**TABLE 3** SYMBAD causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out	SAR

the curve method, assuming linear change between assessment points.<sup>51</sup> Six-week costs and outcome measures were reported but a full cost-effectiveness analysis of the CMAI outcome at 6 weeks was not undertaken, given the very short time horizon for observing changes in service utilisation.

In addition, a model-based cost-effectiveness analysis was planned, examining lifetime costs and QALY gain beyond the intervention period. However, on the basis of the clinical and cost-effectiveness findings, this was not progressed and no results have been reported.

### Resource use

Comprehensive costs of care for participants with dementia were calculated (including the costs of formal/paid care such as that provided by health and social services and also the costs associated with unpaid care) using data gathered using the CSRI<sup>52</sup> at baseline, 6 and 12 weeks.

### Unit costs

The base year for prices was 2016–17. Unit costs were taken from nationally representative published sources.<sup>53–55</sup> The price of generic mirtazapine was taken from the NHS Prescription costs analysis.<sup>53</sup> Unpaid carer time was valued at opportunity cost in the main analyses (following the lost productivity approach described elsewhere).<sup>56,57</sup> The costs of unpaid care were estimated as either the cost of time spent in caring or of time taken off from work to care, whichever cost was the greater. In estimating the cost of unpaid carer time in caring, those in work were considered to have given up work time (lost production), valued at the national average wage;<sup>58</sup> those not working were considered to have given up leisure time, valued at 35% of national average wage. The CSRI, which was used to estimate carers' caring hours, covered time spent over the previous week in all caring tasks (including supervision and also care home visiting). Unpaid carers chose a time band for the hours of care provided per week (ranging from no hours to 100+ hours per week). A continuous variable for total hours of care was calculated by taking the mid-point of each band. The maximum of the topmost band was first adjusted to account for nightly sleep time (assumed to be 8 hours if carers reported no lost sleep in caring or the hours remaining once hours of lost sleep were deducted). All time spent in caring tasks received the same valuation (rather than attributing a lower value to supervision than hands-on care tasks).

## Cost estimation

Items of resource use were grouped into categories for the purposes of costing: hospital services, primary and community health, mental health, accommodation (domestic/communal), overnight respite care (in communal settings), community social care, day services, equipment and adaptations (including memory aids), medications and unpaid care provided to participants. Unpaid care included lost working time (work cut down/given up) and hours of help and support provided by the main carer and family/friends.

## Health economic statistical analysis

The cost per unit of effect of the intervention is known as the incremental cost-effectiveness ratio (ICER). It is calculated as the mean difference in costs in mirtazapine and placebo groups ( $\Delta C$ ) divided by the mean difference in outcome ( $\Delta E$ ) between groups.

Mirtazapine would be considered cost-effective if it was significantly more effective and less expensive than placebo. The treatment would also be cost-effective if it was significantly more effective and more expensive than placebo, but the decision-maker was willing to pay the additional cost (up to a threshold,  $\lambda$ ) to achieve the additional effect; or, put another way, if the ICER was below some threshold of willingness to pay for a unit of additional effectiveness,  $\lambda$ .<sup>59</sup> The cost-effectiveness decision rule in this case can be expressed as:

$$\Delta C / \Delta E < \lambda \quad (1)$$

Mirtazapine might also be considered cost-effective if it was significantly less effective and less expensive and the decision-maker considered the sacrifice of some effectiveness worth making to achieve the savings. Mirtazapine would be considered unambiguously to be not cost-effective if it is both significantly less effective and more expensive.

The incremental net monetary benefit (NMB)<sup>59,60</sup> is the monetary value of gains in effects associated with the treatment at a given value of  $\lambda$ , once the additional cost of the treatment has been deducted. Rearranging the decision rule in (1), NMB is expressed as:

$$\lambda \times \Delta E - \Delta C > 0 \quad (2)$$

Multilevel bivariate regressions were estimated for costs and outcomes with fixed effects for baseline cost/outcome and living arrangement at randomisation (stratifying variable) and a random effect for centre. Multilevel models (MLM) were estimated by restricted maximum likelihood. Where the sample providing data consisted of 50 or fewer observations, models applied small sample inference for fixed effects and residual denominator degrees of freedom in tests of fixed effects.<sup>61</sup> NMB over a range of willingness-to-pay values was derived from model estimates and their 95% CIs were calculated following Fieller's theorem.<sup>62,63</sup>

There is no societal consensus on what should be paid for a minimum clinically significant difference in the CMAI. A NMB plot and a cost-effectiveness acceptability curve (CEAC) were produced to show the extent to which the primary outcome could be judged cost-effective. The plot of the NMB and its confidence limits over a range of willingness-to-pay thresholds illustrates not only the size of any positive values of NMB but also whether the ICER has confidence limits. The point ICER is found where the NMB line intersects with the x-axis (the net benefit for a unit of effect is zero), that is the point where the decision-maker is prepared to pay just the cost of achieving a benefit.<sup>59</sup> The confidence limits of the ICER are found where the confidence limits of the NMB line intersect with the x-axis.<sup>60</sup> An unbounded ICER (when the NMB confidence limit lines never intersect with the x-axis) indicates that neither the intervention nor the control strategy can be considered more cost-effective.<sup>63</sup> The CEAC depicts the probability that the NMB at a given level of willingness to pay ( $\lambda$ ) is  $> 0$ .<sup>64</sup> This approach is useful for demonstrating the level of uncertainty associated with deciding that mirtazapine is cost-effective at different levels of willingness-to-pay values.

For secondary analyses of QALY and health and social care costs outcomes, the ICER and the NMB at £20,000 (the lower limit of the NICE threshold for a QALY gain)<sup>65</sup> were calculated and presented alongside descriptive and cost-effectiveness analysis results. Probability of cost-effectiveness over a range of willingness-to-pay thresholds was calculated for narrative commentary in the text. MLM analyses were conducted in Stata 16.<sup>66</sup>

### **Sensitivity analyses**

Sensitivity analyses explored the impact on results of varying key assumptions made in the base case for primary and secondary analyses: including accommodation of participants in domestic as well as residential care in total health and social care costs; examining total (EQ-5D-5L) QALY and costs for the dyad (person with dementia and unpaid carer); and using an alternative valuation and definition of unpaid carer time. Accommodation costs of domestic residence were sourced from UK Household expenditure statistics (Office for National Statistics 2019) and 'sheltered' domestic housing.<sup>54</sup> Unpaid carer time was valued at replacement cost, using the hourly cost of a home care worker. This valuation was also used to calculate unpaid care time defined as the hours of the day that the person with dementia could not be left alone by the carer.

In addition, we explored the impact on results of varying the modelling approach in the primary cost-effectiveness analyses. First, we included a covariate for gender in the MLM to adjust for a baseline imbalance between groups. Second, as an alternative approach to the MLM and to address skewness typical of cost data, we applied seemingly unrelated regressions<sup>67</sup> (where cost and outcome equations were the same as in the MLM) to 4000 replicates generated by a two-stage bootstrapping procedure suitable for clustered data.<sup>68</sup> This analysis was conducted in R (The R Foundation for Statistical Computing, Vienna, Austria).<sup>69</sup>

### **Ethics and regulatory approvals**

The study was approved by the Hampshire A South Central Research Ethics Committee (15/SC/0606), and the MHRA. It received local NHS Trust approvals and consent or assent (with legal representative consent) was obtained from all participants (see trial protocol for more details). This protocol was submitted to the UK national competent authority (MHRA).

This is a clinical trial of an IMP as defined by the EU Directive 2001/20/EC. The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, was reported to the competent authority (MHRA).

### **Patient and public involvement**

Ensuring the involvement of people living with dementia and their carers has been integral to the SYMBAD trial. This section provides further information on their important role in the trial.

#### ***Application for funding and trial design***

SN is a co-applicant and has been leading on public/carers involvement in the trial throughout, from support and active involvement in the initial application of funding and trial design to the dissemination of results. Trial design also received input from a Lived Experience Advisory Panel (LEAP) group hosted by Sussex Partnership Foundation Trust (SPFT) and the Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) group. The need for this trial received tremendous support from patients, public representatives and service users, keen to express the great need for a specific, effective and safe medicinal treatment for those with dementia and agitation. The protocol design was influenced

through patient and public involvement (PPI) feedback, with increased attention to monitoring of AEs and review of participant burden, particularly with regard to data completion. It was felt that community-based data collection would be appropriate for this population and provide carers with additional support to make trial-based decisions in this vulnerable population.

### ***Trial set up***

Our PPI lead co-applicant (SN), along with SPFT LEAP co-ordinators (JF and JS), was involved in frequent communication to develop the trial documents and review the participant/carer-facing information. Among other points, this resulted in the 'patient summary sheet', aimed specifically at informing people living with dementia themselves about what being a participant in the trial would entail. Although the ethics committee felt this document alone was not sufficiently detailed to allow informed consent to be taken, it did mean that a concise summary could be provided to participants with dementia and enable them to be fully included in the decision-making process. PPI members also reviewed and advised on initial recruitment strategies, posters and information leaflets. SN, a former carer for her husband, is a member of the Alzheimer's Society Research Network of volunteers working to raise awareness of the trial. The lead Trust (SPFT) was also supportive in raising awareness through the Clinical Research Network and leading on hosting the 'Join Dementia Research' website recruitment strategy [Join dementia research – register your interest in dementia research: Home (nih.ac.uk)].

### ***Delivery and support of the trial***

SN and JF have been members of the Trial Management Group (TMG) throughout. The group had a standing agenda item to discuss trial management and delivery from the patient, carer and public perspective. This included support of the trial when recruitment became challenging and looking at ways to engage further with clinicians in order to raise awareness of the trial for potential participants.

The trial team has been grateful for the input of the two PPI members on the Trial Steering Committee (TSC), who have balanced their support for the trial to continue alongside closely reviewing recruitment levels and strategies, thus ensuring the trial achieved its objectives.

The trial team has also been grateful for the input from the dedicated LEAP, co-ordinated initially by JS, then by JF. Over the course of the trial, nine people were members of the LEAP. All of the members had experience of living with dementia, whether diagnosed themselves or as a family carer. They have asked challenging questions of the trial team and provided excellent and thoughtful guidance on the writing and phrasing of patient facing information, including advising on the content of a participant newsletter where and how to raise awareness of the trial and suggested ways to disseminate the findings accordingly. The LEAP members were keen to balance the need for this trial to answer the important question it posed while stressing the need to reduce participant burden as far as possible.

A video was produced with support from patients and their carers in Norfolk and Suffolk Foundation Trust and CRN Eastern Patient and Public Involvement Manager, as one of the strategies to overcome potential clinician 'gatekeeper' behaviours and increase recruitment. Previous participants in the trial volunteered to share their experiences and support of the trial.

### ***Dissemination***

SN, JF and our LEAP panel have been involved with the dissemination activities and helped with appropriate wording to convey the, perhaps less hopeful, findings of the trial from a patient and public perspective, while stressing the value of the trial findings. This has been invaluable, since although the results are extremely important in understanding what should (or should not) be prescribed in this population, it is not a step forward regarding finding a treatment that helps. The PPI team have helped in reading the main academic outputs, as well as the preparation of the plain language summary of this report and the end-of-study information sheet for trial participants. They will continue to be involved in the most effective ways to communicate the important outcomes of the trial through their respective networks.





## Chapter 3 Mirtazapine versus placebo results

### Patient flow

We recruited participants between January 2017 and February 2020 and completed week 12 follow-up interviews by May 2020 (See [Figure 1](#)). See [Appendix 2](#) for recruitment by site and month.

### Baseline characteristics

[Table 4](#) shows baseline demographic and clinical characteristics of participants and carers. Groups were similar at baseline except for sex with more females randomised to mirtazapine ( $n = 77, 75\%$ ) than placebo ( $n = 59, 58\%$ ). In light of this difference, sex was included in an additional model as a sensitivity analysis. By week 12, similar numbers remained in the mirtazapine (80/102, 78%) and the placebo group (89/102, 87%).

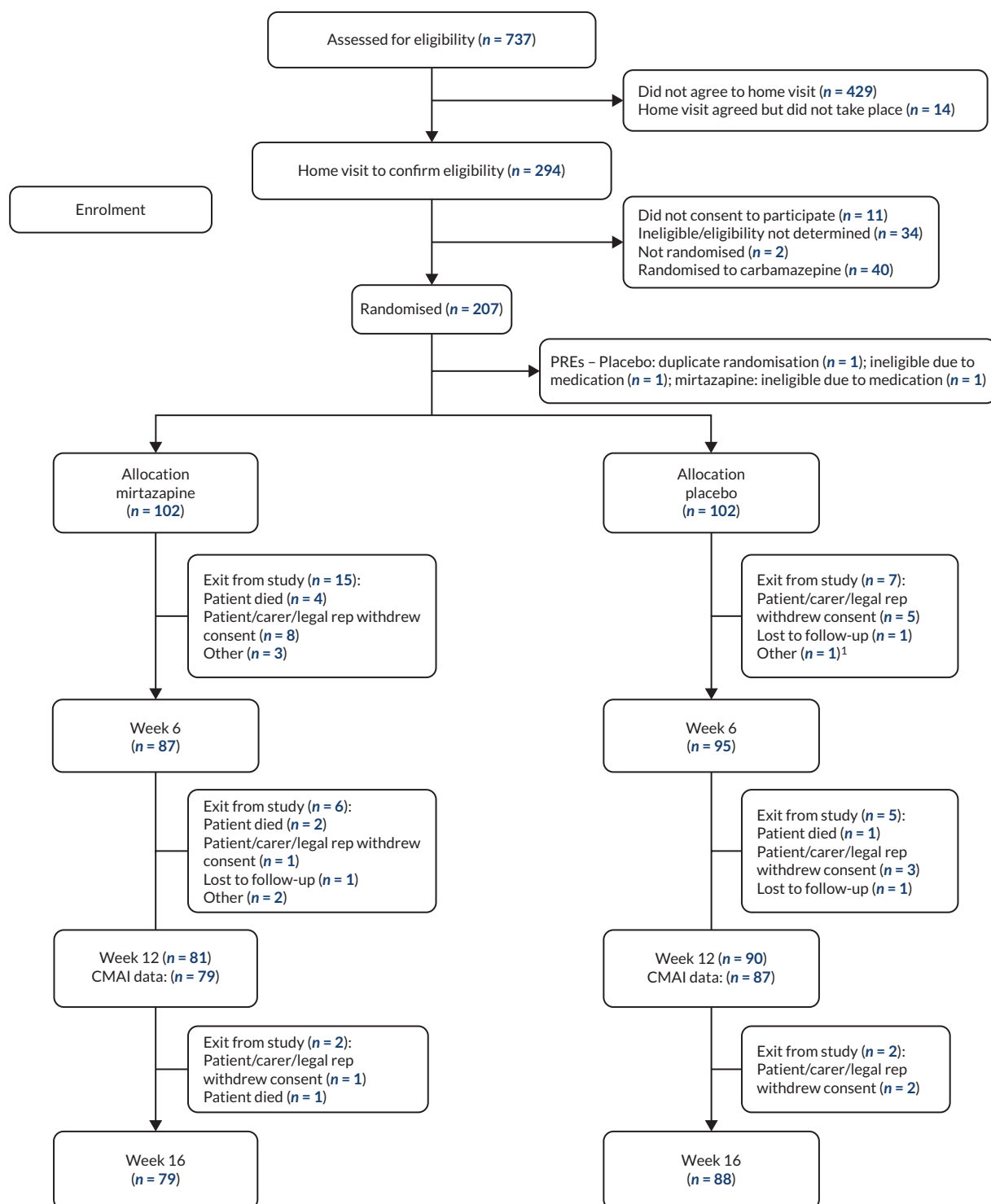
### Primary outcome measures

Severity of agitation decreased in both groups at 6 weeks by around 10 points and continued to be lower than baseline scores at 12 weeks (see [Figure 2](#)); this change between baseline and 6- and 12-week outcomes is illustrated by the separation in 95% confidence limits. At no point was the unadjusted or adjusted CMAI difference between the groups statistically significant (see [Table 5](#)). [Table 5](#) presents the results from the general linear mixed modelling for the primary outcome. There was no evidence that mirtazapine improved agitation relative to placebo. The estimated adjusted effect on the CMAI was  $-1.74$  (95% CI  $-7.17$  to  $3.69$ ;  $p = 0.530$ ). This changed little with the addition of sex into the model.

### Secondary outcome measures

[Table 5](#) shows the effect of mirtazapine compared with placebo on secondary outcomes in participants and [Table 6](#) in carers. Again, there was no evidence of difference between the groups, apart from: a single statistically significant difference in the Zarit Carer Burden Inventory at 12 weeks which indicated higher carer burden in the mirtazapine group (adjusted difference 5.01 points, 95% CI 0.80 to 9.23;  $p = 0.020$ ); weaker evidence at 6 weeks (3.76,  $-0.03$  to 7.83);  $p = 0.069$ ) in the same variable; and a weak association between higher proxy-rated ED-5D quality of life in the placebo group at 6 weeks ( $-0.07$ ,  $-0.13$  to 0.00,  $p = 0.061$ ) that was not maintained at 12 weeks ( $-0.01$ ,  $-0.08$  to 0.07,  $p = 0.822$ ).

Adverse events and severe AEs were ascertained to 16 or 4 weeks after last dose of IMP; deaths were recorded up to 16 weeks after randomisation. Examining AEs by week 16, there were 192 in 102 participants in the placebo group, of whom 65 (64%) individuals had at least one AE, compared with 225 events in 102 participants in the mirtazapine group of whom 67 (66%) had at least one. There were 35 SAEs in 18 individuals in the placebo group, compared with 13 in 8 individuals in the mirtazapine group. Mortality differed between groups with a potentially higher rate in the mirtazapine group (seven deaths in the mirtazapine and one in the placebo group by 16-week safety follow-up). Post hoc statistical analysis suggested weak evidence of a mortality difference between groups (Fisher's exact test  $p = 0.065$ ). Causes of death coded with MedDRA (Medical Dictionary for



**FIGURE 1** CONSORT flow diagram of recruitment and testing for mirtazapine and placebo groups.

Regulatory Activities) terms showed no consistent pattern with the one death in the placebo group attributed to dementia, and the seven in the mirtazapine group to: (i) dementia; (ii) pneumonia, aspiration; (iii) emphysema, dementia, pneumonia, aspiration; (iv) dementia Alzheimer's type; (v) cardiac failure; (vi) pelvic fracture, osteoporosis, vascular dementia; and (vii) chronic kidney disease, dementia, congestive cardiac failure. See [Table 7](#). See [Appendix 3](#) for a summary of AEs and severe AEs by randomisation group.

**TABLE 4** Baseline demographics and clinical characteristics of participants and carers

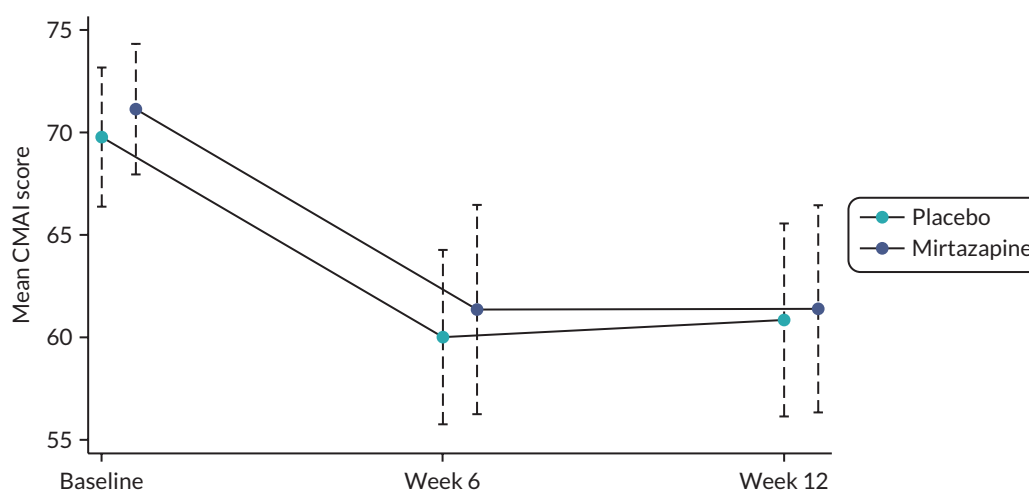
	Mirtazapine (n = 102)	Placebo (n = 102)
Participants		
Age (years) (SD)	82.2 (7.8)	82.8 (7.7)
Sex	n = 102	n = 102
Female	76 (75%)	59 (58%)
Residence	n = 102	n = 102
Own household	55 (54%)	57 (56%)
Care home	47 (46%)	45 (44%)
Agitation	n = 102	n = 102
CMAI (29–203)	71.1 (16.4)	69.8 (17.1)
Cognition	n = 52	n = 50
Standardised MMSE (0–30)	13.4 (8.1)	16.1 (6.7)
Condition-specific quality of life	n = 41	n = 37
DEMQOL (28–122)	92.4 (10.8)	95.8 (10.2)
DEMQOL-Proxy (31–124)	n = 100	n = 99
	92.3 (15.0)	90.9 (14.4)
Generic quality of life	n = 100	n = 101
EQ-5D (proxy report by carer) (0–1)	0.46 (0.34)	0.50 (0.32)
Neuropsychiatric symptoms	n = 98	n = 102
NPI total score (0–144)	32.7 (16.7)	34.9 (18.2)
NPI agitation/aggression subscore (0–12)	n = 99	n = 102
	5.6 (3.2)	5.6 (3.4)
NPI depression/anxiety/irritability subscore (0–36)	n = 99	n = 102
	9.9 (6.2)	10.5 (7.0)
Suicidality		
CSSRS	n = 102	n = 102
Suicidal ideation (lifetime)	18 (18%)	13 (13%)
Suicidal ideation (past month)	11 (11%)	11 (11%)
Suicidal behaviour (lifetime)	4 (4%)	0
Suicidal behaviour (past 3 months)	2 (2%)	0
Carers		
Carer		
Paid	39 (38%)	31 (30%)
Family	63 (62%)	71 (70%)

continued

**TABLE 4** Baseline demographics and clinical characteristics of participants and carers (continued)

	Mirtazapine (n = 102)	Placebo (n = 102)
Family carer relationship		
Partner or spouse	34 (54%)	35 (49%)
Son or daughter	21 (33%)	31 (44%)
Sibling	1 (2%)	0
Other relative	5 (8%)	3 (4%)
Friend	1 (2%)	2 (3%)
Other	1 (2%)	0
Family carer occupation (pre-retirement)		
Professional	13 (21%)	13 (18%)
Managerial and technical	23 (37%)	22 (31%)
Skilled non-manual	9 (14%)	11 (15%)
Skilled manual	11 (17%)	8 (11%)
Partly skilled	2 (3%)	8 (11%)
Unskilled	3 (5%)	0
Unemployed or unwaged	2 (3%)	5 (7%)
Unanswered	0	4 (6%)
Carer mental health (family carers only)		
GHQ-12	n = 61 15.0 (5.8)	n = 66 14.5 (4.9)
Carer burden (family carers only)		
Zarit Carer Burden Inventory (CBI)	n = 58 33.8 (15.7)	n = 66 34.1 (13.9)
Carer generic quality of life (family carers only)		
EQ-5D	n = 61 0.79 (0.21)	n = 66 0.81 (0.22)
NPI carer distress subscore (0–60)		
	n = 94 14.1 (8.6)	n = 99 15.5 (9.0)

CSSRS, Columbia Suicide Severity Rating Scale.

**FIGURE 2** Unadjusted mean CMAI scores (95% CI) by treatment group.

**TABLE 5** Comparisons of participant primary outcomes at 12 weeks and secondary outcomes at 6 and 12 weeks

	Mirtazapine (n = 102)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference <sup>a</sup>	(95% CI)	p-value
12-week primary outcome							
Agitation (CMAI)	n = 79	n = 87					
	61.4 (SD 22.6)	60.8 (SD 21.8)	0.59	(-6.22 to 7.40)	-1.74	(-7.17 to 3.69)	0.530
					-0.93 <sup>b</sup>	(-6.42 to 4.56)	0.739
6-week secondary outcomes							
Agitation (CMAI)	n = 84	n = 88					
	61.4 (23.5)	60.0 (19.9)	1.39	(-5.15 to 7.93)	-0.55	(-6.18 to 5.08)	0.848
Cognition (sMMSE)	n = 33	n = 31					
	15.5 (7.1)	16.2 (7.2)	-0.68	(-4.25 to 2.89)	0.14	(-1.17 to 1.45)	0.836
Quality of life (DEMQOL)	n = 32	n = 32					
	95.1 (10.2)	96.8 (8.4)	-1.69	(-6.38 to 3.00)	1.12	(-2.74 to 4.97)	0.570
Quality of life (DEMQOL-Proxy)	n = 79	n = 86					
	96.6 (14.7)	94.6 (16.2)	2.03	(-2.74 to 6.79)	0.80	(-3.18 to 4.77)	0.694
Quality of life EQ-5D (proxy report by carer)	n = 82	n = 87					
	0.48 (0.33)	0.56 (0.30)	-0.08	(-0.17 to 0.02)	-0.07	(-0.13 to 0.00)	0.061
Neuropsychiatric symptoms							
NPI total score	n = 84	n = 88					
	27.1 (20.0)	24.8 (20.0)	2.29	(-3.73 to 8.31)	2.03	(-2.89 to 6.95)	0.419
NPI agitation/ aggression subscore	n = 84	n = 88					
	4.0 (3.6)	4.2 (3.5)	-0.20	(-1.28 to 0.87)	-0.34	(-1.30 to 0.62)	0.490
NPI depression/ anxiety/irritabil- ity subscore	n = 84	n = 88					
	7.9 (7.7)	7.2 (8.2)	0.68	(-1.72 to 3.07)	0.70	(-1.24 to 2.63)	0.482
12-week secondary outcomes							
Cognition (sMMSE)	n = 23	n = 27					
	18.0 (6.0)	15.6 (7.5)	2.44	(-1.48 to 6.37)	1.45	(-0.20 to 3.10)	0.084
Quality of life (DEMQOL)	n = 24	n = 24					
	94.3 (7.1)	97.1 (8.4)	-2.83	(-7.35 to 1.68)	-1.36	(-5.82 to 3.10)	0.549
Quality of life (DEMQOL-Proxy)	n = 71	n = 82					
	98.4 (14.5)	97.5 (12.4)	0.93	(-3.37 to 5.23)	0.44	(-3.09 to 3.96)	0.809
Quality of life EQ-5D (proxy report by carer)	n = 77	n = 84					
	0.46 (0.35)	0.50 (0.33)	-0.04	(-0.14 to 0.07)	-0.01	(-0.08 to 0.07)	0.822

continued

**TABLE 5** Comparisons of participant primary outcomes at 12 weeks and secondary outcomes at 6 and 12 weeks (continued)

	Mirtazapine (n = 102)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference <sup>a</sup>	(95% CI)	p-value
Neuropsychiatric symptoms	n = 75	n = 84					
NPI total score	23.9 (17.8)	25.7 (19.6)	-1.80	(-7.69 to 4.09)	-2.02	(-6.67 to 2.62)	0.393
NPI agitation/ aggression subscore	n = 76 4.1 (3.4)	n = 84 4.5 (3.6)	-0.40	(-1.49 to 0.70)	-0.52	(-1.52 to 0.47)	0.305
NPI depression/ anxiety/irritabil- ity subscore	n = 75 6.9 (6.7)	n = 84 7.3 (8.0)	-0.44	(-2.77 to 1.88)	-0.58	(-2.43 to 1.27)	0.541

a Adjusted for pre-specified factors: baseline CMAI, household status and centre.

b Adjusted for sex and pre-specified factors: baseline CMAI, household status and centre.

**TABLE 6** Comparisons of carer secondary outcomes at 6 and 12 weeks

	Mirtazapine (n = 102)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference <sup>a</sup>	(95% CI)	p-value
6-week outcomes							
Carer GHQ-12 <sup>b</sup>	n = 50	n = 54					
	12.8 (6.2)	12.1 (4.9)	0.69	(-1.47 to 2.85)	0.61	(-1.21 to 2.42)	0.512
Carer EQ-5D <sup>b</sup>	n = 50	n = 55					
	0.83 (0.16)	0.83 (0.15)	0.00	(-0.06 to 0.06)	0.01	(-0.04 to 0.05)	0.821
Zarit CBI <sup>b</sup>	n = 46	n = 49					
	34.7 (16.3)	29.4 (13.9)	5.35	(0.82 to 11.53)	3.76	(-0.30 to 7.83)	0.069
NPI carer distress subscore	n = 78	n = 84					
	11.5 (1.1)	10.2 (8.8)	1.37	(-1.45 to 4.19)	1.48	(-0.78 to 3.73)	0.199
12-week outcomes							
Carer GHQ-12 <sup>b</sup>	n = 44	n = 52					
	13.1 (6.0)	12.2 (5.4)	0.88	(-1.43 to 3.19)	0.36	(-1.58 to 2.31)	0.714
Carer EQ-5D <sup>b</sup>	n = 46	n = 49					
	0.80 (0.16)	0.82 (0.19)	-0.02	(-0.09 to 0.06)	0.02	(-0.04 to 0.07)	0.561
Zarit CBI <sup>b</sup>	n = 42	n = 48					
	35.5 (17.2)	29.0 (15.8)	6.48	(-0.43 to 13.39)	5.01	(0.80 to 9.23)	0.020
NPI carer distress subscore	n = 72	n = 81					
	10.0 (8.6)	10.5 (8.3)	-0.52	(-3.22 to 2.17)	-0.27	(-2.34 to 1.80)	0.798

a Adjusted for pre-specified factors: baseline CMAI, household status and centre.

b Asked of family carers only.

TABLE 7 Adverse events and mortality

	Mirtazapine (n = 102)	Placebo (n = 102)
AE		
Number of events	225	192
Number of individuals	67 (66%)	65 (64%)
SAE		
Number of events	13	35
Number of individuals	8 (8%)	18 (18%)
Deaths	7 (7%)	1 (1%)
MedDRA codes for deaths	<ol style="list-style-type: none"> <li>1. Dementia</li> <li>2. Pneumonia, aspiration</li> <li>3. Emphysema, dementia, pneumonia, aspiration</li> <li>4. Dementia Alzheimer's type</li> <li>5. Cardiac failure</li> <li>6. Pelvic fracture, osteoporosis, vascular dementia</li> <li>7. Chronic kidney disease, dementia, Congestive cardiac failure</li> </ol>	<ol style="list-style-type: none"> <li>1. Dementia</li> </ol>

**Note**

Adverse events and severe adverse events ascertained to 16 or 4 weeks after last dose of IMP, deaths recorded up to 16 weeks after randomisation.

**Long-term outcomes at 26 and 52 weeks****CMAI outcomes at 26 and 52 weeks**

CMAI outcomes at 26 and 52 weeks are presented in [Table 8](#). There were no statistically significant differences between mirtazapine and placebo at either time point. This applied to both the raw and adjusted differences.

**Hospitalisation at 26 and 52 weeks**

Hospitalisation by 26 weeks and between 26 and 52 weeks are presented in [Table 9](#). There were no statistically significant differences between mirtazapine and placebo for either time period.

**Deaths at 26 and 52 weeks**

The cumulative number of deaths at 26 and 52 weeks are presented in [Table 10](#). The marginal differences observed at 12 weeks were not maintained at 26 and 52 weeks and there were no statistically significant differences between mirtazapine and placebo at either time point.

**Economic evaluation**

Data were reasonably complete for most service-use items (see [Table 11](#)) (ranging from 96% to 100% at baseline, 94% to 100% at 6 weeks, 94% to 100% at 12 weeks). Data on carers' care time and service use were similarly complete at baseline (94–99%) but slightly less so at 6 weeks (87–90%) and 12 weeks (91–94%). A filter question in the database classified informants as paid or unpaid carers to determine which carer measures should be completed. A few cases that were reported to be family/friend carers in the demographics question were classified as paid carers on this question, resulting in the loss of unpaid carer resource-use data from placebo participants (three cases at baseline; four at 6 and 12 weeks).

**TABLE 8** CMAI scores at 26 and 52 weeks: mirtazapine vs. placebo

Mirtazapine (n = 102)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference <sup>a</sup>	(95% CI)	p-value
26 weeks						
n = 67	n = 62					
61.9 (SD = 21.0)	56.8 (SD = 19.7)	5.1	(-2.02 to 12.20)	1.36	(-4.32 to 7.05)	0.638
52 weeks						
n = 53	n = 56					
56.8 (SD = 16.2)	58.5 (SD = 20.8)	-1.6	(-8.76 to 5.46)	-3.26	(-9.91 to 3.39)	0.337

a Adjusted for pre-specified factors: baseline CMAI, household status and centre.

**TABLE 9** Hospitalisations by 26 weeks and between 26 and 52 weeks: mirtazapine vs. placebo

	Mirtazapine (n = 102)	Placebo (n = 102)
Hospitalisations by 26 weeks		
Yes	4 (5.6%)	10 (14.3%)
No	68 (94.4%)	60 (85.7%)
No information	30	32
Days in hospital by 26 weeks		
N	4	10
Mean (SD)	8.3 (4.9)	16.8 (30.6)
Median (IQR)	10 (5.5-11)	5.5 (1-14)
N missing	0	0
Hospitalisations between 26 and 52 weeks		
Yes	6 (10.2%)	9 (15.0%)
No	53 (89.8%)	51 (85.0%)
No information	43	42
Days in hospital between 26 and 52 weeks		
N	6	8
Mean (SD)	16.3 (23.0)	20.1 (30.3)
Median (IQR)	2 (1-44)	9 (3-22)
N missing	0	1

IQR, interquartile range.



**TABLE 10** Deaths by 26 and 52 weeks: mirtazapine vs. placebo

	Mirtazapine (n = 102)	Placebo (n = 102)
By 26 weeks		
Died	7 (9.0%)	6 (8.1%)
Alive	71 (91.0%)	68 (91.9%)
No information	24	28
By 52 weeks		
Died	15 (19.7%)	13 (18.6%)
Alive	61 (80.3%)	57 (81.4%)
No information	26	32

[Table 11](#) sets out paid and unpaid care services used by participants at baseline and follow-ups. Less than half of participants had used a mental health service in the 12 weeks prior to baseline. Participant use of community and mental health services between the 6-week and 12-week follow-up was similar to use between baseline and 6-week assessment. Relatively few participants (15% mirtazapine; 14% placebo) had home care in the pre-baseline period, for means of 2.5 and 3.8 hours per week of home care in the mirtazapine and placebo groups. In the sample participating at 12 weeks, proportions using home care were similar (11% mirtazapine; 10% placebo), although mirtazapine participants had used less than an hour a week (0.86) while the placebo participants had used almost 3 hours (2.92) in the prior 6 weeks. At baseline, hours provided by unpaid carers greatly exceeded paid home care hours (71 and 60 hours per week in mirtazapine and placebo, respectively). At 12-week follow-up, mirtazapine participants received approximately 80 hours per week while placebo participants received 56 hours per week of unpaid care.

Carers' own use of health and support services is presented in [Table 12](#). Data were fairly complete from carers classified as unpaid (95–99% at baseline, 90–94% at 6 weeks and 91–94% at 12 weeks). More than half had made use of at least one service over the 12 weeks prior to baseline, and approximately half made use of a service over each follow-up. Carers were asked to estimate the proportion of all services related to their caring role, judging this to be 22% and 23% in mirtazapine and placebo groups, respectively at baseline. Estimated proportions were similar at 6 weeks; however, the sample completing 12-week assessments reported divergent estimates (mirtazapine: mean of 50.8% vs. placebo mean of 19.2%). Carers were also asked at each point whether they felt that their care situation had improved since they had used these services and whether their health had been affected as a result of caring (see [Table 13](#)). While groups did not differ on the status of their care situation at baseline or 6 weeks, at 12 weeks, more mirtazapine than placebo carers in receipt of at least one service agreed their situation had improved [12/24 (50%) vs. 4/24 (16.7%), respectively]. The proportion of carers reporting that their health was affected by their caring role was at least 50% at each time point and proportions were similar between groups. At baseline, carers of people with dementia living at home reported substantial numbers of hours of sleep lost per week as a result of assisting the person or because of the person's agitation (approximately 8 and 7 hours weekly in mirtazapine and placebo, respectively) (see [Table 14](#)). Hours of lost sleep were similar at the 6- and 12-week follow-ups. At baseline, approximately half of the carers in each group reported that the person could be left alone at home. Participants could be left alone for an average of < 3 hours a day. These estimates were similar at 6- and 12-week follow-ups.

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Baseline (prior 12 weeks)		Expected = 103			Expected = 103		
<i>Community health</i>							
GP	Visits	99	65 (66)	1.61 (0.28)	101	71 (70)	1.84 (0.30)
Practice nurse	Visits	98	25 (26)	0.52 (0.20)	101	19 (19)	0.25 (0.06)
Community nurse	Visits	98	23 (23)	0.69 (0.20)	101	19 (19)	0.75 (0.28)
Physiotherapist	Visits	98	6 (6)	0.11 (0.06)	101	...	...
OT	Visits	99	...	...	102	...	...
Geriatrician	Visits	99	...	...	102	...	...
Neurologist	Visits	99	...	...	102	...	...
Specialist nurse	Visits	98	8 (8)	0.12 (0.05)	101	14 (14)	0.25 (0.09)
<i>Mental health</i>							
Mental health nurse	Visits	99	37 (37)	0.75 (0.18)	101	43 (43)	0.74 (0.11)
Psychiatrist	Visits	98	33 (34)	0.39 (0.06)	101	31 (31)	0.38 (0.06)
Psychologist	Visits	99	...	...	102	...	...
Mental health team	Visits	98	11 (11)	0.27 (0.12)	101	6 (6)	0.15 (0.07)
<i>Community care</i>							
Home care	Visits	101	15 (15)	9.73 (3.07)	102	14 (14)	13.28 (4.31)
Home care	Hours	101	15 (15)	30.54 (20.19)	102	14 (14)	46.13 (27.81)
Social worker	Visits	98	16 (16)	0.19 (0.05)	101	17 (17)	0.36 (0.13)

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Cleaner	Visits	101	10 (10)	2.56 (1.68)	102	8 (8)	1.07 (0.41)
Meals on Wheels	Visits	102	...	...	103	...	...
Sitting service	Visits	102	...	...	103	...	...
Carer support worker	Visits	102	...	...	103	...	...
<i>Day services</i>							
Day centre	Attendances	99	15 (15)	3.84 (1.77)	101	10 (10)	1.52 (0.56)
Lunch club	Attendances	99	...	...	102	...	...
<i>Hospital care</i>							
ED	Attendances	99	18 (18)	0.24 (0.06)	101	15 (15)	0.20 (0.05)
Inpatients services	Days	99	12 (12)	1.86 (0.79)	101	9 (9)	0.95 (0.43)
Day hospital services	Days	99	...	...	102	...	...
Outpatients services	Visits	99	21 (21)	0.29 (0.07)	101	19 (19)	0.32 (0.09)
<i>Care home resident</i>							
Residential home	Days	100	14 (14)	16.17 (3.30)	102	12 (12)	13.73 (3.03)
Nursing home	Days	100	32 (32)	30.01 (4.02)	102	32 (31)	29.17 (3.95)
<i>Residential respite</i>							
Residential home	Days	100	...	...	102	...	...
Nursing home	Days	100	...	...	102	...	...
<i>Medications</i>							
Number of medications	Units	102	92 (90)	5.00 (0.34)	102	95 (93)	5.25 (0.33)
<i>Equip. &amp; adaptations</i>							
Equip. (HSC)	Items	102	11 (11)	0.25 (0.08)	103	10 (10)	0.24 (0.08)

continued

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
<i>Unpaid care,<sup>a</sup> out-of-pocket</i>							
Equipment (private)	Items	101	11 (11)	0.15 (0.05)	102	...	...
Unpaid care – carer <sup>b</sup>	Hours	60	60 (100)	857.90 (68.60)	67	67 (100)	716.78 (66.00)
Carer cut down work	Hours	61	...	...	68	...	...
Carer stopped work	Weeks	60	...	...	68	...	...
Unpaid care oth. carers	Hours	60	37 (62)	106.27 (22.33)	67	44 (66)	178.02 (46.29)
Time off work oth. carers	Days	60	...	...	67	8 (12)	1.47 (1.19)
Week 6 (prior 6 weeks)		Expected = 87			Expected = 95		
<i>Community health</i>							
GP	Visits	83	36 (43)	0.81 (0.14)	90	31 (34)	0.89 (0.20)
Practice nurse	Visits	84	11 (13)	0.29 (0.15)	90	7 (8)	0.10 (0.05)
Community nurse	Visits	84	13 (15)	0.18 (0.05)	90	13 (14)	0.69 (0.25)
Physiotherapist	Visits	84	...	...	90	...	...
OT	Visits	84	...	...	90	...	...
Geriatrician	Visits	84	...	...	90	...	...
Neurologist	Visits	84	...	...	90	...	...
Specialist nurse	Visits	84	6 (7)	0.08 (0.03)	90	6 (7)	0.14 (0.06)
<i>Mental health</i>							
Mental health nurse	Visits	84	8 (10)	0.20 (0.08)	90	16 (18)	0.26 (0.07)
Psychiatrist	Visits	84	9 (11)	0.12 (0.04)	90	9 (10)	0.14 (0.06)
Psychologist	Visits	84	...	...	90	...	...
Mental health team	Visits	84	...	...	90	7 (8)	0.10 (0.04)

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
<i>Community care</i>							
Home care	Visits	86	12 (14)	3.48 (1.34)	95	12 (13)	7.21 (3.06)
Home care	Hours	86	12 (14)	5.58 (1.95)	95	12 (13)	14.23 (10.65)
Social worker	Visits	84	...	...	90	12 (13)	0.17 (0.05)
Cleaner	Visits	86	8 (9)	0.77 (0.39)	95	7 (7)	0.60 (0.24)
Meals on Wheels	Visits	86	...	...	95	...	...
Sitting service	Visits	86	...	...	95	7 (7)	0.51 (0.24)
Carer support worker	Visits	86	...	...	95	...	...
<i>Day services</i>							
Day centre	Attendances	84	10 (12)	1.39 (0.59)	91	8 (9)	0.63 (0.25)
Lunch club	Attendances	84	...	...	91	...	...
<i>Hospital care</i>							
ED	Attendances	84	...	...	89	9 (10)	0.12 (0.04)
Inpatients services	Days	84	...	...	90	...	...
Day hospital services	Days	84	...	...	89	...	...
Outpatients services	Visits	84	8 (10)	0.12 (0.05)	89	7 (8)	0.09 (0.03)
<i>Care home resident</i>							
Residential home	Days	85	16 (19)	10.05 (1.92)	91	14 (15)	8.48 (1.75)
Nursing home	Days	85	23 (27)	14.00 (2.16)	91	29 (32)	15.82 (2.15)
<i>Residential respite</i>							
Residential home	Days	84	...	...	91	...	...
Nursing home	Days	84	...	...	91	...	...

continued

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
<i>Medications</i>							
Number of medications	Units	87	80 (92)	5.54 (0.40)	95	91 (96)	5.96 (0.35)
<i>Equip. &amp; adaptations</i>							
Equip. (HSC)	Items	86	7 (8)	0.15 (0.06)	95	...	...
<i>Unpaid care<sup>a</sup>; out-of-pocket</i>							
Equipment (private)	Items	86	8 (9)	0.13 (0.05)	95	8 (8)	0.18 (0.07)
Unpaid care - carer <sup>b</sup>	Hours	49	49 (100)	471.49 (35.34)	55	54 (98)	353.62 (35.07)
Carer cut down work	Hours	51	...	...	59	...	...
Carer stopped work	Weeks	51	...	...	59	...	...
Unpaid care oth. carers	Hours	50	33 (66)	65.37 (16.14)	56	33 (59)	61.17 (14.94)
Time off work oth. carers	Days	50	...	...	56	...	...
Week 12 (prior 6 weeks)		Expected = 81			Expected = 90		
<i>Community health</i>							
GP	Visits	78	35 (45)	0.73 (0.13)	86	38 (44)	0.94 (0.20)
Practice nurse	Visits	78	9 (12)	0.14 (0.05)	86	9 (10)	0.12 (0.04)
Community nurse	Visits	78	10 (13)	0.27 (0.12)	86	14 (16)	0.51 (0.18)
Physiotherapist	Visits	78	...	...	86	...	...
OT	Visits	78	...	...	86	...	...
Geriatrician	Visits	78	...	...	86	...	...
Neurologist	Visits	78	...	...	86	...	...
Specialist nurse	Visits	78	...	...	86	...	...
<i>Mental health</i>							
Mental health nurse	Visits	78	9 (12)	0.15 (0.05)	86	10 (12)	0.16 (0.05)
Psychiatrist	Visits	78	...	...	86	6 (7)	0.06 (0.03)

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/Item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Psychologist	Visits	78	...	...	86	...	...
Mental health team	Visits	78	...	...	86	...	...
<i>Community care</i>							
Home care	Visits	81	9 (11)	3.27 (1.41)	89	9 (10)	6.10 (2.35)
Home care	Hours	81	9 (11)	5.18 (2.15)	89	9 (10)	17.53 (11.69)
Social worker	Visits	78	...	...	86	...	...
Cleaner	Visits	81	6 (7)	0.30 (0.13)	89	6 (7)	0.34 (0.15)
Meals on Wheels	Visits	81	...	...	89	...	...
Sitting service	Visits	81	...	...	89	6 (7)	0.46 (0.21)
Carer support worker	Visits	81	...	...	89	...	...
<i>Day services</i>							
Day centre	Attendances	78	8 (10)	1.53 (0.65)	86	...	...
Lunch club	Attendances	78	...	...	86	...	...
<i>Hospital care</i>							
ED	Attendances	78	...	...	86	6 (7)	0.07 (0.03)
Inpatients services	Days	78	...	...	87	...	...
Day hospital services	Days	78	...	...	86	...	...
Outpatients services	Visits	78	8 (10)	0.12 (0.04)	86	7 (8)	0.13 (0.05)
<i>Care home resident</i>							
Residential home	Days	78	15 (19)	11.05 (2.11)	87	13 (15)	9.14 (1.86)

continued

TABLE 11 Participants' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Nursing home	Days	78	23 (29)	14.65 (2.25)	87	28 (32)	15.64 (2.18)
<i>Residential respite</i>							
Residential home	Days	77	...	...	85	...	...
Nursing home	Days	77	...	...	85	...	...
<i>Medications</i>							
Number of medications	Units	81	76 (94)	5.99 (0.44)	90	83 (92)	5.98 (0.40)
<i>Equip. &amp; adaptations</i>							
Equip. (HSC)	Items	80	8 (10)	0.19 (0.07)	90	...	...
<i>Unpaid care:<sup>a</sup> out-of-pocket</i>							
Equipment (private)	Items	80	...	...	90	8 (9)	0.17 (0.07)
Unpaid care - carer <sup>b</sup>	Hours	46	46 (100)	481.37 (35.50)	52	52 (100)	336.46 (36.89)
Carer cut down work	Hours	46	...	...	52	...	...
Carer stopped work	Weeks	45	...	...	52	...	...
Unpaid care oth. carers	Hours	46	30 (65)	46.13 (11.93)	52	30 (58)	71.66 (18.35)
Time off work oth. carers	Days	46	...	...	52	...	...

HSC, health and social care providers; OT, occupational therapist; oth. carers, other relatives and friends who provide care.

a Asked of unpaid carers only.

b Care time reported by the participating unpaid carer.

**Note**

Where there were five or fewer users of the service, numbers have been suppressed, denoted by three dots ( ...).



TABLE 12 Unpaid carers' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks

Service/Item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Baseline (prior 12 weeks)		Expected = 63			Expected = 68		
<i>Community health</i>							
GP	Visits	60	21 (35)	0.83 (0.23)	67	24 (36)	0.58 (0.12)
Practice nurse	Visits	60	15 (25)	0.27 (0.07)	67	18 (27)	0.45 (0.14)
Community nurse	Visits	60	...	...	67	...	...
<i>Mental health</i>							
Admiral Nurse	Visits	60	...	...	67	...	...
Psychiatrist	Visits	60	...	...	67	...	...
Psychologist	Visits	60	...	...	67	...	...
Mental health team	Visits	60	...	...	67	...	...
Counsellor	Visits	60	...	...	67	...	...
<i>Hospital care</i>							
Outpatients services	Visits	60	16 (27)	0.63 (0.24)	67	15 (22)	0.31 (0.08)
<i>Support services</i>							
Online support	Visits	60	6 (10)	0.18 (0.09)	67	...	...
Support groups	Visits	60	...	...	67	...	...
Education groups	Visits	60	...	...	67	...	...
Expert relative groups	Visits	60	6 (10)	0.20 (0.11)	67	...	...
Alternative therapies	Visits	60	6 (10)	0.18 (0.09)	67	...	...
Proportion of use related to caring role – care <sup>a</sup>	Percentage	60	41 (68)	22.20 (4.68)	67	37 (55)	23.27 (4.58)
<i>Medications</i>							
Prescription medications	Any used	60	42 (70)		67	46 (69)	
OTC medications	Any used	60	25 (42)		67	28 (42)	

continued

TABLE 12 Unpaid carers' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Week 6 (prior 6 weeks)		Expected = 53			Expected = 60		
<i>Community health</i>							
GP	Visits	50	11 (22)	0.30 (0.09)	55	12 (22)	0.29 (0.08)
Practice nurse	Visits	50	...	...	55	7 (13)	0.13 (0.05)
Community nurse	Visits	50	...	...	55	...	...
<i>Mental health</i>							
Admiral Nurse	Visits	50	...	...	55	...	...
Psychiatrist	Visits	50	...	...	55	...	...
Psychologist	Visits	50	...	...	55	...	...
Mental health team	Visits	50	...	...	55	...	...
Counsellor	Visits	50	...	...	55	...	...
<i>Hospital care</i>							
Outpatients services	Visits	50	8 (16)	0.36 (0.18)	55	11 (20)	0.27 (0.08)
<i>Support services</i>							
Online support	Visits	50	...	...	55	...	...
Support groups	Visits	50	...	...	55	...	...
Education groups	Visits	50	...	...	55	...	...
Expert relative groups	Visits	50	...	...	55	...	...
Alternative therapies	Visits	50	...	...	55	...	...
Proportion of use related to caring role - carer <sup>a</sup>	Percentage	50	24 (48)	36.04 (6.09)	55	25 (45)	33.38 (5.87)
<i>Medications</i>							
Prescription medications	Use - y/n	50	32 (64)		54	35 (65)	
OTC medications	Use - y/n	50	18 (36)		54	19 (35)	

TABLE 12 Unpaid carers' use of health, social and unpaid care, mirtazapine and placebo, for observations with economic data available at baseline, 6 and 12 weeks (continued)

Service/item	Units	Valid N	Mirtazapine No. users (%)	Mirtazapine Mean (SE)	Valid N	Placebo No. users (%)	Placebo Mean (SE)
Week 12 (prior 6 weeks)		Expected = 49			Expected = 56		
<i>Community health</i>							
GP	Visits	46	12 (26)	0.43 (0.12)	52	10 (19)	0.29 (0.09)
Practice nurse	Visits	46	7 (15)	0.41 (0.26)	52	6 (12)	0.12 (0.04)
Community nurse	Visits	46	...	...	52	...	...
<i>Mental health</i>							
Admiral Nurse	Visits	46	...	...	52	...	...
Psychiatrist	Visits	46	...	...	52	...	...
Psychologist	Visits	46	...	...	52	...	...
Mental health team	Visits	46	...	...	52	...	...
Counsellor	Visits	46	...	...	52	...	...
<i>Hospital care</i>							
Outpatients services	Visits	46	8 (17)	0.67 (0.46)	52	8 (15)	0.17 (0.06)
<i>Support services</i>							
Online support	Visits	46	...	...	52	...	...
Support groups	Visits	46	...	...	52	...	...
Education groups	Visits	46	...	...	52	...	...
Expert relative groups	Visits	46	...	...	52	...	...
Alternative therapies	Visits	46	...	...	52	...	...
Proportion of service use related to caring – carer <sup>a</sup>	Percentage	46	26 (57)	50.80 (6.52)	52	25 (48)	19.20 (5.23)
<i>Medications</i>							
Prescription medications	Use – y/n	46	33 (72)		51	34 (67)	
OTC medications	Use – y/n	46	20 (43)		52	23 (44)	
OTC = over the counter.							
<sup>a</sup> Number of users in this case is the number of carers that reported using at least one service.							
<b>Note</b>							
Sample of carers who were classified as unpaid. Where there were five or fewer users of the service, numbers have been suppressed, denoted by three dots ( ... ).							

**TABLE 13** Unpaid carers of participants: service impacts on care situation and health impacts of caring

	Care situation improved by services <sup>a</sup>			Health affected as a result of caring <sup>b</sup>		
	Mirtazapine	Placebo	<i>p</i> (Fisher's)	Mirtazapine	Placebo	<i>p</i>
	Users/N (%)	Users/N (%)		Users/N (%)	Users/N (%)	
Baseline	10/37 (27.03)	8/37 (21.62)	<i>p</i> = 0.787	32/60 (53.33)	39/67 (58.21)	$\chi^2 = 0.305, p = 0.581$
6 weeks	4/22 (18.18)	9/24 (37.5)	<i>p</i> = 0.197	29/50 (58)	33/54 (61.11)	$\chi^2 = 0.104, p = 0.747$
12 weeks	12/24 (50)	4/24 (16.67)	<i>p</i> = 0.030	23/46 (50)	27/51 (52.94)	$\chi^2 = 0.084, p = 0.772$

a Asked of carers using at least one health and support service: Do you feel that your care situation has improved since you began using these services?  
b Asked of all unpaid carers: Do you feel that your health has been affected as a result of caring for (participant)?

### Costs

At baseline, of cases with economic data available, there were no differences between groups in any subcategory of cost, in total health and social care or in societal costs of participants with dementia (see [Table 15](#)). [Appendix 4](#) presents the unit costs used. Apart from the costs of trial medication, there were no between-group cost differences in the sample participating at 6 weeks. Of those participating in the 12-week follow-up, the costs of unpaid care by the dyadic carer over the prior 6 weeks were significantly higher in the mirtazapine than placebo group [difference: £1120 (95% CI £56 to £2184)]. There were no between-group differences in carers' health and social care costs (see [Table 16](#)).

### Outcome measures

Raw CMAI scores in both groups summarised from available cases' data were similar at baseline and both follow-ups (see [Table 17](#)). Mean CMAI scores in the sample participating at 6 and 12 weeks (regardless of allocation) were approximately 10 points lower than those in the baseline sample. Raw index scores (utilities) derived from informant-reported quality-of-life measures were similar between groups. EQ-5D-5L-derived utilities were much lower than those derived from the DEMQOL-Proxy-U. Utilities derived from the participant-reported DEMQOL-U (completed by less than half of the people with dementia participating at each time point) were somewhat higher than scores of the proxy-completed version in both groups. At each assessment point, carers' EQ-5D-5L scores were similar between groups (see [Table 18](#)).

## Cost-effectiveness analyses

### Primary analysis

Mean raw outcome scores and costs of the complete cases samples showed no differences between groups (see [Table 19](#)). Adjusting for baseline measure and living arrangement, the estimate for the difference between groups in both CMAI and costs had wide CIs crossing zero. The point estimate for the ICER on CMAI was negative because costs were slightly lower and outcome slightly better in the mirtazapine group compared to the placebo group. The NMB line (see [Figure 3](#)) shows that net benefit is positive at all willingness-to-pay thresholds from £0 to £30,000: there is monetary benefit once the cost of the intervention has been deducted. However, the CIs of the line do not cross zero, illustrating that 95% confidence limits of the ICER could not be defined and therefore neither mirtazapine nor placebo can be judged to be the more cost-effective strategy with a high level of confidence. The CEAC (see [Figure 4](#)) illustrates that probability of cost-effectiveness was 81% at a willingness to pay of £3000 and 80% at £20,000; also that a 10% CI for the ICER can be defined between willingness to pay of approximately £0 and £3000 per QALY, giving a low degree of certainty that mirtazapine is cost-effective (see Glick *et al.*<sup>63</sup> 2014; Gray *et al.*<sup>59</sup>).

TABLE 14 Unpaid carers of participants in domestic accommodation: hours able to leave the participant alone and hours of lost sleep

Service/item	Units	Valid N	Mirtazapine Yes (%)	Mirtazapine Mean (SE)	Valid N	Placebo Yes (%)	Placebo Mean (SE)
Baseline		Expected = 52			Expected = 57		
Left alone at home <sup>a</sup>	Hours/day	51	28 (55)	2.50 (0.59)	57	32 (56)	2.76 (0.66)
Sleep disrupted	Hours lost/week	51	28 (55)	7.71 (1.38)	57	33 (58)	6.89 (1.24)
Week 6		Expected = 46			Expected = 47		
Left alone at home <sup>a</sup>	Hours/day	45	22 (49)	1.62 (0.36)	46	27 (59)	3.02 (0.79)
Sleep disrupted	Hours lost/week	45	25 (56)	6.30 (1.27)	44	21 (48)	5.91 (1.35)
Week 12		Expected = 40			Expected = 45		
Left alone at home <sup>a</sup>	Hours/day	40	17 (43)	1.53 (0.46)	45	26 (58)	2.89 (0.81)
Sleep disrupted	Hours lost/week	40	22 (55)	6.31 (1.41)	45	17 (38)	5.24 (1.25)

<sup>a</sup> Assuming that anyone who could not be left alone needed to have someone at home 24 hours a day.

**TABLE 15** Mean costs (standard errors): health and social care services for participant; societal costs (unpaid care, out-of-pocket costs), total health and social care and societal costs, at baseline, weeks 6 and 12 assessments (£, 2016–17)

Cost categories	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	95% CI
Baseline (prior 12 weeks)	Expected = 102			Expected = 102					
<i>Health and social care costs</i>									
Hospital	97	649	253	101	446	162	203		-384 to 790
Primary and community health care	96	171	29	101	197	37	-27		-120 to 67
Community social care	98	553	172	100	511	184	43		-455 to 540
Community mental health	97	68	13	101	62	7	6		-22 to 34
Day care services	98	170	66	100	82	30	88		-54 to 230
Equipment – NHS and social services	101	2	1	102	3	1	-1		-4 to 2
Respite in residential/nursing home	100	0	0	101	103	62	-103		-225 to 20
Residential/nursing home residence	100	3850	444	102	3988	482	-138		-1431 to 1155
Trial medication	102	0	0	102	0	0	0		0 to 0
Concomitant medications	102	95	12	102	109	18	-15		-58 to 28
<i>Total health and social care<sup>a</sup></i>	93	5504	501	99	5475	530	29		-1412 to 1471
<i>Unpaid care and out-of-pocket costs</i>									
Opportunity cost to participating carer	Expected = 63			Expected = 68					
Opportunity cost to other carers	59	6653	673	67	5512	536	1140		-546 to 2827
Equipment – self or family	57	1808	376	67	3000	758	-1192		-2959 to 575
<i>Total societal<sup>b</sup></i>	62	3	2	68	2	1	1		-3 to 6
	52	11,488	894	65	11,924	1126	-436		-3390 to 2519

**TABLE 15** Mean costs (standard errors): health and social care services for participant, societal costs (unpaid care, out-of-pocket costs), total health and social care and societal costs, at baseline, weeks 6 and 12 assessments (£, 2016–17) (continued)

Cost categories	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	95% CI
Week 6 (prior 6 weeks)	Expected = 87			Expected = 95					
<i>Health and social care costs</i>									
Hospital	84	21	6	89	228	157	-207		-527 to 112
Primary and community health care	83	78	13	90	109	22	-31		-81 to 19
Community social care	84	211	64	89	296	97	-85		-318 to 147
Community mental health	84	19	5	90	23	5	-4		-19 to 10
Day care services	84	103	60	90	38	14	66		-52 to 183
Equipment – NHS and social services	86	0	0	95	0	0	0		-1 to 1
Respite in residential/nursing home	85	44	32	91	45	37	0		-97 to 97
Residential/nursing home residence	85	1968	237	91	2197	262	-229		-929 to 472
Trial medication	87	11	0	95	0	0	11**		11 to 11
Concomitant medications	87	63	8	95	61	9	1		-23 to 26
<b>Total health and social care<sup>a</sup></b>	83	2522	229	89	3043	299	-521		-1273 to 231
<i>Unpaid care and out-of-pocket costs</i>									
Opportunity cost to participating carer	49	3719	404	54	2897	324	822		-197 to 1840
Opportunity cost to other carers	49	1150	273	56	1111	256	39		-703 to 781
Equipment – self or family	52	2	1	60	4	2	-1		-5 to 3
<b>Total societal<sup>b</sup></b>	48	6167	496	54	5797	501	371		-1035 to 1776
Week 12 (prior 6 weeks)	Expected = 81			Expected = 90					
<i>Health and social care costs</i>									

continued

**TABLE 15** Mean costs (standard errors): health and social care services for participant, societal costs (unpaid care, out-of-pocket costs), total health and social care and societal costs, at baseline, weeks 6 and 12 assessments (£, 2016–17) (continued)

Cost categories	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	95% CI
Hospital	78	321	219	86	305	225	16		-606 to 638
Primary and community health care	78	77	14	86	96	19	-18		-66 to 29
Community social care	78	203	76	85	280	115	-77		-354 to 200
Community mental health	78	14	4	85	13	3	1		-9 to 11
Day care services	78	104	63	86	33	15	71		-51 to 194
Equipment – NHS and social services	80	2	1	90	0	0	2*		0 to 4
Respite in residential/nursing home	78	104	60	86	21	15	83		-35 to 201
Residential/nursing home residence	78	2131	257	87	2250	271	-119		-860 to 622
Trial medication	81	17	0	90	0	0	17***		16 to 17
Concomitant medications	81	62	8	90	64	10	-2		-27 to 24
Total health and social care <sup>a</sup>	77	3072	310	85	2895	281	177		-647 to 1002
Unpaid care and out-of-pocket costs	Expected = 49			Expected = 56					
Opportunity cost to participating carer	45	3772	416	51	2652	344	1120*		56 to 2184
Opportunity cost to other carers	45	816	202	52	1303	312	-487		-1250 to 276
Equipment – self or family	48	2	1	56	3	1	-1		-5 to 3
Total societal <sup>b</sup>	43	6642	640	50	5456	470	1186		-364 to 2736

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

<sup>a</sup> Total in cases with data available for each category of health and social care cost.

<sup>b</sup> Total in cases with data available for each category of health and social care, unpaid care and out-of-pocket cost.



**TABLE 16** Mean costs (standard errors): health and support services for carers, unpaid carer costs, out-of-pocket costs, total health and support and societal costs and dyad's total health and social care costs, at baseline, weeks 6 and 12 assessments (£, 2016–17)

Cost categories	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	95% CI
Baseline (prior 12 weeks)	Expected = 63			Expected = 68					
<i>Carer costs</i>									
Primary care	60	31	8	67	27	6	5		-15 to 24
Community mental health	60	72	25	67	51	12	21		-33 to 75
Hospital Outpatient Department	60	67	25	67	33	8	34		-16 to 84
Support services	60	10	5	67	1	1	9		-0 to 17
Health and support attributable to role <sup>a</sup>	60	25	9	67	20	9	5		-19 to 30
Opportunity cost to participating carer over period	59	6653	673	67	5512	536	1140		-546 to 2827
Opportunity cost to other carers over period	57	1808	376	67	3000	758	-1192		-2959 to 575
Costs of equipment – self or family	62	3	2	68	2	1	1		-3 to 6
Societal costs <sup>b</sup>	56	8639	833	67	8532	923	107		-2397 to 2610
<i>Dyad costs</i>									
Dyadic total health and social care	56	2763	485	65	3298	608	-536		-2109 to 1038
Week 6 (prior 6 weeks)	Expected = 53			Expected = 60					
<i>Carer costs</i>									
Primary care	50	12	3	55	32	13	-20		-49 to 9
Community mental health	50	45	19	55	38	11	7		-35 to 49
Hospital Outpatient Department	50	38	19	55	29	9	9		-30 to 49
Support services	50	2	1	55	16	14	-14		-42 to 14

continued

**TABLE 16** Mean costs (standard errors): health and support services for carers, unpaid carer costs, out-of-pocket costs, total health and support and societal costs and dyad's total health and social care costs, at baseline, weeks 6 and 12 assessments (£, 2016-17) (continued)

Cost categories	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	95% CI	
Health and support attributable to role <sup>a</sup>	50	21	8	54	30	14	-9	-42 to 24	
Opportunity cost to participating carer over period	49	3719	404	54	2897	324	822	-197 to 1840	
Opportunity cost to other carers over period	49	1150	273	56	1111	256	39	-703 to 781	
Costs of equipment - self or family	52	2	1	60	4	2	-1	-5 to 3	
Societal costs <sup>b</sup>	48	4969	545	53	4129	445	841	-544 to 2226	
<b>Dyad costs</b>									
Dyadic total health and social care	50	1208	222	54	1834	375	-626	-1508 to 256	
Week 12 (prior 6 weeks)	Expected = 49			Expected = 56					
<b>Carer costs</b>									
Primary care	46	20	5	52	38	28	-18	-78 to 42	
Community mental health	46	79	49	52	26	9	53	-39 to 146	
Hospital Outpatient Department	46	71	49	52	18	6	53	-39 to 144	
Support services	46	2	1	52	1	1	0	-2 to 3	
Health and support attributable to role <sup>a</sup>	45	86	52	52	7	4	79	-17 to 175	
Opportunity cost to participating carer over period	45	3772	416	51	2652	344	1120*	56 to 2184	
Opportunity cost to other carers over period	45	816	202	52	1303	312	-487	-1250 to 276	
Costs of equipment - self or family	48	2	1	56	3	1	-1	-5 to 3	
Societal costs <sup>b</sup>	44	4668	503	51	3949	445	719	-609 to 2047	
<b>Dyad costs</b>									
Dyadic total health and social care	44	2031	454	51	1592	326	439	-650 to 1529	

\* p < 0.05.

<sup>a</sup> Total in cases with data available for each category of health and social care cost, multiplied by the proportion of use attributable to carer reported by the carer.

<sup>b</sup> Total in cases with data available for each category of health and social care, unpaid care and out-of-pocket cost.

TABLE 17 Participant outcome measures at baseline, weeks 6 and 12 assessments

	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	95% CI
Baseline	Expected = 102			Expected = 102					
CMAI	102	71.108	1.622	102	69.794	1.695	1.314	1.695	-3.312 to 5.939
EQ-5D-5L-PROXY	100	0.458	0.034	101	0.498	0.032	-0.039	0.032	-0.132 to 0.053
DEMQOL-U	44	0.85	0.017	38	0.874	0.018	-0.024	0.018	-0.074 to 0.025
DEMQOL-PROXY-U	101	0.684	0.014	101	0.68	0.013	0.003	0.013	-0.034 to 0.041
Week 6	Expected = 87			Expected = 95					
CMAI	84	61.357	2.567	88	59.966	2.116	1.391	2.116	-5.151 to 7.933
EQ-5D-5L-PROXY	82	0.482	0.037	88	0.553	0.032	-0.071	0.032	-0.168 to 0.025
DEMQOL-U	34	0.883	0.014	33	0.893	0.014	-0.011	0.014	-0.050 to 0.029
DEMQOL-PROXY-U	82	0.709	0.015	87	0.7	0.015	0.009	0.015	-0.032 to 0.050
Week 12	Expected = 81			Expected = 90					
CMAI	79	61.392	2.539	87	60.805	2.341	0.588	2.341	-6.221 to 7.397
EQ-5D-5L-PROXY	78	0.467	0.04	85	0.494	0.037	-0.027	0.037	-0.133 to 0.080
DEMQOL-U	26	0.89	0.014	24	0.882	0.022	0.009	0.022	-0.043 to 0.061
DEMQOL-PROXY-U	73	0.724	0.016	84	0.711	0.015	0.012	0.015	-0.031 to 0.055

**TABLE 18** Carers' outcome measures at baseline, weeks 6 and 12 assessments

	Mirtazapine			Placebo			Mirtazapine-placebo difference	
	N	Mean	SE	N	Mean	SE	Mean	95% CI
Baseline	Expected = 63			Expected = 68				
EQ-5D-5L	61	0.789	0.027	66	0.814	0.028	-0.025	-0.101 to 0.052
Week 6	Expected = 53			Expected = 60				
EQ-5D-5L	50	0.826	0.023	54	0.826	0.021	0	-0.061 to 0.062
Week 12	Expected = 49			Expected = 56				
EQ-5D-5L	46	0.806	0.024	50	0.825	0.027	-0.019	-0.092 to 0.054

**TABLE 19** Primary outcome/costs: CMAI score and health and social care costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratio

Outcomes and costs	Mirtazapine	Placebo	Mirtazapine-placebo difference			ICER
	Mean (SE)	Mean (SE)	Mean (95% CI)	Adjusted (95% CI)	p	Cost per 6-point difference <sup>a</sup>
<i>Health and social care</i>						
Observations	N = 72	N = 79				
CMAI score	61.847 (2.659)	60.848 (2.49)	0.999 (-6.193 to 8.191)	-2.446 (-8.243 to 3.352)	0.408	-273/0.408 = -670
Total costs	5752 (513)	5877 (591)	-125 (-1686 to 1435)	-273 (-1754 to 1208)	0.718	

a Reversed so that a higher score indicates a better outcome.

### Secondary analyses

Raw mean outcomes and costs from the health and social care and societal perspectives are presented alongside their raw and adjusted between-group differences, ICER and NMB at £20,000 in [Table 20](#).

## Participant outcomes

### Health and social care perspective

On raw participant QALY derived from EQ-5D-5L, DEMQOL-U and DEMQOL-U-Proxy and costs from a health and social care perspective, there were no differences between groups. Similarly, on adjusted mean differences between groups from the multilevel analyses, there were no differences between groups. Cost-effectiveness results on the DEMQOL-U are not discussed further because of the small numbers involved.

The ICER of EQ-5D-5L-derived QALYs and costs from the health and social care perspective was positive as the sign of the cost difference was negative and there was a small QALY loss. Results are not discussed further given the latter result.

The ICER from the DEMQOL-U-Proxy was negative as there was a small QALY gain and the sign of the cost difference was negative. The probability of cost-effectiveness ranged from 70% to 72% across a WTP range of £0–50,000. NMB at the lower NICE threshold (£20,000) was positive,

but the 95% CIs crossed zero. The ICER was unbounded, indicating that neither mirtazapine nor placebo could be considered a cost-effective strategy at any level of willingness to pay to gain a QALY.

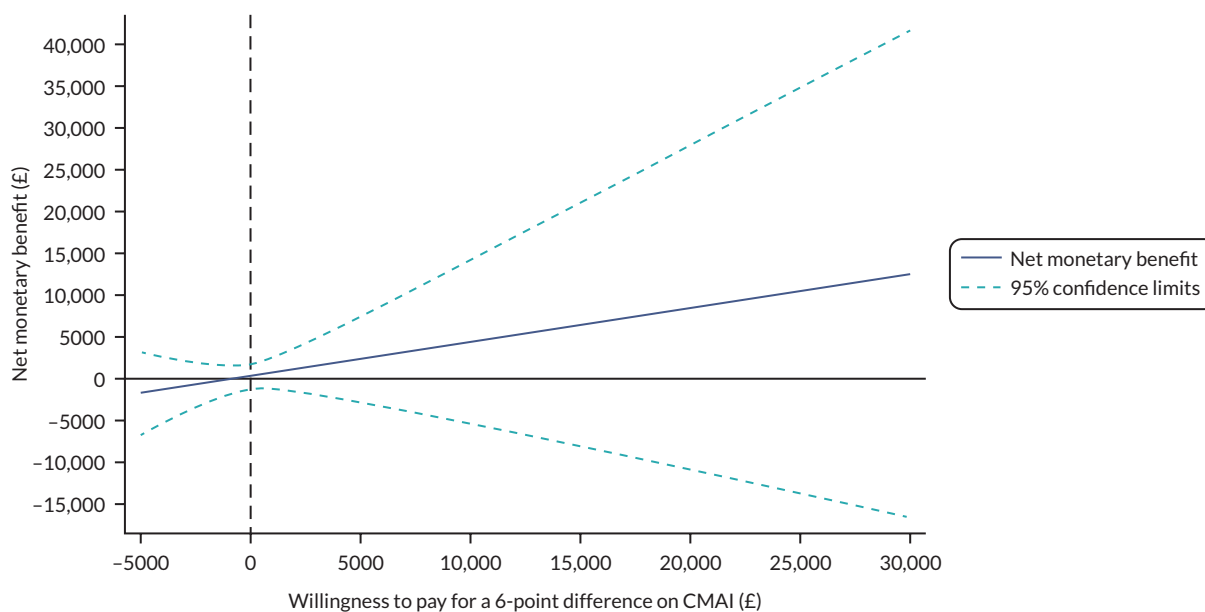


FIGURE 3 Primary outcome: NMB plot.

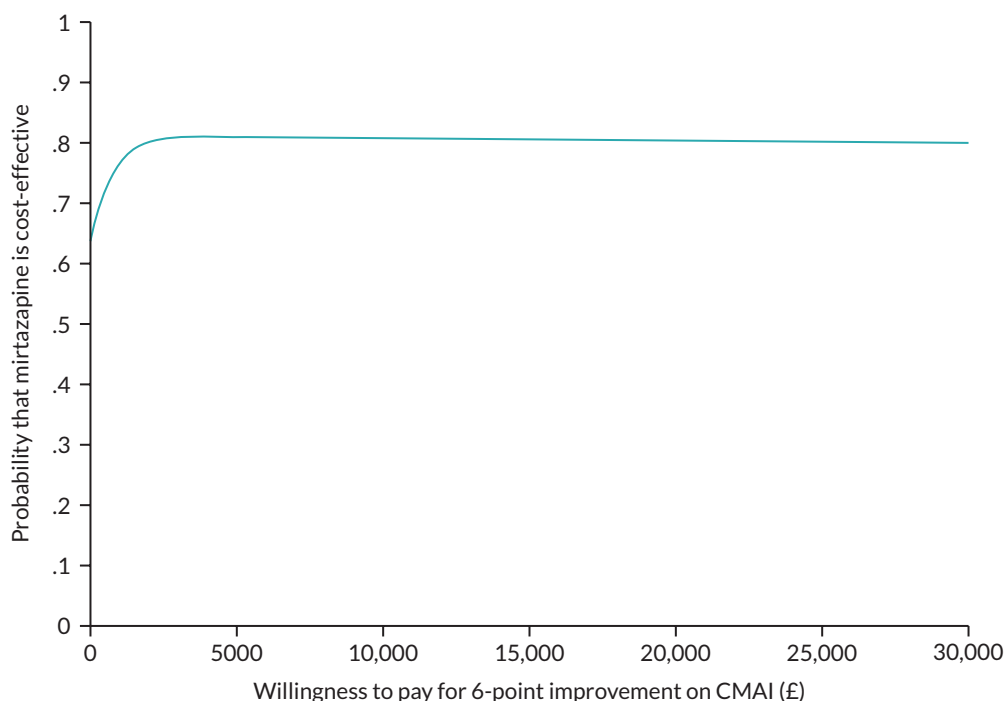


FIGURE 4 Primary outcome: cost-effectiveness acceptability curve.

TABLE 20 Secondary participant outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios

Outcomes and costs	Mirtazapine		Placebo		Mirtazapine-placebo difference		ICER	NMB at £20,000
	Mean (SE)	N	Mean (SE)	N	Mean (95% CI)	Adjusted (95% CI)		
<b>QALY</b>								
<i>Health and social care</i>								
Observations	N = 70	N = 77						
QALY-EQ-5D-5L	0.107 (0.008)	0.128 (0.007)	-0.021 (-0.043 to 0.001)		-0.007 (-0.021 to 0.007)	0.314	60,976	289 (-1347 to 1925)
Total costs	5689 (526)	5844 (596)	-155 (-1740 to 1429)		-430 (-1920 to 1061)	0.572		
Observations	N = 67	N = 76						
QALY-DEMQOL-Proxy-U	0.162 (0.003)	0.163 (0.003)	-0.002 (-0.010 to 0.007)		0.002 (-0.004 to 0.008)	0.540	-227,589	449 (-1102 to 1999)
Total costs	5604 (535)	5816 (604)	-211 (-1824 to 1402)		-412 (-1942 to 1117)	0.597		
Observations	N = 18	N = 20						
QALY-DEMQOL-U	0.203 (0.004)	0.205 (0.004)	-0.002 (-0.014 to 0.009)		0.001 (-0.006 to 0.007)	0.832	692,101	-406 (-2521 to 1710)
Total costs	2858 (800)	2512 (735)	346 (-1853 to 2545)		458 (-1677 to 2592)	0.674		
<i>Societal</i>								
Observations	N = 37	N = 43						
QALY-EQ-5D-5L	0.124 (0.009)	0.145 (0.007)	-0.021 (-0.044 to 0.003)		-0.003 (-0.017 to 0.011)	0.708	-848,348	-2320 (-5382 to 742)
Total costs	13,235 (1219)	10,940 (1026)	2295 (-853 to 5444)		2266 (-855 to 5388)	0.153		
Observations	N = 36	N = 43						
QALY-DEMQOL-Proxy-U	0.157 (0.005)	0.158 (0.003)	-0.001 (-0.012 to 0.01)		0.004 (-0.005 to 0.012)	0.395	638,829	-2239 (-5405 to 928)

TABLE 20 Secondary participant outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios (continued)

Outcomes and costs	Mirtazapine		Placebo		Mirtazapine-placebo difference		ICER	NMB at £20,000
	Mean (SE)	N	Mean (SE)	N	Mean (95% CI)	Adjusted (95% CI)		
Total costs	13,252 (1254)	N = 14	10,940 (1026)	N = 18	2313 (-880 to 5506)	2311 (-869 to 5491)	0.153	
Observations								
QALY-DEMQOL-U	0.204 (0.004)		0.206 (0.005)		-0.002 (-0.015 to 0.011)	-0.001 (-0.015 to 0.014)	0.923	-775,304
Total costs	10,325 (1705)		9790 (1963)		536 (-4955 to 6026)	536 (-4226 to 5299)	0.822	-550 (-5372 to 4272)
<i>CMAI and societal</i>								
Observations								
CMAI score	61,895 (2,829)	N = 38	59,778 (3,139)	N = 45	2,117 (-6,425 to 10,659)	-3,028 (-9,702 to 3,646)	0.374	1944/0.505 = 3851
Total costs	13,169 (1189)		11,204 (1001)		1965 (-1104 to 5034)	1944 (-1076 to 4964)	0.207	

a Reversed so that a higher score indicates a better outcome.  
C, mean adjusted cost difference, E, mean adjusted outcome difference

### Societal perspective

Groups did not differ on costs or CMAI outcomes from the societal perspective. The societal cost per 6-point difference was £3851, the ICER being unbounded. The net benefit at a willingness to pay of £0 was -£1944 (95% CI -£4964 to £1076) and at a WTP of £20,000 was £8150 (95% CI -£14,195 to £30,494). Probability of cost-effectiveness ranged between 10% and 77% over this range.

There were no between-group differences in QALYs derived from EQ-5D-5L, DEMQOL-U or DEMQOL-U-Proxy and costs from the societal perspective, before or after adjustment. Given the low numbers on the DEMQOL-U, cost-effectiveness results have not been discussed.

The ICER of EQ-5D-5L-derived QALYs and costs from the societal perspective was negative as the sign of the cost difference was positive and there was a small QALY loss. Results are not discussed further for this reason. The ICER from the DEMQOL-U-Proxy was positive and very large; probability of cost-effectiveness ranged from 8% to 10% across WTP values from £0 to £50,000.

### Carer outcomes

In cases with complete health and support and QALY data, unadjusted and adjusted between-group differences in QALYs were not significant (see [Table 21](#)). The NMB of mirtazapine at £20,000 was negative but the CI crossed zero. The ICER on this measure was unbounded. Results for carers' societal costs and QALY were similar. Probability of cost-effectiveness from the health and social care perspective did not exceed 45% over WTP-per-QALY thresholds ranging between £0 and £50,000; probability of cost-effectiveness from the societal perspective did not exceed 19% over the same range.

### Sensitivity analysis

Mean costs used in sensitivity analyses are reported in [Table 22](#) and results of sensitivity analyses of the primary outcome are displayed in [Table 23](#). Results of analysis of CMAI scores and health and social care costs that included the costs of domestic accommodation were similar to the base case results, with no significant differences between groups. The cost per 6-point difference was slightly lower than in the primary analysis but unbounded as in the base case results. Analyses adjusting for the baseline imbalance between groups in proportion of female participants yielded similar results to the base case, with an unbounded ICER. Results of a SUR model applied to samples from a two-stage bootstrapping routine indicated no differences between groups in costs or CMAI scores; model estimates produced a small positive unbounded ICER of £136 per 6-point difference.

In terms of secondary outcomes, analyses explored the impact on results for EQ-5D-5L QALY and societal costs of valuing unpaid carer time at replacement cost, alone and in combination with an alternative method of estimating hours of unpaid carer time (see [Table 24](#)). The societal costs were significantly greater in the mirtazapine group if valuing unpaid carer time at replacement cost. Valuation at replacement cost resulted in a negative NMB at £20,000 with negative upper and lower confidence limits (the costs outweighed the benefit of the intervention). Using an alternative calculation of unpaid carer hours increased the cost of both groups (doubling it in the placebo group) but the groups did not differ. Valuation of the alternative estimation of unpaid care time at replacement cost resulted in an unbounded ICER and negative NMB at £20,000 with CIs crossing zero.

Examining combined QALY and health and social care costs of participant and dyadic carer, the groups did not differ. The ICER was unbounded and had a negative sign because the mirtazapine group had slightly lower QALY and slightly higher costs.



TABLE 21 Carer outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios

Outcomes and costs	Mirtazapine		Placebo		Mirtazapine-placebo difference		Adjusted (95% CI)	p	ICER C/E	NMB at £20,000 Mean (95% CI)
	Mean (SE)	N	Mean (SE)	N	Mean (95% CI)	Mean (95% CI)				
<i>Health and social care</i>										
Observations		N = 44		N = 45						
QALY (EQ-5D-5L)	0.186 (0.005)		0.19 (0.006)		-0.004 (-0.019 to 0.011)	0.001 (-0.008 to 0.01)	0.764	70,668		-286 (-69 to 149)
Total costs	111 (55)		22 (10)		90 (-20 to 199)	96 (-12 to 203)	0.082			
<i>Societal</i>										
Observations		N = 41		N = 43						
QALY (EQ-5D-5L)	0.187 (0.005)		0.189 (0.006)		-0.003 (-0.018 to 0.013)	0.004 (-0.006 to 0.013)	0.437	361,088		-1283 (-4045 to 1480)
Total costs	9648 (1073)		8245 (983)		1403 (-1488 to 4294)	1358 (-1491 to 4206)	0.348			

TABLE 22 Sensitivity analyses of mean costs (standard errors) over prior 3 months, at baseline, weeks 6 and 12 assessments (£, 2016–17)

Cost categories	Mirtazapine			Placebo			Mirtazapine-placebo difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	95% CI
Baseline (prior 12 weeks)									
Accommodation costs									
Domestic residence (includes sheltered)	100	1596	146	101	1662	144	-66		-469 to 338
Permanent residence	100	5447	308	101	5555	345	-108		-1020 to 804
Total accommodation, health and social care costs	93	7136	403	99	7112	422	24		-1130 to 1178
	Expected = 63			Expected = 68					
Total societal, replacement cost	53	29,461	2002	65	27,514	2076	1947		-3847 to 7740
Total societal, alternative care time	49	50,224	1488	58	51,220	1466	-995		-5162 to 3171
Week 6 (prior 6 weeks)									
Accommodation costs									
Domestic residence (includes sheltered)	85	771	79	91	769	77	2		-215 to 219
Permanent residence	85	2739	162	91	2966	192	-227		-726 to 273
Total accommodation, health and social care costs	83	3294	160	89	3797	242	-503		-1084 to 79
	Expected = 53			Expected = 60					
Total societal, replacement cost	48	15,774	1008	55	12,899	1027	2875*		3 to 5748
Total societal, alternative care time	45	26,039	475	50	25,364	952	675		-1510 to 2860
Week 12 (prior 6 weeks)									
Accommodation costs									
Domestic residence (includes sheltered)	78	731	83	86	756	79	-25		-251 to 201
Permanent residence	78	2862	180	86	3032	200	-170		-705 to 365
Total accommodation, health and social care costs	77	3794	267	85	3643	220	151		-527 to 830
	Expected = 49			Expected = 56					
Total societal, replacement cost	44	16,078	1125	51	12,415	1008	3663*		671 to 6654
Total societal, alternative care time measure	40	26,754	742	47	25,026	963	1728		-754 to 4211

**TABLE 23** Sensitivity analyses of primary participant outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios

Outcomes and costs	Mirtazapine		Placebo		Mirtazapine-placebo difference		Adjusted (95% CI)	p	Cost per 6-point difference <sup>a</sup>	
	Mean (SE)	N	Mean (SE)	N	Mean (95% CI)	C/E				
CMAI – participant										
Total HSC costs including domestic accommodation										
Observations		N = 72		N = 79						
CMAI	61.847 (2.659)		60.848 (2.490)		0.999 (-6.193 to 8.191)		-2.506 (-8.299 to 3.287)	0.396		-212/0.418 = -507
Total costs	7234 (390)		7380 (462)		-146 (-1353 to 1060)		-212 (-1375 to 951)	0.721		
Statistical model adding sex as covariate										
Observations		N = 72		N = 79						
CMAI	61.847 (2.659)		60.848 (2.49)		0.999 (-6.193 to 8.191)		-1.726 (-7.613 to 4.162)	0.566		-278/0.288 = -956
Total HSC costs	5752 (513)		5877 (591)		-125 (-1686 to 1435)		-275 (-1756 to 1206)	0.716		
Alternative statistical model <sup>b</sup>										
Observations		N = 72		N = 79						
CMAI	61.847 (2.659)		60.848 (2.49)		0.999 (-6.193 to 8.191)		-2.253 (-9.847 to 7.794)	0.453		51/0.376 = 136
Total HSC costs	5752 (513)		5877 (591)		-125 (-1686 to 1435)		51 (-1304 to 1432)	0.900		

\* p < 0.05

HSC, health and social care providers.

<sup>a</sup> Reversed so that a higher score indicates a better outcome.

<sup>b</sup> Seemingly unrelated regression; adjusted difference estimate is presented with bias corrected and accelerated 95% CIs generated from 4000 replications of 2-stage bootstrap.

**TABLE 24** Sensitivity analyses of secondary participant outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios

Outcomes and costs	Mirtazapine		Placebo		Mirtazapine-placebo difference		ICER		NMB at £20,000	
	Mean (SE)		Mean (SE)		Mean (95% CI)		p	C/E	Mean (95% CI)	
<i>Societal</i>										
Replacement cost of unpaid care										
Observations	N = 38		N = 45							
QALY-EQ-5D-5L	0.125 (0.009)		0.147 (0.007)		-0.022 (-0.045 to 0.001)		0.589		-3,366,204	-8169 (-14,178 to -2160)
Total costs	33,090 (2246)		24,966 (2105)		8125* (1989 to 14,260)		0.017		7263 (1328 to 13,197)	
<i>Societal</i>										
Replacement cost of unpaid care + alternative unpaid care estimate										
Observations	N = 35		N = 39							
QALY-EQ-5D-5L	0.129 (0.010)		0.150 (0.008)		-0.022 (-0.046 to 0.003)		0.518		-842,854	-3730 (-8173 to 712)
Total costs	53,241 (1145)		49,685 (1887)		3556 (-966 to 8079)		0.143		3242 (-1114 to 7597)	
<i>QALY - participant and carer</i>										
<i>HSC</i>										
Observations	N = 40		N = 44							
QALY-EQ-5D-5L	0.311 (0.010)		0.336 (0.009)		-0.025 (-0.051 to 0.001)		0.988		-4,439,387	-465 (-2242 to 1312)
Total costs	3291 (632)		2987 (696)		303 (-1580 to 2187)		0.617		463 (-1362 to 2288)	

\*  $p < 0.5$ .

HSC, health and social care providers.

# Chapter 4 Carbamazepine versus placebo results

## Introduction

As discussed above, this trial was designed to include a carbamazepine arm as well as mirtazapine and placebo arms. The carbamazepine arm was discontinued after 40 randomisations due to slower than projected recruitment. In this chapter, we present the rationale for this arm and mirrored analyses of the clinical effectiveness of carbamazepine versus placebo in the treatment of agitation in dementia using the same methodology that was used for mirtazapine versus placebo.

## Carbamazepine for agitated behaviours in dementia

Carbamazepine stabilises the inactivated state of voltage-gated sodium channels and potentiates GABA receptors. It is recommended in the BNF for epilepsy, prophylaxis of bipolar disorder and trigeminal neuralgia. It is generally safe within the proposed dose ranges; there are few data on people with AD, but it seems that there is no increase in mortality as in antipsychotics for AD.<sup>35</sup> Carbamazepine has been widely used in psychiatric disorders and AD, off licence, to treat symptoms including agitation, aggression, irritability and impulsivity. Open-label studies and case reports have indicated promise in agitation in AD.<sup>36</sup> Two small 6-week parallel-group RCTs of carbamazepine for BPSD have been published.<sup>37,38</sup> The first in 55 patients (modal dose 300 mg) showed significant symptom decrease. It was well tolerated with no decrease in cognition, function or increased side effects relative to placebo. The second (400 mg in 21 patients not responding to antipsychotics) showed a trend but not a significant advantage over placebo. Meta-analysis indicated significant benefit compared with placebo treatment on the Brief Psychiatric Rating Scale (mean difference -5.5 points, 95% CI -8.5 to -2.5 points) and on the Clinical Global Impression Scale (OR 10.2, 95% CI 3.1 to 33.1).<sup>39</sup> A third small trial of the similar compound oxcarbazepine ( $n = 103$ ) indicated a trend towards benefit ( $p = 0.07$ ) with active drug performing better than placebo in all analyses.<sup>40</sup>

## Aim

To determine if carbamazepine is more clinically effective in reducing agitated behaviours in dementia than placebo measured by change in CMAI score 12 weeks post randomisation.

## Methods

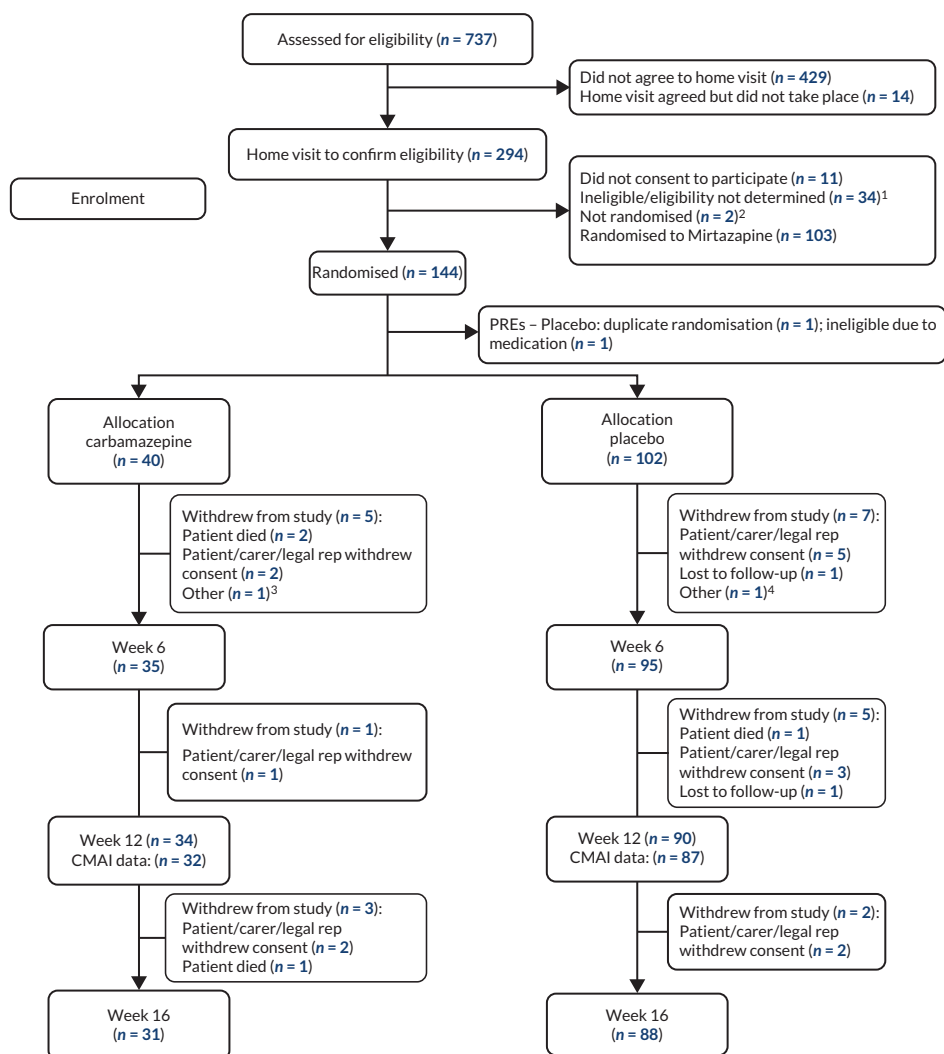
Please see [Chapter 3](#).

## Results

### *Patient flow*

We recruited participants between January 2017 and August 2018 to the three-arm trial and recruitment continued until February 2020 for mirtazapine and placebo arms. Follow-up interviews were completed accordingly. See [Figure 5](#).

# CARBAMAZEPINE VERSUS PLACEBO RESULTS



<sup>1</sup>Reasons for ineligibility

No diagnosis of probable/possible Alzheimer's disease	1
No diagnosis of co-existing agitated behaviour	1
No evidence that behavior not responding to management according to AS/DH algorithm	1
No assessment of Cohen-Mansfield Agitation Inventory score of 45 or greater	15
No written informed consent to enter and be randomized into the trial	1
Current treatment with antidepressant (including MAOIs), anticonvulsants, or antipsychotics	1
Case too critical for randomisation	2
Reason other/unknown (info below taken from text entries)	12
Psychiatrist decided to proceed with an alternative medication	
Patient admitted to hospital. No longer appropriate	
Patient not eligible. Completed no further assessments after CMAI	
Participant ineligible	
Patient not eligible	
Participant ineligible	
Patient scored below 45 on the CMAI	
Pt started memantine which reduced agitation	
Not randomised as behaviour settled and did not require medication	
Participant ineligible	
Participant ineligible	
Participant ineligible	
Total	34

<sup>2</sup>Not randomised (n = 2)

→ Abnormal blood results (n = 1)

→ Patient/legal rep withdrew consent (n = 1)

<sup>3</sup>Patient collapsed evening after baseline completed, consumed no trial medication, diagnosed with cancer

<sup>4</sup>Participant withdrawn from trial due to deteriorating health and readmission to hospital

**FIGURE 5** CONSORT flow diagram of recruitment and testing for carbamazepine and placebo groups.

### Baseline characteristics

[Table 25](#) shows baseline demographic and clinical characteristics of participants. Groups were similar at baseline except for sex with more females randomised to carbamazepine ( $n = 32$ , 80%) than placebo ( $n = 59$ , 58%). [Table 26](#) shows baseline demographics for carers.

### Primary outcome measures

Severity of agitation decreased in the placebo group by 9.6 points on the CMAI and by 4.4 points in the carbamazepine group. At 12 weeks, the placebo group was 60.8 and the carbamazepine group 63.9 (see [Figure 6](#)). At no point was the unadjusted or adjusted CMAI difference between the groups statistically significant (see [Tables 27](#) and [28](#)). [Table 27](#) presents the results from the general linear mixed modelling for the primary outcome. There was no evidence that carbamazepine improved agitation relative to placebo. The estimated adjusted effect on the CMAI was 2.46 (95% CI  $-5.01$  to  $9.93$ ;  $p = 0.518$ ). This changed little with the addition of sex into the model.

### Secondary outcome measures

[Table 28](#) shows the effect of carbamazepine compared with placebo on secondary outcomes in participants and [Table 29](#) in carers. Again, there was no evidence of difference between the groups, apart from: a single statistically significant difference in the NPI carer distress subscore at 6 weeks which indicated higher carer distress in the carbamazepine group (adjusted difference 3.31 points, 95% CI 0.44 to 6.18;  $p = 0.024$ ) which did not persist at 12 weeks. [Table 30](#) presents data on dose escalation and compliance with carbamazepine and placebo.

Adverse events and SAEs were ascertained to 16 or 4 weeks after last dose of IMP; deaths were recorded up to 16 weeks after randomisation (see [Table 31](#)). Examining AEs by week 16, there were 192 in 102 participants in the placebo group, of whom 65 (64%) individuals had at least one AE, compared with 106 events in 40 participants in the mirtazapine group of whom 27 (68%) had at least one. There were 35 SAEs in 18 individuals in the placebo group, compared with 12 in 5 individuals in the carbamazepine group. There was one death (1%) in the placebo group and two (5%) in the carbamazepine group.

### Long-term outcomes at 26 and 52 weeks

#### CMAI outcomes at 26 and 52 weeks

CMAI outcomes at 26 and 52 weeks are presented in [Table 32](#). There were no statistically significant differences between carbamazepine and placebo at either time point. This applied to both the raw and adjusted differences.

#### Hospitalisation at 26 and 52 weeks

Hospitalisation by 26 weeks and between 26 and 52 weeks are presented in [Table 33](#). There were no statistically significant differences between carbamazepine and placebo at either time period.

#### Deaths at 26 and 52 weeks

The cumulative number of deaths at 26 and 52 weeks are presented in [Table 34](#). There were no statistically significant differences between death rates on carbamazepine and placebo at either time point.

**TABLE 25** Baseline demographics and clinical characteristics of participants

	Carbamazepine (n = 40)	Placebo (n = 102)
Age (years) (SD)	83.2 (8.1)	82.8 (7.7)
Sex	n = 40	n = 102
Female	32 (80%)	59 (58%)
Residence	n = 40	n = 102
Own household	20 (50%)	57 (56%)
Care home	20 (50%)	45 (44%)
Agitation	n = 40	n = 102
CMAI (29–203)	70.0 (21.0)	69.8 (17.1)
Cognition	n = 23	n = 50
Standardised MMSE (0–30)	12.0 (6.0)	16.1 (6.7)
Condition-specific quality of life	n = 17	n = 37
DEMQOL (28–122)	93.5 (12.7)	95.8 (10.2)
DEMQOL-Proxy (31–124)	n = 39	n = 99
	94.7 (14.8)	90.9 (14.4)
Generic quality of life	n = 40	n = 101
EQ-5D (proxy report by carer) (0–1)	0.47 (0.35)	0.50 (0.32)
Neuropsychiatric symptoms	n = 40	(n = 102)
NPI total score (0–144)	40.5 (26.1)	34.9 (18.2)
NPI agitation/aggression subscore (0–12)	n = 40	n = 102
	6.5 (4.0)	5.6 (3.4)
NPI depression/anxiety/irritability subscore (0–36)	n = 40	n = 102
	11.6 (8.9)	10.5 (7.0)
Suicidality	n = 40	n = 102
CSSRS		
Suicidal ideation (lifetime)	10 (25%)	13 (13%)
Suicidal ideation (past month)	5 (13%)	11 (11%)
Suicidal behaviour (lifetime)	1 (3%)	0
Suicidal behaviour (past 3 months)	0	0

CSSRS, Columbia Suicide Severity Rating Scale.

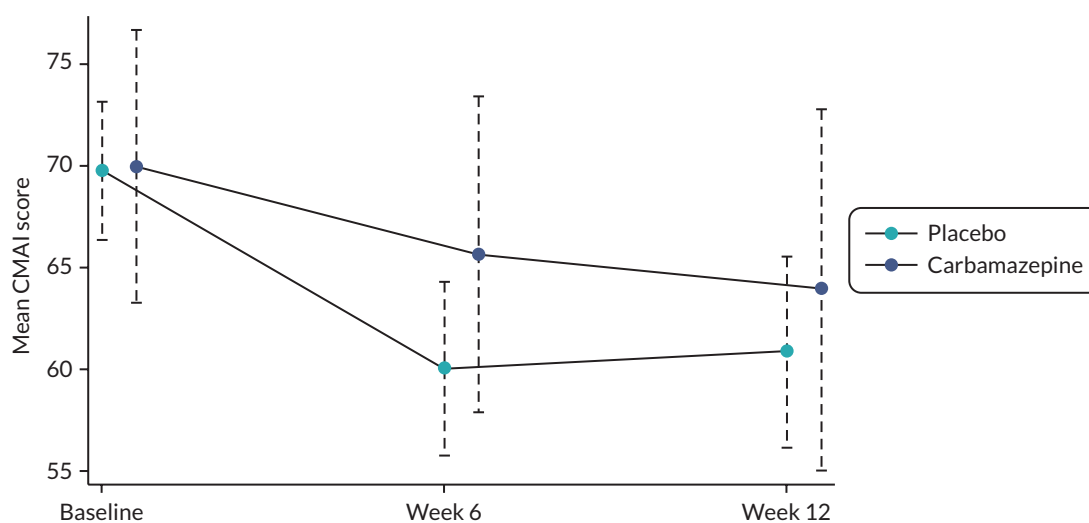
**TABLE 26** Baseline demographics and clinical characteristics of carers

	Carbamazepine (n = 40)	Placebo (n = 102)
Carer		
Paid	16 (40%)	31 (30%)
Family	24 (60%)	71 (70%)
Family carer relationship		
Partner or spouse	13 (54%)	35 (49%)
Son or daughter	9 (38%)	31 (44%)
Sibling	0	0
Other relative	2 (8%)	3 (4%)
Friend	0	2 (3%)



**TABLE 26** Baseline demographics and clinical characteristics of carers (continued)

	Carbamazepine (n = 40)	Placebo (n = 102)
Other	0	0
Family carer occupation (pre-retirement)		
Professional	6 (25%)	13 (18%)
Managerial and technical	5 (21%)	22 (31%)
Skilled non-manual	5 (21%)	11 (15%)
Skilled manual	6 (25%)	8 (11%)
Partly skilled	1 (4%)	8 (11%)
Unskilled	1 (4%)	0
Unemployed or unwaged	0	5 (7%)
Unanswered	0	4 (6%)
Carer mental health (family carers only)	n = 24	n = 66
GHQ-12	13.2 (5.2)	14.5 (4.9)
Carer burden (family carers only)	n = 21	n = 66
Zarit CBI	29.4 (13.2)	34.1 (13.9)
Carer generic quality of life (family carers only)	n = 24	n = 66
EQ-5D	0.82 (0.15)	0.81 (0.22)
NPI carer distress subscore (0–60)	n = 38	n = 99
	14.5 (11.5)	15.5 (9.0)

**FIGURE 6** Unadjusted mean CMAI scores (95% CI) by treatment group, carbamazepine vs. placebo.**TABLE 27** Primary outcomes of research worker rated CMAI score at 12 weeks

Carbamazepine (n = 40)	Placebo (n = 102)	Difference	(95% CI)	Adj diff <sup>a</sup>	(95% CI)	p-value	Adj diff <sup>b</sup>	(95% CI)	p-value
n = 32	n = 87								
63.9 (sd 24.7)	60.8 (sd 21.8)	3.1	(-6.17 to 12.37)	2.46	(-5.01 to 9.93)	0.518	2.67	(-5.05 to 10.40)	0.498

a Adjusted for pre-specified factors: baseline CMAI, household status and centre.

b Adjusted for sex and pre-specified factors: baseline CMAI, household status and centre.

TABLE 28 Comparisons of participant secondary outcomes at 6 and 12 weeks

	Carbamazepine (n = 40)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference	(95% CI)	p-value
<b>6-week outcomes</b>							
Agitation (CMAI)	n = 35 65.6 (22.7)	n = 88 60.0 (19.9)	5.66	(-2.52 to 13.85)	4.51	(-2.37 to 11.39)	0.199
Cognition (sMMSE)	n = 12 12.5 (6.1)	n = 31 16.2 (7.2)	-3.69	(-8.46 to 1.08)	0.64	(-1.35 to 2.62)	0.531
Quality of life (DEMQOL)	n = 11 94.6 (15.8)	n = 32 96.8 (8.4)	-2.11	(-9.68 to 5.45)	-1.79	(-7.90 to 4.33)	0.566
Quality of life (DEMQOL-Proxy)	n = 33 100.6 (13.8)	n = 86 94.6 (16.2)	6.07	(-0.26 to 12.39)	1.94	(-3.19 to 7.08)	0.459
Quality of life EQ-5D (proxy report by carer)	n = 35 0.49 (0.35)	n = 87 0.56 (0.30)	-0.06	(-0.19 to 0.06)	-0.03	(-0.12 to 0.05)	0.427
Neuropsychiatric symptoms NPI total score	n = 34 34.3 (4.3)	n = 88 24.8 (20.0)	9.48	(0.86 to 18.01)	4.88	(-2.03 to 11.78)	0.166
NPI agitation/aggression subscore	n = 34 5.4 (3.7)	n = 88 4.2 (3.5)	1.14	(-0.30 to 2.58)	0.40	(-0.82 to 1.62)	0.519
NPI depression/anxiety/irritability subscore	n = 34 9.1 (8.1)	n = 88 7.2 (8.2)	1.88	(-1.39 to 5.14)	0.47	(-2.05 to 3.00)	0.712
<b>12-week outcomes</b>							
Cognition (sMMSE)	n = 14 12.3 (6.8)	n = 27 15.6 (7.5)	-3.27	(-8.12 to 1.58)	0.39	(-1.67 to 2.45)	0.709

TABLE 28 Comparisons of participant secondary outcomes at 6 and 12 weeks (continued)

	Carbamazepine (n = 40)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference	(95% CI)	p-value
Quality of life (DEMQOL)	n = 11 96.8 (9.9)	n = 24 97.1 (8.4)	-0.31	(-6.89 to 6.27)	-1.49	(-6.74 to 3.77)	0.579
Quality of life (DEMQOL-Proxy)	n = 29 101.7 (11.9)	n = 82 97.5 (12.4)	4.26	(-1.00 to 9.52)	0.11	(-4.04 to 4.26)	0.958
Quality of life EQ-5D (proxy report by carer)	n = 31 0.43 (0.34)	n = 84 0.50 (0.33)	-0.07	(-0.21 to 0.07)	-0.02	(-0.11 to 0.08)	0.743
Neuropsychiatric symptoms	n = 31 31.1 (25.0)	n = 84 25.7 (19.6)	5.43	(-3.39 to 14.25)	0.35	(-6.10 to 6.80)	0.916
NPI agitation/aggression subscore	n = 31 4.6 (4.0)	n = 84 4.5 (3.6)	0.12	(-1.42 to 1.67)	-0.60	(-1.92 to 0.72)	0.374
NPI depression/anxiety/irritability subscore	n = 31 8.0 (8.3)	n = 84 7.3 (8.0)	0.67	(-2.67 to 4.03)	-0.53	(-3.04 to 1.98)	0.680

continued

TABLE 29 Comparisons of carer secondary outcomes at 6 and 12 weeks

	Carbamazepine (n = 40)	Placebo (n = 102)	Difference	95% CI	Adjusted difference	95% CI	p-value
<b>6-week outcomes</b>							
Carer GHQ-12 <sup>a</sup>	n = 18 13.0 (4.8)	n = 54 12.1 (4.9)	0.85	(-1.80 to 3.50)	1.55	(-0.46 to 3.56)	0.130
Carer EQ-5D <sup>a</sup>	n = 18 0.81 (0.14)	n = 55 0.83 (0.15)	-0.02	(-0.10 to 0.07)	-0.02	(-0.08 to 0.03)	0.428
Zarit CBI <sup>a</sup>	n = 16 29.2 (14.7)	n = 49 29.4 (13.9)	-0.20	(-8.33 to 7.93)	2.23	(-3.40 to 7.86)	0.438
NPI carer distress subscore	n = 32 13.1 (11.3)	n = 84 10.2 (8.8)	2.97	(-0.95 to 6.89)	3.31	(0.44 to 6.18)	0.024
<b>12-week outcomes</b>							
Carer GHQ-12 <sup>a</sup>	n = 14 13.1 (5.3)	n = 52 12.2 (5.4)	0.93	(-2.29 to 4.15)	0.75	(-1.58 to 3.08)	0.527
Carer EQ-5D <sup>a</sup>	n = 16 0.82 (0.13)	n = 49 0.82 (0.19)	0.00	(-0.10 to 0.11)	0.01	(-0.05 to 0.07)	0.750
Zarit CBI <sup>a</sup>	n = 13 28.6 (14.4)	n = 48 29.0 (15.8)	-0.41	(-10.11 to 9.30)	-0.64	(-6.34 to 5.07)	0.827
NPI carer distress subscore	n = 28 11.0 (10.3)	n = 81 10.5 (8.3)	0.48	(-3.36 to 4.32)	0.64	(-1.88 to 3.17)	0.615

<sup>a</sup> Asked of family carers only.

**TABLE 30** Dose escalation and compliance with carbamazepine and placebo

	Carbamazepine (n = 40)	Placebo (n = 102)
End of week 4	n = 35	n = 97
3 study meds/day	20 (57%)	59 (61%)
2 study meds/day	2 (6%)	16 (16%)
1 study med/day	3 (9%)	8 (8%)
0 study meds/day <sup>a</sup>	10 (29%)	14 (14%)
Dose information missing/inconsistent	0	0
End of week 6	n = 33	n = 95
3 study meds/day	15 (45%)	49 (52%)
2 study meds/day	4 (12%)	23 (24%)
1 study med/day	5 (15%)	8 (8%)
0 study meds/day <sup>a</sup>	5 (15%)	7 (7%)
Dose information missing/inconsistent	4 (12%)	8 (8%)
In trial at 6 weeks		
% compliance: <sup>a</sup> mean (SD)	79 (20)	84 (16)
Compliance missing or inconsistent	n = 13	n = 49
In trial at 12 weeks	n = 31	n = 88
Taking trial medication at 12 weeks	n = 24	n = 76
% compliance: <sup>b</sup> mean (SD)	60 (28)	74 (27)
Compliance missing or inconsistent	n = 13	n = 50

a Combining those reported on 0 tablets a day and those choosing or advised to stop.

b Compliance: number of tablets taken/expected number of tablets taken × 100 where: number of tablets taken is based upon expected number of tablets, minus number of tablets returned at 6- or 12-week visits; expected number of tablets calculated using prescribed number of tablets at each stage of the trial.

**TABLE 31** Adverse events and mortality

	Carbamazepine (n = 40)	Placebo (n = 102)
Adverse events		
Number of events	106	192
Number of individuals	27 (68%)	65 (64%)
Serious adverse events		
Number of events	12	35
Number of individuals	5 (13%)	18 (18%)
Deaths	2 (5%)	1 (1%)
MedDRA codes for deaths	1 cause unknown 1 gastric haemorrhage	1. Dementia

**Note**

Adverse events and severe adverse events ascertained to 16 or 4 weeks after last dose of IMP, deaths recorded up to 16 weeks after randomisation.

**TABLE 32** Outcome of carer-rated CMAI scores at 26 and 52 weeks carbamazepine vs. placebo

Carbamazepine (n = 40)	Placebo (n = 102)	Difference	(95% CI)	Adjusted difference <sup>a</sup>	(95% CI)	p-value
26 weeks						
n = 26	n = 62					
58.5 (SD = 18.0)	56.8 (SD = 19.7)	1.7	(-7.26 to 10.57)	0.08	(-7.16 to 7.33)	0.982
52 weeks						
n = 17	n = 56					
56.8 (SD = 21.8)	58.5 (SD = 20.8)	-1.7	(13.29 to -9.97)	-6.18	(-16.02 to 3.66)	0.218

a Adjusted for pre-specified factors: baseline CMAI, household status and centre.

**TABLE 33** Hospitalisations by 26 weeks and between 26 and 52 weeks mirtazapine vs. placebo

	Carbamazepine (n = 40)	Placebo (n = 102)
Hospitalisations by 26 weeks		
Yes	1 (3.8%)	10 (14.3%)
No	25 (96.2%)	60 (85.7%)
No information	14	32
Days in hospital by 26 weeks		
N	1	10
Mean (SD)	4 (-)	16.8 (30.6)
Median (IQR)	4	5.5 (1 to 14)
N missing	0	0
Hospitalisations between 26 and 52 weeks		
Yes	1 (5.3%)	9 (15.0%)
No	18 (94.7%)	51 (85.0%)
No information	21	42
Days in hospital between 26 and 52 weeks		
N	1	8
Mean (SD)	7 (-)	20.1 (30.3)
Median (IQR)	7	9 (3 to 22)
N missing	0	1

IQR, interquartile range.

**TABLE 34** Deaths by 26 and 52 weeks: carbamazepine vs. placebo

	<b>Carbamazepine (n = 40)</b>	<b>Placebo (n = 102)</b>
By 26 weeks		
Died	4 (13.4%)	6 (8.1%)
Alive	25 (86.6%)	68 (91.9%)
No information	11	28
By 52 weeks		
Died	5 (17.9%)	13 (18.6%)
Alive	23 (82.1%)	57 (81.4%)
No information	12	32





## Chapter 5 Discussion

This is a trial with negative findings, but these have important clinical implications for practice. Our results indicate that mirtazapine, given with normal clinical care, is not clinically effective compared with placebo for the treatment of clinically significant agitation in people with dementia. This finding implies a need to change the present practice of prescription of mirtazapine, and possibly other antidepressants, for agitation in dementia. In this study, there were clear decreases in agitation scores overall, with a clinically and statistically significant 10-point drop in the first 6 weeks of treatment, which was then maintained from 6 to 12 weeks; however, this drop was not attributable to mirtazapine since it was also seen in the placebo group. These clinical effectiveness data taken with those from the cost-effectiveness analyses make clear that there is no evidence to support the use of mirtazapine for agitation in dementia. These data are unequivocal in there is no clinical or economic reason for mirtazapine being used for the treatment of agitation in dementia. The data presented here are novel. While there is economic literature on psychosocial interventions for agitation, to our knowledge, no other formal economic analyses have been published of an RCT of an IMP for agitation in dementia. As such, this study provides data that may be of use in subsequent analyses of the cost-effectiveness of other IMPs for agitation in dementia.

### Limitations

Our study has important potential limitations. First, there was a major adjustment to the initial trial protocol. We dropped the proposed carbamazepine arm from the trial in response to slower-than-anticipated recruitment, which means we are unable to test hypotheses concerning the clinical effectiveness of carbamazepine in the treatment of agitation in dementia with any confidence. The data presented on carbamazepine versus placebo must therefore be seen as exploratory only. The incomplete recruitment into the carbamazepine arm also meant that we could not complete an economic evaluation on this group. Stopping recruitment to this arm did not affect our ability to compare the clinical effectiveness of mirtazapine with placebo. However, the data from this trial apply only to mirtazapine and it is possible that other antidepressants from other classes might have a different effect; in the CitAD trial,<sup>21</sup> citalopram, a SSRI, was reported to have had a modest positive effect, though with concerning adverse effects.

Second, the difference in mortality observed at 12 weeks may have been by chance. This study was not powered to investigate a mortality difference between the groups. The analysis was post hoc, its statistical significance was marginal and the difference was not observed at 6 or 12 months. In our previous study of depression in dementia, there were no more deaths in 108 randomisations to mirtazapine than in 111 randomised to placebo.<sup>70</sup> We therefore need to be careful in the interpretation of the mortality data in this study with the most likely conclusion being that in the long run, there are no mortality differences between taking mirtazapine or placebo. Third, recruitment beyond February 2020 was constrained by health research restrictions secondary to the COVID-19 pandemic. We only recruited 204 (92%) of our target of 222, but the closeness of the findings in both groups makes it highly unlikely that the results we found would have been different had there been another 18 randomisations as planned. Fourth, there was a relatively high level of missing data in descriptive (e.g. MMSE score) and secondary outcomes. This was most likely a function of participant ability to complete multiple questionnaires given their having clinically significant agitation. This is not likely to have introduced bias since there is no reason falling differentially between the randomisation groups, but it may limit inferences on secondary outcomes due to power, even with imputation.

## Generalisability

This study was designed to reflect clinical populations and interventions as closely as possible. We kept exclusion criteria to a minimum and had permissive inclusion criteria, but the findings will not apply to individuals who are too critically ill to risk random allocation (such as those with high risk of harm to themselves or others). Only two potential participants were excluded for this reason, but there will have been others who were not referred to the trial. However, there are potential limits in generalisability that come from our having recruited most participants from old-age psychiatry services and care homes; outcomes might possibly have been different in those living in the community treated by primary care services alone. In the UK, those with significant agitation at home are likely to be referred to psychiatric services and would represent those for whom drug treatment might be indicated. In terms of generalisability, participants were not drawn only from specialist research clinics or tertiary care, but from 26 geographically diverse areas with a correspondingly high number of clinicians who therefore are likely to cover the range of services in general.

## Strengths

The three main strengths of our study were high follow-up rates, large sample size and the broad nature of the study group (in terms of severity of agitation as measured by CMAI score and severity and type of dementia with mean sMMSE scores in the moderately severe range [for mirtazapine vs. placebo 25.4% mild (sMMSE 21–30), 46.1% moderate (10–20), 28.4% severe (0–9)]). We were able to follow up 81 (79%) of the mirtazapine group and 90 (87%) of the placebo group at 12 weeks and complete primary outcome assessment. Dropouts might introduce bias if those not followed up had a different response to mirtazapine or placebo compared with those completing the trial. However, our rates of follow-up are relatively high, and the difference between the groups seems attributable to the six additional deaths in the mirtazapine group compared with placebo. We included individuals with probable and possible AD, not just narrowly defined AD; this is important since agitation can affect dementia of all causes and most people with dementia have mixed aetiology. Participants were therefore closer to populations encountered in clinical practice, in which there is often mixed dementia. However, our inclusion criteria mean that we should restrict generalisation of our findings to AD and mixed dementia and be cautious in applying them to other subtypes (e.g. vascular, Lewy body or frontotemporal dementia).

## Carbamazepine

We only have data on 40 people randomised to carbamazepine. This number, even when compared to the whole placebo group does not have sufficient statistical power for us to be able to draw definitive conclusions from the analyses presented above; these will therefore not be discussed in detail here. However, the data that we do have provide no signal that carbamazepine might have any positive effect on agitation in dementia above that seen in the placebo group.

## Economic evaluation

The mirtazapine group had a marginally lower mean CMAI score than the placebo group at 12-week primary outcome follow-up. This difference was not statistically significant and much smaller than the pre-specified effectiveness criterion of a 6-point difference in favour of the mirtazapine group. The groups had similar costs from both the health and social care and societal perspectives. On the secondary analyses, groups were similar in both costs and health-related quality-of-life outcomes. Sensitivity analyses of the primary outcome yielded similar results to the base case. Results of sensitivity analyses of most secondary outcomes were also similar to base-case findings. Between-group differences in societal costs were sensitive to assumptions about valuing unpaid care time. Valuing carer

time at replacement cost resulted in mirtazapine being definitely less cost-effective than placebo at a willingness to pay per QALY threshold of £20,000.

Taken with our findings that carers in the mirtazapine group attributed a higher proportion of their use of health and support services to their caring role, reported more hours of unpaid care at 12 weeks and more improvement in their care situation because of these services than did carers in the placebo group, it is possible that receipt of mirtazapine resulted in increased carer burden and related help-seeking and help-giving.

The substantial costs of caring reported by unpaid carers should be of concern. Carers from both groups lost approximately an hour of sleep nightly to care for the agitated person; the mean number of hours they felt able to leave the person alone at home was < 3 hours. Agitation is a distressing state for people experiencing it and for those around them. Effective strategies for managing agitation and supporting carers are required, tailored to the needs of the person with dementia and their families.

We were unable to locate previous trial-based economic evaluations of pharmacological interventions specifically focused on agitation in dementia. The cost-effectiveness of non-pharmacological interventions to manage agitation in care home residents with dementia has been evaluated in trials<sup>71,72</sup> and model-based studies.<sup>73</sup> Non-pharmacological management approaches included person-centred care, communication, care mapping and care planning, and combinations of interventions in multicomponent programmes, in care home settings.<sup>73</sup> A trial of a person-centred care intervention in English care homes was found to be cost-effective in terms of agitation and quality of life, and the intervention was no more costly from the health and social care perspective than usual care.<sup>71</sup> Little is known on the effectiveness of any interventions for people with dementia and agitation living in the community.<sup>73</sup> There is a need for further research to address this evidence gap and future trials should include economic evaluations such as those completed here, given the high costs experienced by carers in terms of hours of care, sleep loss and carer burden identified across the SYMBAD effectiveness and cost-effectiveness studies.

## Clinical context

The US National Health and Nutrition Examination Survey showed that the highest rates of antidepressant use between 2015 and 2018 were in those over 60, where 19.0% of people were prescribed such medication.<sup>74</sup> Mirtazapine is commonly prescribed for older adults. In a study of people living in long-term care facilities in Helsinki, there was a marked increase in use of mirtazapine between 2003 and 2017: from 15.7% to 22.7% in nursing homes, and 14.0% to 23.8% in assisted-living facilities, both settings with very high prevalence of residents with dementia.<sup>75</sup> In the MEDALZ cohort of 70,718 community-dwelling people with AD in Europe, mirtazapine was responsible for most new prescriptions ( $n = 6462$ , 39.2%).<sup>76</sup> One reason for high rates of prescription of mirtazapine in later life is to avoid the use of antipsychotics.<sup>77</sup> The influential NICE dementia guideline for the management of dementia is clear that antipsychotics should only be used in 'agitation, aggression, distress and psychosis' when the person with dementia is at risk of harming themselves or others or where the agitation or psychosis is causing the person with dementia severe distress.<sup>23</sup> The only other medication advice is that valproate should not be offered; there is no mention of antidepressants. This absence of guidance on the use of alternative medications for agitation in all but the most extreme clinical situations means that clinicians will seek to use other medications. Antidepressants that are perceived to have sedative effects such as mirtazapine, with which they are familiar, may appear an attractive and safe alternative to proscribed antipsychotics. However, there are reports that this may not be the case. Analyses of a primary care cohort showed increased all-cause mortality in people aged 20–64 prescribed mirtazapine.<sup>78</sup> The reports of potentially serious adverse effects of citalopram in the CitAD trial,<sup>21</sup> of increased falls in trials of dextromethorphan-quinidine,<sup>79</sup> and the higher mortality in mirtazapine group in this trial, present a growing evidence base that the assumption that

the substitution of antidepressants, or other novel compounds, for antipsychotics for the treatment of agitation in dementia is a safe alternative may well not be tenable.

In terms of secondary outcomes, the absence of any positive effects on participant and carer quality of life, on participant cognition and on broader neuropsychiatric symptoms as measured by the NPI is striking. The potential positive effects for people with agitation in dementia and for their family carers observed in secondary analyses of our HTA-SADD<sup>28</sup> study of people with depression in dementia were not found in this definitive study of people with agitation in dementia. Our study provides strong evidence that the overall improvement seen over the 12 weeks of the study is not attributable to mirtazapine, but SYMBAD cannot tell us what has caused it. The improvement may be a function of the non-drug treatment-as-usual provided by old-age psychiatric and primary care services, or it could be part of the natural course of agitation in dementia. The latter is perhaps less likely given the observed persistence of agitation.<sup>7,80</sup> It might also be due in part to artefacts such as regression to the mean or the Hawthorne effect, though the magnitude of the effect means that these are unlikely to be the whole reason for the changes observed. In current systems, the data therefore suggest that waiting for a 6-week period (by which the improvement was noted), with reassessment following that might be a reasonable and safe course of action for agitation in dementia. A policy of such 'active monitoring' without the prescription of medication is recommended in the NICE guideline for depression as part of its stepped-care model for the treatment of depression in adults.<sup>81</sup> As with our earlier study of the treatment of depression in dementia (the HTA-SADD trial),<sup>28</sup> our data suggest that finding agitation in dementia may be an appropriate trigger for referral to specialist services in which detailed assessment can be completed and non-drug treatments and active monitoring deployed, perhaps avoiding the use of medication.

Our findings suggest that there is little reason to recommend the use of mirtazapine for people living with dementia who experience agitation. Effective and cost-effective medicinal management strategies for agitation in dementia are needed, particularly where non-pharmacological approaches have been unsuccessful, and for people with dementia and their carers living in community settings.

## Equality, diversity and inclusion

Attention was taken to ensure the inclusion of people with dementia and family carers at each stage of the research from design to reporting via our study specific PPIE group. We collected data on participants and our recruitment was designed to ensure the research sample is representative of the population the study is targeted at. We recruited from 26 geographically diverse areas across England and Northern Ireland, which were selected to be representative of the range of services in general. We designed the study so that it could be completed in any recruiting location with access to normal NIHR CRN support.

## Interpretation

The main message from this trial is that the NASSA, mirtazapine, one of the most widely prescribed antidepressants for older people, is no more effective than placebo in the treatment of agitation in dementia. The carbamazepine data, while limited and lacking statistical power provide no support for its use in agitation in dementia either. In terms of economic benefits, there appears no evidence for there being any value in the use of mirtazapine for agitation in dementia. Just as our clinical effectiveness data concluded there was no clinical benefit over placebo, these data are unequivocal in there being no economic reason for mirtazapine being used for the treatment of agitation in dementia. Costs to dyadic unpaid carers were higher in those receiving mirtazapine at 12 weeks, suggesting that the intervention could be associated with higher costs to unpaid carers.

The first line of management for agitation in dementia is a full assessment to identify if there is a modifiable cause for the behaviour. In all but the most urgent of situations, the next line is non-pharmacological treatment since such approaches have been shown to be at least as effective as drug treatment. The data from this study provide support for 'active monitoring' of agitation in dementia without the prescription of medication as recommended in guidelines for depression. Antipsychotics and SSRI antidepressants are associated with significant harms when used for the treatment of agitation in dementia. This study suggests that substituting the antidepressant mirtazapine in order to avoid such harms is not a clinically or cost-effective treatment strategy.



# Chapter 6 Conclusions

## Implications for health care

This study finds no evidence to support the use of mirtazapine as a treatment for people with agitation in dementia as many cases will resolve with usual care and without mirtazapine. An important exclusion to this is the most critical of cases (by reason, e.g. 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 in the community. The first step is provision of 'low-intensity psychosocial interventions' with more complex psychosocial interventions as an alternative to antidepressants at the next stage of severity. Those recruited into this trial had received non-drug treatment and also during the study received non-drug 'treatment as usual' provided largely 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 community psychiatric nurses, often in their own household. This will have focused on problems encountered by the person with dementia and the carer, covering aspects of dementia as well as agitation, 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 agitation 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 ARs.

The practical implications of this study are that we should reframe the way we think about the treatment of people with dementia who are agitated, as the evidence does not support the routine prescription of antidepressants for agitation in dementia. It suggests that potential cases might be more appropriately managed by specialist services that are able to offer non-drug interventions for agitation and case management, which may not be available in primary care. Based on the data (a decrease at 12 weeks and this then maintained), except for those for whom medication is indicated by risk or extreme severity, and in the absence of evidence to the contrary, it might be appropriate to refrain from prescribing for 12 weeks and only reconsider prescribing for those who have not 'responded' or recovered within that period. There is also no reason to support mirtazapine being the drug to be prescribed at that point in this trial.

Overall, this study adds to the evidence base that shows pharmacological interventions for agitation in dementia are limited in their effectiveness<sup>82,83</sup> and associated with significant risk of harm. The implications of this study are just that, with the minor limitations in generalisability noted above, that mirtazapine does not work in terms of clinical or cost-effectiveness. There are also reasons to be positive that 'treatment as usual' by current primary and secondary health care services may well enable people with agitation and dementia to recover from that agitation without the use of medication and its potential harms. Antipsychotics and SSRI antidepressants are associated with significant harms when used for the treatment of agitation in dementia. This study suggests that substituting the antidepressant mirtazapine in order to avoid such harms is not a clinically effective strategy.

Recommendations for research:

1. Given the multiple demonstrations of the clinical and cost-ineffectiveness of antidepressants in the treatment of agitation and depression in dementia and their high level of prescription alongside possible harm, a RCT of the effects of withdrawal of antidepressants in people with dementia who have been prescribed these drugs is needed.
2. Research into the overall effectiveness of community mental health services in the treatment of agitation would be useful along with analyses of what elements of care provided are effective in decreasing agitation.

## CONCLUSIONS

3. Further formulation and testing of stepped care protocols for agitation in dementia are needed to expand the limited advice in current NICE guidance.
4. Epidemiological work is needed on the natural history of symptoms of agitation in dementia in the community including those managed in primary care alone.
5. This trial covered probable and possible AD, further work is needed in dementia with a different aetiology.
6. Further work is needed to examine the heterogeneity of the syndrome of agitation in dementia and the extent to which blanket approaches to treatment such as the prescription of antidepressants and other sedative medication is appropriate for the syndrome as a whole.

This report shares data with the paper published in the *Lancet* presenting a summary of the findings reported here and reproduces some sections of that paper as well as the study protocol published under licence CC-BY-NC-ND.<sup>84</sup>



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## Publication

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## Ethics and regulatory approval

The study was approved by the Hampshire A South Central Research Ethics Committee (15/SC/0606), and the Medicines and Healthcare Products Regulatory Agency (Clinical Trial Authorisation Number: 58810/0001/001-0001).

### **Data-sharing statement**

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference. The Chief Investigator and trial statistician at NCTU will have access to the full trial data set. All data requests should be submitted to the corresponding author for consideration.

### **Disclaimers**

None.

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# Appendix 1 Summary of changes to the SYMBAD protocol

## Amendments made to protocol v1.1

Version 1.0 was considered a draft version and did not meet full trial requirements, the version submitted to ethics for initial approvals was v1.1. Therefore, changes made to v1.0 are numerous and not included here.

## Amendments made to protocol v1.2

1. Version and date details updated.
2. Exclusions criteria amended in line with MHRA comments; pages 3, 18–19.
3. New abbreviations added in line with amended text.
4. New section 4.1.7 added 'Risks and benefits' in line with MHRA discussions.
5. Safety blood and ECG testing and Columbia Suicide Rating Scale (C-SSRS) added as requested by MHRA; pages 20–21, 23–25, 29.
6. Clarification of week 16 phone call added in line with MHRA comments; pages 21, 25.
7. Expanded list of con-meds to be more specific, as requested by MHRA, new sections 5.4.8.1 and 5.4.8.2; pages 29, 30–31.
8. Amended wording for notification of SAEs to Clinical Trials Unit (CTU) from 'one working day' to 'within 24 hours'; pages 41, 43.
9. Approval of protocol amendments wording changed to clarify that competent authority and European Commission (EC) approval must be received before being implemented, where relevant. Page 46.

## Amendments made to protocol v1.3

1. Version and date details updated.
2. Minor typographical errors and amendments for consistency and clarity added throughout.
3. New abbreviations added in line with amended text.
4. TMG lists updated, there haven't been any changes to the groups themselves, but not all names were listed on the protocol when it was first produced.
5. CMAI questionnaire should be the Long Form and this has been updated throughout the protocol for clarity and *Appendix 3* has been amended to show the correct version; pages 11–12, 17, 19, 31.
6. The word 'tablet' has been changed to 'capsule' throughout the protocol, procedures haven't changed but as the product will be a capsule the wording has been made consistent for clarity; pages 10, 23, 26–29, 36.
7. In some places, the word 'bottle' had been used to describe packaging, as with point 6, this has been amended for clarity and consistency to packs/boxes as relevant; page 34.
8. Wording has been added to the participant timeline table (5.3.1) to clarify windows of acceptability for visits/tests and confirm that face-to-face visits may take place over more than one visit if required.
9. Window for acceptability of blood tests has been amended from 4 weeks to 28 days, to be consistent throughout all documents. Postdosing blood test window has been changed from 7 days to 28 days as requested by TMG, to aid compliance.
10. Stratifying has been changed from 'by centre' to 'by independent living' and text has been updated; pages 11, 33–34.

11. Safety e-mail address has been updated with the new contact details, the procedure remains the same, it's just the e-mail address that has been updated – recruitment hasn't started so this doesn't need to be immediately notified to sites.
12. This section (8) has been updated as there was no previous record of amendments.

### **Amendments made to protocol v1.4**

1. Version and date details updated.
2. The trial is now registered in the publicly accessible ISRCTN database, number added as the primary registry reference, page 10.
3. Inclusion criteria wording changed to make clear that dose of cholinesterase inhibitors and memantine must be stable, only if the patient is already on these medications. (Also updated on page 25.)
4. Exclusion criteria amended following cardiologists review; previously worded that atrioventricular block is always excluded, this has been clarified to exclude as follows: Patients with second-degree atrioventricular block (patients with third-degree heart block, with a pacemaker fitted, may be included at PI discretion). This exclusion has been given its own bullet point, for clarity. (Also updated on pages 21 and 25.)
5. Secondary outcome point 4 has been amended to reflect that AE data are collected from week 0 to week 16 and will be analysed as such (also updated on page 39).
6. Blood AEs should be graded according to the CTCAE criteria, to further operationalise the MHRA requirement for blood safety tests and reporting. The previous system for classifying AEs would not always be relevant to blood AEs, so text has been inserted to explain this new requirement. Text has been added in section 5.10.2.3 to clarify that a blood AE grade 3 or higher is a notifiable event and should be reported using a SAE form. CTCAE full reference has been added to the references in section 9.
7. Minor amendments for consistency and clarity have been added throughout, these include:
  - Page 13, Martin Knapp's affiliation changed to LSE.
  - Page 22, secondary objective 3 amended, removing 'patients' from this sentence, to show that the emphasis is on carers in this objective.
  - Page 23, clarity added on pilot phase recruitment period, in line with delayed start.
  - Page 24, section 5.1.2.1 PI agreement amended to reflect process for this trial.
  - Pages 27–29, minor clarity updates to information in table.
  - Page 31, clarity about the meaning of 'absence of symptoms'.
  - Page 32, section 5.3.5.8 defined long-term follow-up period.
  - Pages 41–45, minor clarity changes in statistical analysis section, including making clear that the statistics team are not blinded.
  - Page 46, SAE reporting previously defined as up to '30 days' after last IMP dose, changed to '4 weeks' to be consistent with other areas of the protocol.
  - Page 52, defined main trial closure and made clear that this is separate to long-term follow-up.

### **Amendments made to protocol v1.5**

1. Version and date details updated.
2. Removal of inclusion criteria; participants taking memantine or other cholinesterase inhibitors do not need to be on a stable dose of 3 months or more when trial drug is initiated.
3. Exclusion criteria amended following review, to align prohibited medications washout periods with normal clinical practice. For MAOIs, this should still be 2 weeks. Antidepressants (and MAOIs), anti-convulsants and antipsychotics are still prohibited medications during trial drug administration.
4. Absolute requirement for blood and ECG tests prior to trial medication being prescribed has been replaced with a recommendation for these tests to be carried out and a reasonable attempt should be made to collect them in all cases. If this is not possible, PI judgement should be used. Text referring to this has been amended throughout the protocol, including table in section 5.3.4.

5. Wording added regarding approval for recruitment from Participant Identification Centres, which may also include GP practices.
6. Wording added to give clarity to what a treatment interruption is and appropriate circumstances for a participant to continue in the trial after a break in treatment.
7. Minor amendments for consistency and clarity, these include:
  - Clearer wording on who receives randomisation e-mails and who receives semi-blinded treatment allocation e-mails.
  - Section 5.3.4, participant timeline, clarifications added on interpretation of baseline visit window, for greater consistency across sites.

## Amendments made to protocol v2.0

This version of the protocol is for a re-designed two-arm study, continuing with the existing study set-up and patients recruited to date, but with no further patients being recruited to the carbamazepine arm and a statistical re-design to reflect the requirements of the change to two-arm.

1. Version and date details updated.
2. Removal of references to carbamazepine throughout, including change of title.
3. Exclusion criteria 'patients with a history of bone marrow depression or history of hepatic porphyrias' removed as this risk related only to carbamazepine.
4. Exclusion criteria related to prohibited concomitant medications updated to remove anticonvulsants as these were only prohibited with carbamazepine.
5. Outcomes and objectives have small amendments to reflect new main analyses.
6. Update to introduction and background, to remove carbamazepine-specific information and references.
7. Trial diagram updated to reflect two-arm design.
8. Study will now open to recruitment in more locations, text added to reflect this throughout.
9. Participant timeline (page 27) updated for clarity and to reflect that all future visits are calculated from the week 0 dispensing visit (to match practice and the rest of the protocol).
10. Clarity added that week 16 phone call is not required where patients stopped trial medication prior to week 8, but that a call is required within 4 weeks of stopping trial medication (pages 29, 32).
11. Pharmacy review of medicines no longer requiring additional monitoring at removal of carbamazepine and addition of a few others for mirtazapine, to reflect current standard practice (list is not exhaustive and these changes should have been considered by clinicians prior to this update).
12. Sample size and statistical considerations updated to reflect requirements of two-arm trial and change to 80% power with 10% attrition rate.
13. Reference to GDPR included, to reflect change in law.
14. Archive period clarified as 10 years throughout (sponsor decision as current trial documents have a variety of dates, all will be made consistent with this).
15. Health economics analysis more clearly demarcated from statistical section but no change of procedures.
16. Minor changes for consistency and clarity in the safety reporting section, no change of procedures.



## Appendix 2 Recruitment by site and by month

Number of participants reported refers to patient-carer dyads in this trial. Names of sites were accurate at the time of recruitment.

### ***Sussex Partnership NHS Foundation Trust (34 patients, opened 15 December 2016)***

Naji Tabet (PI), Andrew Risbridger, Gosia Raczek, Richard Hoile, Andrea Meredith, Angela Ozduran, Elise Armsby, Keren Teichmann, Kim McCabe, Marcela Carvajal, Natalie Portwine, Rachel Russell, Sam Holden, Sharne Berwald, Tamsin Eperson, Yvonne Feeney. Pharmacy: James Atkinson, Jed Hewitt, Nana Tomova, Sinead Clarke-O'Neill

### ***Norfolk and Suffolk NHS Foundation Trust (16 patients, opened 15 December 2016)***

Chris Fox (PI), Heather Cooke, Nigel Gill, Caroline Sheldon, Claire Rischmiller, Kim Clipsham, Zoe Inman. Pharmacy: Dennis Liew

### ***Gateshead Health NHS Foundation Trust (36 patients, opened 15 December 2016)***

Alan Thomas (PI), Karen Franks, Bryony Storey, Elaine Siddle. Pharmacy: David Sproates

### ***Greater Manchester Mental Health NHS Foundation Trust (13 patients, opened 19 December 2016)***

Ross Dunne (PI), Iracema Leroi (previous PI), Alistair Burns, Clare Smith, Preeti Tekur, Anita Davies, Dee Leonard, Emma Oughton, Lewis Harpin, Phillip Tinkler, Rebecca Davies, Robert Bedford, Selina Sonola. Pharmacy: Maxine Syme

### ***Camden and Islington NHS Foundation Trust (28 patients, opened 13 January 2017)***

Gill Livingston (PI), Rob Howard, Alessandro Borca, Beena Bauluck, Liam Pikett, Narin Aker. Pharmacy: Jonathan Flor, Silvia Ceci

### ***Birmingham and Solihull Mental Health NHS Foundation Trust (29 patients, opened 16 December 2016)***

Peter Bentham (PI), Abdul Patel, Analisa Smythe, Di Baines, Jan Wright, Jane Dyer. Pharmacy: Akram Ali, Nigel Barnes

### ***Cambridgeshire and Peterborough NHS Foundation Trust (nine patients, opened 16 December 2016)***

Annabel Price (PI), Catherine Hatfield, Catherine Inkley, Julie Philips, Naomi Thomas. Pharmacy: Christine Rowe

### ***Surrey and Borders Partnership NHS Foundation Trust (17 patients, opened 15 December 2016)***

Ramin Nilforooshan (PI), Brian Parsons, Gareth O'Leary, George Shaya, Jessica True, Mariana Gavrilla, Sally Gosling. Pharmacy: Sam Francis

### ***Devon Partnership NHS Trust (24 patients, opened 12 July 2017)***

Clive Ballard, Carol Bannister (previous PI), Joseph Butchart, Simona Brown, Amanda Henderson, Anna Grice, Olga Borejko, Sarah Broom, Stacey Horne, Sue Dyson

***Barnet Enfield and Haringey Mental Health NHS Trust (four patients, opened 28 November 2017)***

Elizabeth Sampson (PI), Ayesha Dar, Luiza Grycuk, Serafeim Papakostas, Tom Freeth. Pharmacy: Neil Spencer, Helen Tsegay-Seyoum

***Bradford District Care NHS Foundation Trust (two patients, opened 15 January 2019)***

Sushanth Kamath (PI), Gregor Russell, Nasir Khan, Jason Cook, Sarah Kirkland, Zarina Mirza. Pharmacy: Jaspreet Sohal, Edward Sykes

***Midlands Partnership NHS Foundation Trust (two patients, opened 18 March 2019)***

Rashi Negi (PI), Caroline Wnkle, Sajeev Kshemendran, Lucy Hamilton, Paula Coventry, Susan Lavendar. Pharmacy: Rachel Walsh

***Dudley and Walsall Mental Health Partnership NHS Foundation Trust (now Black Country Healthcare NHS Foundation Trust, three patients, opened 13 February 2019)***

Udaya Balakrishna (PI), Dee Gayan, Sharada Abilash, Aurora Balalia. Pharmacy: Lisa Stanton

***South West London and St George's Mental Health NHS Trust (six patients, opened 30 January 2019)***

Robert Lawrence (PI), Heloise Mongue-Din, Na'ilah Firdaws. Pharmacy: Seema Shah

***2Gether NHS Foundation Trust (now Gloucestershire Health and Care NHS Foundation Trust, one patient, opened 24 January 2019)***

Emma Abbey (PI), Marelle Harvey, Sarah Little. Pharmacy: Bethan Cartwright

***South West Yorkshire Partnership NHS Foundation Trust (no patients recruited, opened 4 April 2019)***

Suba Thiyagesh (PI), Amber Hemingway, Lisa Horner, Mark Harper, Wajid Khan. Pharmacy: Mark Payne, Peter Bermingham

***Central and North West London NHS Foundation Trust (seven patients, opened 8 March 2019)***

Erum Nomani (PI), Desiree Fyle, Narin Aker. Pharmacy: Nawal Arif, Shradha Patel

***Northamptonshire Healthcare NHS Foundation Trust (two patients, opened 27 August 2019)***

Paul Koranteng (PI), Chetan Lakhani, Sharon Aujla. Pharmacy: Alpa Patel

***Coventry and Warwickshire Partnership NHS Trust (one patient, opened 4 April 2019)***

Demi Onalaja (PI), Emily Benson, Nyaradzo Nyamayaro. Pharmacy: Wendy Roughan

***Sheffield Health and Social Care NHS Foundation Trust (five patients, opened 9 May 2019)***

Aparna Mordekar (PI), Janet Hutchinson, Katherine Mewton, Poovanna Pemmaiah, Hannah Gower. Pharmacy: Shrewti Moerman



**Leicestershire Partnership NHS Trust (four patients, opened 11 March 2019)**

Matthew Noble (PI), Matthew Critchfield (previous PI), Iain Termie, Sarah Ballion. Pharmacy: Robyn McAskill

**Kings College Hospital NHS Foundation Trust (two patients, opened 15 October 2019)**

Adenike Dare (PI), Fabio Speranza, Shaula Candido. Pharmacy: Kam Sahota

**Worcestershire Health and Care NHS Trust (no patients recruited, opened 10 June 2019)**

Dhanjeev Marrie (PI), Sinha Tandrila, Angela Hoadley, Harriet Davies, Remi George. Pharmacy: Amanda Critchley

**The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust (now University Hospitals Dorset NHS Foundation Trust, no patients recruited, opened 10 July 2019)**

Divya Tiwari (PI), Emma Gunter. Pharmacy: Cathy Howe

**Rotherham Doncaster and South Humber NHS Foundation Trust (one patient, opened 8 August 2019)**

Oluwafemi Adio (PI), Kevin Williamson, Helen Oldknow, Ken Hindle-May. Pharmacy: Steve Davies

**Belfast Health and Social Care Trust (no patients recruited, opened 18 September 2019)**

Bernadette McGuinness (PI), Alison Clinton, Debbie Rainey, Nicola Milligan. Pharmacy: Peter Gray

PIC sites assisting with recruitment included the following:

**South East England:** Care Homes: Autumn Lodge (Care home), Weald Hall (Care home), Windlesham Manor (Care home), Havelock House (Care home), Garland House (Care home), Birchwood House (Care home), Beaconsfield Medical Practice (GP), Preston Park Surgery (GP), Stanford Medical Centre (GP), Warmdene Surgery (GP), Poundhill Medical Group (GP), Parklands Surgery (GP), Furnace Green Surgery (GP), Charter Medical Centre (GP), Brighton Health and Wellbeing Centre (GP), Trinity Medical Centre (GP), Benfield Valley Healthcare Hub (GP), Park Surgery (GP), St John's Practice (GP), Maidstone and Tunbridge Wells NHS Trust (MTW), Brighton and Sussex University Hospital (BSUH), Kent and Medway NHS Social Care Partnership Trust (KMPT).

**East England:** Hoveton and Wroxham Medical Centre (GP), Cambridge University Hospitals Trust

**North East England:** Tees, Esk and Wear Valley NHS Trust (TEWV), Newcastle Tyne and Wear NHS Trust (NTW) and Northumbria Healthcare NHS Trust (NHCT)

**Northwest England:** Pennine Care NHS Foundation Trust

**South West England:** Dorset Healthcare NHS Trust (linked with King's College London).



## Appendix 3 SYMBAD adverse events and severe adverse events by randomisation group

TABLE 35 SYMBAD adverse events and severe adverse events – mirtazapine

System organ class	Adverse event	Serious
Cardiac disorders (2)	Atrioventricular block (1)	
	Angina pectoris (1)	
Gastrointestinal disorders (23)	Abdominal pain (2)	
	Anal incontinence (1)	
	Constipation (4)	
	Diarrhoea (1)	
	Dry mouth (1)	
	Dyspepsia (1)	
	Faecaloma (1)	
	Gastric dilatation (1)	
	Haematochezia (1)	
	Mouth ulceration (1)	
	Nausea (1)	
	Salivary hypersecretion (2)	
	Toothache (1)	
	Vomiting (5)	
	General disorders and administration site conditions (14)	Crepitations (1)
Death (3)		(2)
Fatigue (2)		
Gait disturbance (2)		
Oedema (2)		
Peripheral swelling (1)		
Pyrexia (1)		
Swelling face (1)		
	Swelling; contusion (1)	

continued

TABLE 35 SYMBAD adverse events and severe adverse events – mirtazapine (continued)

System organ class	Adverse event	Serious	
Infections and infestations (25)	Infection (1)	(1)	
	Influenza (1)		
	Low respiratory tract infection (5)		
	Nasopharyngitis (6)		
	Pneumonia (1)	(1)	
	Sepsis (1)		
	Urinary tract infection (9)	(1)	
	Vulvovaginal candidiasis (1)		
Injury, poisoning and procedural complications (28)	Accidental overdose (2)		
	Fall (24)	(3)	
	Femoral neck fracture (1)		
	Forearm fracture (1)		
Investigations (12)	Blood alkaline phosphatase increased (1)		
	Blood creatinine increased (1)		
	Blood urea abnormal (1)		
	Electrocardiogram qt prolonged (1)		
	Gamma GT increased (1)		
	Glomerular filtration rate decreased (1)		
	Mean cell volume abnormal (1)		
	Oxygen saturation decreased (1)		
	Platelet count increased (1)		
	Protein total decreased (1)		
	Weight decreased (1)		
	Weight increased (1)		
	Metabolism and nutrition disorders (9)	Decreased appetite (3)	
		Dehydration (1)	(1)
Fluid intake reduced (1)			
Hyperglycaemia (1)			
Increased appetite (3)			
Musculoskeletal and connective tissue disorders (9)	Arthralgia (1)		
	Back pain (2)		
	Joint swelling (1)		
	Muscular weakness (1)		
	Musculoskeletal pain (1)		
	Neck pain (1)		
	Posture abnormal (2)		

TABLE 35 SYMBAD adverse events and severe adverse events – mirtazapine (continued)

System organ class	Adverse event	Serious	
Nervous system disorders (29)	Depressed level of consciousness (1)		
	Dizziness (1)		
	Drooling (1)		
	Facial paralysis (1)		
	Headache (1)		
	Lethargy (8)		
	Sedation (1)		
	Somnolence (14)		
	Syncope (1)		
	Psychiatric disorders (45)	Abnormal behaviour (1)	
		Abnormal dreams; sleep talking (2)	
Aggression (5)			
Agitation (12)			
Anxiety (3)			
Confusional state (3)			
Delusion (1)			
Depression (2)			
Depressed mood (1)			
Hallucination (2)			
Insomnia (2)			
Irritability (1)			
Mood altered (2)			
Panic attack (1)			
Restlessness (5)			
Sleep disorder (2)			
Renal and urinary disorders (8)		Pollakiuria (2)	
	Renal impairment (2)	(1)	
	Urinary incontinence (4)		
Reproductive system and breast disorders (1)	Genital prolapse (1)		
Respiratory, thoracic and mediastinal disorders (11)	Choking (1)	(1)	
	Chronic obstructive pulmonary disease (1)		
	Cough (3)		
	Dyspnoea (3)		
	Pleural effusion (1)		
	Pleuritic pain (1)		
	Pneumonia aspiration (1)	(1)	

**TABLE 35** SYMBAD adverse events and severe adverse events – mirtazapine (*continued*)

System organ class	Adverse event	Serious
Skin and subcutaneous tissue disorders (4)	Decubitus ulcer (1)	
	Eczema (1)	
	Skin disorder (1)	
	Skin lesion (1)	
Social circumstances (1)	Bedridden (1)	
Surgical and medical procedures (1)	Hospitalisation (1)	(1)
Vascular disorders (2)	Aortic aneurysm (1)	
	Hypertension (2)	

**TABLE 36** SYMBAD adverse events and severe adverse events – placebo

System organ class	Adverse event	Serious
Blood and lymphatic system disorders (1)	Anaemia (1)	
Cardiac disorders (1)	Bradycardia (1)	
Ear and labyrinth disorders (1)	Excessive cerumen production (1)	
Gastrointestinal disorders (18)	Abdominal pain (1)	
	Constipation (7)	(2)
	Diarrhoea (4)	
	Duodenogastric reflux (3)	
	Nausea (1)	
	Vomiting (2)	
General disorders and administration site conditions (10)	Abasia (1)	(1)
	Chest pain (2)	(2)
	Death (1)	(1)
	Fatigue (1)	
	Gait disturbance (1)	
	Malaise (2)	(1)
	Peripheral swelling (1)	
	Swelling; contusion (1)	(1)
Infections and infestations (30)	Bacterial infection (1)	
	Cellulitis (1)	
	COVID-19 (1)	
	Fungal infection (1)	
	Low respiratory tract infection (7)	(1)
	Omphalitis (1)	
	Oral candidiasis (1)	
	Pneumonia (2)	(1)
	Urinary tract infection (15)	(3)

TABLE 36 SYMBAD adverse events and severe adverse events – placebo (continued)

System organ class	Adverse event	Serious
Injury, poisoning and procedural complications (33)	Fall (24)	(4)
	Femoral neck fracture (1)	
	Hip fracture (4)	(4)
	Humerus fracture (1)	(1)
	Joint injury (1)	
	Laceration (1)	
	Skin injury (1)	
Investigations (12)	Alanine aminotransferase increased (1)	
	Blood alkaline phosphatase increased (1)	
	Blood creatinine decreased (1)	
	C-reactive protein increased (1)	(1)
	Gamma GT increased (2)	
	Haemoglobin decreased (1)	
	Neutrophil count increased (1)	(1)
	Protein urine present (1)	
	Red blood cell count decreased (2)	
	White blood cell count increased (1)	(1)
Metabolism and nutrition disorders (5)	Decreased appetite (4)	
	Increased appetite (1)	
Musculoskeletal and connective tissue disorders (6)	Arthralgia (1)	
	Mobility decreased (2)	(1)
	Musculoskeletal stiffness (1)	
	Pain in extremity (2)	
Nervous system disorders (29)	Altered state of consciousness (1)	
	Dementia (1)	(1)
	Depressed level of consciousness (1)	(1)
	Dizziness (5)	(1)
	Hypersomnia (1)	
	Lethargy (4)	
	Somnolence (16)	
		continued

**TABLE 36** SYMBAD adverse events and severe adverse events – placebo (*continued*)

System organ class	Adverse event	Serious
Psychiatric disorders (33)	Abnormal dreams; sleep talking; nightmares (1)	
	Aggression (4)	(1)
	Agitation (11)	(1)
	Anxiety (1)	
	Confusional state (5)	(1)
	Insomnia (2)	
	Irritability (1)	
	Restlessness (4)	
	Sleep disorder (1)	
	Suicidal behaviour (1)	(1)
	Tearfulness (2)	
Respiratory, thoracic and mediastinal disorders (5)	Cough (2)	
	Dyspnoea (2)	(1)
	Epistaxis (1)	
	Blister (1)	(1)
Skin and subcutaneous tissue disorders (6)	Pruritus (2)	
	Rash (3)	
	Haematoma (1)	
Vascular disorders (2)	Pallor (1)	

**TABLE 37** SYMBAD adverse events and severe adverse events – carbamazepine

System organ class	Adverse event	Serious
Eye disorders (1)	Exophthalmos (1)	
Gastrointestinal disorders (16)	Abdominal pain (2)	
	Constipation (2)	
	Diarrhoea (4)	
	Gastric haemorrhage (1)	
	Nausea (3)	
	Oral pain (1)	
	Salivary hypersecretion (1)	
	Vomiting (2)	
General disorders and administration site conditions (5)	Fatigue (1)	
	Gait disturbance (1)	
	General physical health deterioration (1)	
	Malaise (1)	
	Oedema (1)	



TABLE 37 SYMBAD adverse events and severe adverse events – carbamazepine (continued)

System organ class	Adverse event	Serious
Infections and infestations (15)	Cellulitis (2)	
	Fungal infection (1)	
	Herpes zoster (1)	
	Low respiratory tract infection (2)	
	Nasopharyngitis (2)	
	Urinary tract infection (7)	(1)
Injury, poisoning and procedural complications (11)	Fall (9)	
	Hip fracture (1)	(1)
	Laceration (1)	
Investigations (28)	Blood albumin decreased (1)	(1)
	Blood alkaline phosphatase increased (2)	
	Blood creatinine increased (2)	
	Blood urea increased (2)	
	Blood test abnormal (5)	(2)
	Electrocardiogram qt prolonged (1)	
	Gamma GT increased (1)	(1)
	Glomerular filtration rate decreased (2)	
	Haemoglobin decreased (1)	(1)
	Neutrophil count increased (1)	
	Red blood cell count decreased (1)	(1)
White blood cell count increased (1)		
Weight decreased (8)		
Metabolism and nutrition disorders (1)	Diabetes mellitus inadequate control (1)	
Nervous system disorders (11)	Dysarthria (1)	
	Headache (1)	
	Lethargy (2)	
	Somnolence (7)	
Psychiatric disorders (8)	Aggression (1)	
	Agitation (6)	
	Restlessness (1)	
Renal and urinary disorders (2)	Incontinence (1)	
	Renal impairment (1)	(1)
Respiratory, thoracic and mediastinal disorders (5)	Chronic obstructive pulmonary disease (1)	(1)
	Dyspnoea (3)	
	Rhinorrhoea (1)	
Skin and subcutaneous tissue disorders (1)	Skin ulcer (1)	
Surgical and medical procedures (2)	Hospitalisation (2)	(1)



## Appendix 4 Unit costs

Item	Unit cost (£, 2016–17)	Unit	Source	Notes/assumptions
Living and accommodation expenses				
Private sector residential care for older people	94	Day	Unit Costs of Health and Social Care 2017, table 1.2 <sup>54</sup>	Includes personal living expenses
LA residential care for older people	162	Day	Unit Costs of Health and Social Care 2017, table 1.3 <sup>54</sup>	Includes personal living expenses
Private sector nursing home for older people	119	Day	Unit Costs of Health and Social Care 2017, table 1.1 <sup>54</sup>	Includes personal living expenses
Domestic accommodation	239.7	Week	ONS household expenditure: table A17	Living Costs and Food Survey data. All retired households. Includes: food and non-alcoholic drinks, alcoholic drinks, tobacco and narcotics, clothing and footwear, housing (net), fuel and power, household goods and services, health, transport, communication, recreation and culture, education, restaurants and hotels, miscellaneous goods and services. Housing spend is net of mortgage interest payments and council tax
Sheltered accommodation	302.0	Week	Unit Costs of Health and Social Care 2017, table 1.6	Cost of extra care housing. Includes housing management and support, accommodation and living expenses
Community health and social care services				
GP time, home visit	88	Visit	Unit Costs of Health and Social Care 2017, table 10.3b; Unit Costs of Health and Social Care 2013, table 10.3b <sup>54</sup>	Ratio of clinic to home cost minute and average duration of visit in 2013 UC table 10.3b. Assumes average home visit duration of 23.4 minutes
GP time, surgery	28	Visit	Unit Costs of Health and Social Care 2017, table 10.3b <sup>54</sup>	No direct care staff and no qualification costs, surgery consultation of 9.22 minutes
Practice nurse, face-to-face time	9.30	Consultation	Unit Costs of Health and Social Care 2017, table 10.2 <sup>54</sup>	15.5-minute consultation. Excludes qualification costs
Community nursing time	0.73	Minute	Unit Costs of Health and Social Care 2017, table 10.1 <sup>54</sup>	Assumes AfC band 6
Community nursing time	37	Contact	NHS Reference Costs 2016/17 <sup>55</sup>	CHS tab
Specialist nursing	Range: 65–89	Contact	NHS Reference Costs 2016/17 <sup>55</sup>	CHS tab
Nurse (mental health) time	44	Contact	Unit Costs of Health and Social Care 2017, table 12.1	Average visit of 60 minutes in community mental health teams for older people

continued

Item	Unit cost (£, 2016–17)	Unit	Source	Notes/assumptions
Consultant: Psychiatrist time	1.8	Minute	Unit Costs of Health and Social Care 2017, table 15	Excludes qualification costs
Consultant: Neurologist time	1.8	Minute	Unit Costs of Health and Social Care 2017, table 15	Cost of medical consultant. Excludes qualification costs
Consultant: Geriatrician time	1.8	Minute	Unit Costs of Health and Social Care 2017, table 15	Cost of medical consultant. Excludes qualification costs
Social worker, face-to-face time	59	Visit	Unit Costs of Health and Social Care 2017, table 11.2 <sup>54</sup>	Excludes qualification costs. One hour of client-related work
Social worker, face-to-face time	0.98	Minute	Unit Costs of Health and Social Care 2017, table 11.2 <sup>54</sup>	Excludes qualification costs. One hour of client-related work
Physiotherapist	53	Contact	NHS Reference Costs 2016/17 <sup>55</sup>	CHS tab
NHS occupational therapist	76.73	Contact	NHS Reference Costs 2016/17 <sup>55</sup>	CHS tab
NHS community mental health team (CMHT) worker for older people (OP) with mental health problems, team member	44	Contact	Unit Costs of Health and Social Care 2017, table 12.1	Average visit of 60 minutes in community mental health teams for older people
Counselling services in primary care	0.87	Minute	Unit Costs of Health and Social Care 2014, table 2.7	
Counselling services in primary care	47.70	Consultation	Unit Costs of Health and Social Care 2014, table 2.7	55-minute visit
Home care – average of independent and social services	0.44	Minute	Unit Costs of Health and Social Care 2017, table 11.6 <sup>54</sup>	Face-to-face time: average cost of private and Social Services costs; weighted average of weekday and weekend costs
Home care – average of independent and social services	13.21	Contact	Unit Costs of Health and Social Care 2017, table 11.6 <sup>54</sup>	Face-to-face time: average cost of private and Social Services costs; weighted average of weekday and weekend costs. Assumes 30-minute visit
Cleaner	£20	Visit	Commercial websites	Internet search. Assumes 2-hour visit
Meals on Wheels	6	Meal	Unit Costs of Health and Social Care 2014, table 8.1.1 <sup>85</sup>	Uprated with HCHS Pay & Prices Index <sup>54</sup>
Sitting service i.e. Crossroads Carer support worker	45	Visit	Banks and Barnes <sup>86</sup>	Short break for carers, 2.5 hours. Uprated with HCHS Pay & Prices Index
Day care for older people	63	Session	Unit Costs of Health and Social Care 2017, table 1.4 <sup>54</sup>	

Item	Unit cost (£, 2016–17)	Unit	Source	Notes/assumptions
Day care in NHS facilities	132.23	Attendance	NHS Reference Costs 2016/17 <sup>55</sup>	CHS tab
Day care for people with mental health problems	34	Session	Unit Costs of Health and Social Care 2017, table 2.4 <sup>54</sup>	
Lunch club	8	Session	Romeo <i>et al.</i> <sup>87</sup>	Uprated with HCHS Pay & Prices Index
Alternative therapies: Osteopath, Yoga, Tai Chi, Naturopath	Range: 8.2–62.3	Session	Hartfiel, Clarke <i>et al.</i> , <sup>88</sup> General Osteopathic Council, <sup>89</sup> commercial websites	Internet search. Items that were sourced from internet searches were deflated using the Consumer Price Index <sup>90</sup>
Education group	9.0	Session	Dementia Self-Management Programme <sup>91</sup>	
Support/expert relative groups	3.1	Session	Community memory café run by voluntary sector <sup>92</sup>	Uprated with HCHS Pay & Prices Index
Equipment and adaptations				
Various:	Range: 1.10–614.00	Item, per annum	Unit Costs of Health and Social Care 2017, table 7.2 <sup>54</sup> PSSRU unit costs 2013, table 7.3.1; commercial websites	Unit Costs Compendium and internet search Annuitised over 5 years (electronic items) or 10 years (non-electronic items) Cost of the item was calculated for the relevant retrospective period (12 weeks at baseline, 6 weeks at 6 and 12-week follow-up); items that were sourced from internet searches were deflated using the Consumer Price Index <sup>90</sup>
<ul style="list-style-type: none"> <li>• bath lift</li> <li>• bath seat</li> <li>• bath steps</li> <li>• bed raisers</li> <li>• calendar clock</li> <li>• CO monitor</li> <li>• commode</li> <li>• continence pads</li> <li>• door entry sensor</li> <li>• falls alarm</li> <li>• hospital bed</li> <li>• key safe</li> <li>• key trackers</li> <li>• kitchen trolley</li> <li>• mattress elevator</li> <li>• outdoor rail</li> <li>• outdoor ramp</li> <li>• overbath shower</li> <li>• perching stool</li> <li>• riser recliner chair</li> <li>• stair/grab rail</li> <li>• stairlift</li> <li>• toilet equipment</li> <li>• walk-in shower</li> <li>• walking frame</li> <li>• walking stick</li> </ul>				
Medications				
Various	Range: 0.01–225.72	Standard quantity units	Prescription cost analysis, England <sup>53</sup>	
Unpaid carer costs				
National average wage – value of lost work time	16.20	Hour	Annual survey of hours and earnings tables <sup>58</sup>	Gross mean wage for all employee jobs, 2017
National average wage – value of lost leisure time	5.67	Hour	Annual survey of hours and earnings tables <sup>58</sup>	35% of gross mean wage for all employee jobs, 2017

continued

Item	Unit cost (£, 2016–17)	Unit	Source	Notes/assumptions
Hospital services				
A&E attendances, weighted average of admitted and non-admitted attendances	148.36	Attendance	NHS Reference Costs 2016/17 <sup>55</sup>	EM tab
Inpatients				
Subchapter AA: Nervous System Procedures and Disorders	477.75 295.42	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter CB: Ear, Nose, Mouth, Throat and Neck Disorders	521.46 295.1	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter DZ: Respiratory System Procedures and Disorders	402.23 271.11	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter EB: Cardiac Disorders	452.02 291.01	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter EY: Interventional Cardiology for Acquired Conditions	820.12 383.32	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter FD: Digestive System Disorders	452.79 294.18	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter HE:	436.19 276.32	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter HN: Orthopaedic Non-Trauma Procedures	731.69 325.66	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter JD:	433.25 280.84	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter LA: Renal Procedures and Disorders	415.24 272.35	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter LB: Urological and Male Reproductive System Procedures and Disorders	505.19 304.76	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter SA: Haematological Procedures and Disorders	549.53 349.89	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter VC: Rehabilitation	362.06	Day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab
Subchapter WD: Treatment of Mental Health Patients by Non-Mental Health Service Providers	356.25 264.04	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab

Item	Unit cost (£, 2016–17)	Unit	Source	Notes/assumptions
Subchapter WH: Poisoning, Toxic Effects, Special Examinations, Screening and Other Healthcare Contacts	440.99 274.22	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Subchapter WJ:	439.00 287.38	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Inpatients, weighted average across specialities	645 299	Day Excess day	NHS Reference Costs 2016/17 <sup>55</sup>	NEL tab NEL_XS tab
Mental health inpatient stay	451.73	Day	NHS Reference Costs 2016/17 <sup>55</sup>	MHCC tab, weighted average for clusters 18–21, cognitive impairment
Day cases				
Subchapter BZ: Eyes and Periorbita Procedures and Disorders	825.04	Day	NHS Reference Costs 2016/17 <sup>55</sup>	DC tab
Subchapter DZ: Respiratory System Procedures and Disorders	606.65	Day	NHS Reference Costs 2016/17 <sup>55</sup>	DC tab
Subchapter FD:	313.72	Day	NHS Reference Costs 2016/17 <sup>55</sup>	DC tab
Subchapter HE:	553.28	Day	NHS Reference Costs 2016/17 <sup>55</sup>	DC tab
Outpatients				
Service code 101: Urology	102.88	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 103: Breast Surgery	130.51	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 107: Vascular Surgery	141.35	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 110: Trauma and Orthopaedics	109.78	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 120: ENT	87.94	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 130: Ophthalmology	82.93	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 141: Restorative Dentistry	123.26	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 301: Gastroenterology	138.29	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs

continued

Item	Unit cost (£, 2016–17)	Unit	Source	Notes/assumptions
Service code 304: Clinical Physiology	72.41	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 307: Diabetic Medicine	141.00	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 320: Cardiology	117.34	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 324: Anticoagulant Service	30.04	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 330: Dermatology	98.36	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 340: Respiratory Medicine	144.26	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 361: Nephrology	148.53	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 370: Medical Oncology	163.93	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 400: Neurology	149.30	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 430: Geriatric Medicine	194.56	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 653: Podiatry	41.87	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 715: Old Age Psychiatry	179.66	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 800: Clinical Oncology (Previously Radiotherapy)	126.39	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 812: Diagnostic Imaging	80.65	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Service code 840: Audiology	87.04	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs
Memory clinic	406.45	Follow-up att.	Unit Costs of Health and Social Care 2014, table 1.10 <sup>85</sup>	Uprated using HCHS Pay & Prices Index <sup>54</sup>
Weighted average of follow-up attendances across service codes	105.52	Follow-up att.	NHS Reference Costs 2016/17 <sup>55</sup>	Consultant and non-consultant-led follow-up face-to-face attendances, CL and NCL tabs

CL, consultant-led; EM, emergency medicine; NCL, non-consultant-led





EME  
HSDR  
**HTA**  
PGfAR  
PHR

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