Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial

Sube Banerjee, Juliet High, Susan Stirling, Lee Shepstone, Ann Marie Swart, Tanya Telling, Catherine Henderson, Clive Ballard, Peter Bentham, Alistair Burns, Nicolas Farina, Chris Fox, Paul Francis, Robert Howard, Martin Knapp, Iracema Leroi, Gill Livingston, Ramin Nilforooshan, Shirley Nurock, John O'Brien, Annabel Price, Alan J Thomas, Naji Tabet

Summary

Background Agitation is common in people with dementia and negatively affects 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 care is not effective. Current evidence is sparse on safer and effective alternatives to antipsychotics. We assessed the efficacy and safety of mirtazapine, an antidepressant prescribed for agitation in dementia.

Methods This parallel-group, double-blind, placebo-controlled trial—the Study of Mirtazapine for Agitated Behaviours in Dementia trial (SYMBAD)—was done in 26 UK centres. Participants had probable or possible Alzheimer's disease, agitation unresponsive to non-drug treatment, and a Cohen-Mansfield Agitation Inventory (CMAI) score of 45 or more. They were randomly assigned (1:1) to receive either mirtazapine (titrated to 45 mg) or placebo. The primary outcome was reduction in CMAI score at 12 weeks. This trial is registered with ClinicalTrials.gov, NCT03031184, and ISRCTN17411897.

Findings Between Jan 26, 2017, and March 6, 2020, 204 participants were recruited and randomised. Mean CMAI scores at 12 weeks were not significantly different between participants receiving mirtazapine and participants receiving placebo (adjusted mean difference –1·74, 95% CI –7·17 to 3·69; p=0·53). The number of controls with adverse events (65 [64%] of 102 controls) was similar to that in the mirtazapine group (67 [66%] of 102 participants receiving mirtazapine). However, 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 difference was of marginal statistical significance (p=0·065).

Interpretation This trial found no benefit of mirtazapine compared with placebo, and we observed a potentially higher mortality with use of mirtazapine. The data from this study do not support using mirtazapine as a treatment for agitation in dementia.

Funding UK National Institute for Health Research Health Technology Assessment Programme.

Introduction

Dementia is one of the most common and serious public health issues of our time.[1] Over 46 million people have dementia worldwide, a figure set to double in the next 20 years.[2] The most common cause of dementia is Alzheimer's disease; Alzheimer's disease causes irreversible and progressive decline in memory, reasoning, communication skills, and the ability to undertake daily activities. Alongside this cognitive and functional decline, individuals may develop neuro-psychiatric symptoms, such as agitation, sleep disturbance, depression, and psychosis.[3] These symptoms are common, occurring in up to 90% of people with dementia, with agitation being one of the most persistent symptoms.[4] Agitation is defined as inappropriate verbal, vocal, or motor activity that is not thought to be caused by an unmet need; it encompasses physical and verbal aggression and is particularly problematic.[5] It affects nearly half of people with Alzheimer's disease over a month,[6] and 80% of those with clinically significant symptoms still have them 6 months later.[7] 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.[5,7,8]

Agitation in dementia is therefore a legitimate target for therapeutic intervention, but it has a number of possible causes, including pain, physical or psychological distress, misperception of threat (for example during personal care), and response to hallucinations or delusions. Use of non-pharmacological interventions that investigate cause and provide a tailored response as a first-line treatment for agitation in dementia, such as the DICE approach (Describe the

Newcastle University, Newcastle upon Tyne, UK
(Prof A J Thomas PhD)

Correspondence to:
Prof Sube Banerjee, Faculty of Health, University of Plymouth, Plymouth PL4 8AA, UK
sube.banerjee@plymouth.ac.uk

Research in context

Evidence before this study

We searched PubMed and the Cochrane Library databases from inception up to Feb 19, 2021, using the terms "(dement* OR Alzheimer)" and "(agitat* OR aggress*)" and "(RCT OR random*)". Only studies that had a pharmacological treatment arm and an outcome measure of agitation or aggression in people with dementia were included. Studies were required to be randomised controlled trials, or reviews and systematic reviews that reported the results of these trials. There were no language restrictions. A systematic review investigating pharmacological treatments of agitation in people with dementia included 36 randomised controlled trials (5585 participants). A combination of dextromethorphan and quinidine (odds ratio 3·04, 95% CI 1·63–5·66), risperidone (1·96, 1·49–2·59), and selective serotonin reuptake inhibitor antidepressants (SSRIs; 1·61, 1·02–2·53) were found to be more efficacious than placebo. However, both antipsychotics and SSRIs are associated with serious potential harms and the data for the combination of dextromethorphan and quinidine were derived from a single study. Subsequently, a single paper describing two trials of the atypical antipsychotic brexpiprazole has reported mixed results.

Added value of this study

This current study shows that the noradrenergic and specific serotonergic antidepressant 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 observation of potentially higher mortality in the group receiving mirtazapine than the group receiving placebo, although not definitive, provides further reason for caution in its use for this indication.

Implications of all the available evidence

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 because such approaches have been shown to be at least as effective as drug treatment. Data from this study support the active monitoring of agitation in dementia without the prescription of medication as recommended in guidelines for depression. Antipsychotics and SSRIs are associated with substantial harms when used for the treatment of agitation in dementia. This study suggests that substituting the sedative antidepressant mirtazapine to avoid such harms is not a clinically effective strategy.

problem, Investigate the cause, Create a plan, Evaluate its effectiveness), is recommended as best practice.[1,9] 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 causes has not resulted in improvement. The mainstay of drug treatment is antipsychotic medication. These drugs, however, have low efficacy, with the American Psychiatric Association guideline group reporting they "demonstrate minimal or no efficacy with strong placebo effects".[10] They also cause particular harms in those with dementia, including excess dementia-specific mortality. In the UK in 2009, there were an estimated 1800 deaths and 1620 cerebrovascular adverse events attributable to the use of antipsychotics in dementia.[11] Although their rate of prescription to people with dementia has decreased,[12] they are still commonly used; such treatment is largely unlicensed. In most countries, few or no treatments have regulatory approval for such use. In the UK, the only drugs with a relevant licence are risperidone and haloperidol and these are highly restrictive. Risperidone is indicated for "short-term treatment (up to six 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 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]".

Other drug treatments considered for agitation in dementia, such as the acetylcholinesterase inhibitor donepezil[13] and the NMDA receptor inhibitor memantine,[14] have been tested in randomised controlled trials and did not show efficacy. In a large multicentre trial, the anticonvulsant sodium valproate did not delay or prevent neuropsychiatric symptoms in dementia.[15] Benzodiazepines are used short-term clinically, but there are no trials, and adverse effects such as falls are common and of concern.[16] 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 30 mg citalopram per day had a small positive effect on agitation in dementia[17] in those who were less agitated and less cognitively impaired.[18] Adverse cardiac and cognitive effects identified in the trial limit its clinical use. 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,[19] but they are increasingly used to treat agitation in dementia. This substitution strategy to avoid antipsychotic prescription was reported in a large US nursing homes study, which showed that mood stabilisers such as sodium valproate,

carbamazepine, and particularly gabapentin prescription rates increased as antipsychotics decreased.[20,21] Such prescribing of antidepressants is part of the common polypharmacy seen in people with dementia in the community.[22]

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, 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 most commonly prescribed for older people and those with dementia.[23] We examined it as a treatment for depression in dementia in the HTA-SADD trial and found no evidence of efficacy for depression.[24] However, in secondary analyses of this population defined with a depressive illness and probable or possible Alzheimer's dementia, we noted a possible positive effect of mirtazapine on neuropsychiatric symptoms (neuro-psychiatric inventory [NPI] score at 13 weeks). For those with above median raw NPI scores, there was a 7·1 point difference in NPI score (95% CI –0·50 to 14·68; p=0·067) between mirtazapine and placebo, and a 13·2 point difference between mirtazapine and sertraline (4·47 to 21·95; p=0·003).[25] Mirtazapine is a centrally active presynaptic α2-antagonist, increasing central noradrenergic and serotonergic neurotransmission via 5-HT1 receptors, and the histamine H1-antagonistic activity of mirtazapine is associated with sedative properties, suggesting possible mechanisms for action in neuropsychiatric symptoms. It has less anticholinergic activity than many other antidepressants; unlike citalopram, and at therapeutic doses, it has been reported to have minimal effects on the cardiovascular system, suggesting it might not have the safety concerns associated with other drugs.

In this study, we aimed to establish the clinical effectiveness and safety profile of mirtazapine in reducing agitation in Alzheimer's disease relative to placebo.

Methods

Study design and participants

We did a multicentre, parallel-group, double-blind, placebo-controlled, randomised trial of participants recruited from 26 UK National Health Service clinical centres with 6-week and 12-week follow-ups, using the 12-week data for the primary outcome. Assessments were done in person by research workers in participants' own homes or other agreed settings, except for the last individuals who were followed up during the COVID-19 lockdown and thus assessed by telephone. Inclusion criteria mirrored clinical practice. Eligible participants met National Institute of Neurological and Communicative Diseases and Stroke—Alzheimer's Disease and Related Disorders Association criteria for probable or possible Alzheimer's disease[26] (ascertained by referring psychiatrists) and coexisting agitation defined as a Cohen-Mansfield Agitation Inventory[27]

(CMAI) score of 45 or more. The CMAI score was chosen in our study because it is the most commonly used instrument in trials for agitation in dementia, with robust psychometric properties including responsiveness to change. We also required evidence that the aetiology of agitated behaviours had been investigated and not responded to non-pharmacological management according to the Alzheimer's Society and Department of Health algorithm.[28] Participants were ineligible for inclusion if they were considered clinically too critically unwell for participation (eg, suicide risk), had absolute contraindications to trial drugs (hypersensitivity to mirtazapine, hypersensitivity to carbamazepine or structurally related drugs, second-degree atrioventricular block, use of monoamine oxidase inhibitors, or a history of bone marrow depression or hepatic porphyria), were already taking antidepressants or antipsychotics, were in another Investigational Medicinal Product trial, were women under the age of 55 of childbearing potential, or had no family or professional carer informant available. Ethics approval was obtained from the Hampshire A South Central Research Ethics Committee (15/SC/0606) and the Medicines and Healthcare products Regulatory Agency. The study received local NHS Trust approvals, and written consent or assent (with legal representative consent) was obtained from all participants (for more details see trial protocol, section 5.3.6, in the appendix p 3).

Randomisation and masking

After baseline assessment and consent, participants were randomly allocated (1:1) to receive either placebo 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 two or four. The Norwich Clinical Trials Unit generated the randomisation sequence using ASP.net software. The trial was double-blind, with drug and placebo identically encapsulated. Referring clinicians, participants, the trial management team, and the research workers completing baseline and follow-up assessments were masked to group allocation.

Procedures

The target dose was 45 mg per day for mirtazapine. Participants could take up to three capsules orally once a day (up to three doses of mirtazapine 15 mg or matched placebo). Participants started on one capsule, increasing the dose to two capsules at 2 weeks, and three capsules at 4 weeks. The research worker telephoned carers at weeks 2 and 4 and completed questionnaires concerning adverse effects and adherence. Participants with dose-limiting issues, such as side-effects, either remained on the current dose or stopped the study drug. The remaining participants moved to the next dose level. Thereafter, clinicians were free to adjust the dose.
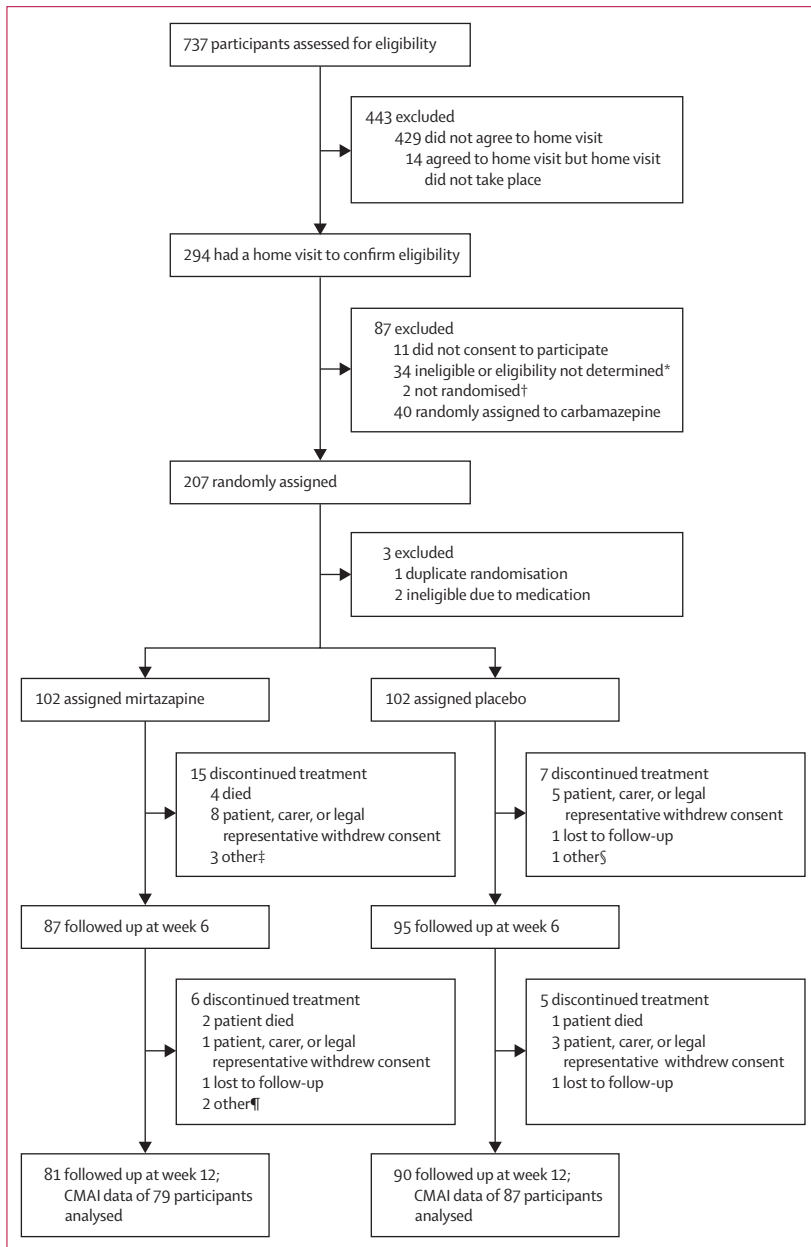
***Figure 1:* Trial profile**
CMAI=Cohen Mansfield Agitation Inventory. *Reasons for ineligibility: one no diagnosis of probable or possible Alzheimer's disease; one no diagnosis of coexisting agitated behaviour; one no evidence that behaviour does not respond to management according to Alzheimer's Society and Department of Health algorithm; 15 no assessment of CMAI score of 45 or greater; one no written informed consent to enter and be randomised into the trial; one current treatment with antidepressant (including monoamine oxidase inhibitors), anticonvulsants, or antipsychotics; two case too critical for randomisation; 12 other or unknown reasons (following text taken from text entries: one psychiatrist decided to proceed with an alternative medication; one patient admitted to hospital and no longer appropriate; one patient not eligible: completed no further assessments after CMAI; six patients ineligible; one patient scored less than 45 on CMAI; one started memantine which reduced agitation; one not randomised as behaviour settled and did not require medication). †One abnormal blood results, one patient, carer, or legal representative withdrew consent. ‡One non-compliance and general practitioner prescription of mirtazapine, one too agitated to continue, one transient ischaemic attack. §One deteriorating health and readmission to hospital. ¶One local Principal Investigator determined that it was no longer in patient's best interests, one compliance problems due to participant and carer capability and ill health.

Outcomes

The primary outcome was clinical effectiveness of mirtazapine in terms of reduction of agitation, measured by CMAI score at 12 weeks. Secondary outcomes were: CMAI score at 6 weeks, disease-specific health-related quality of life (DEMQOL and DEMQOL-proxy), generic health-related quality of life (EQ-5D-5L assessed by the carer for the participant and themselves), neuropsychiatric symptoms (NPI), carer mental health (12-item General Health Questionnaire), carer burden (Zarit Carer Burden Inventory), and cognition (standardised mini-mental state examination; for references see appendix p 2). Safety outcomes were death, withdrawal, drug adherence, adverse events, and Columbia Suicide Severity Rating Scale score. The cost-effectiveness of the intervention, using data collected with the Client Service Receipt Inventory, will be reported elsewhere. All outcomes were assessed at 6 and 12 weeks by a home visit completed by a study research worker until the COVID-19 lockdown when they were completed by telephone. Adverse events were recorded up to 4 weeks after the last dose of medication. Percentage compliance was estimated as the proportion of tablets taken compared with number of tablets returned at 6-week or 12-week visits. Carer telephone interviews including the CMAI were completed at 26 and 52 weeks and these long-term follow-up data will be reported elsewhere.

Protocol changes

SYMBAD was designed as a three-arm trial, including carbamazepine, mirtazapine, and placebo groups with randomisation on a 1:1:1 basis. Due to slower than projected recruitment, the trial protocol was reviewed with the funder and through consultation with the Data Monitoring Committee and Trial Steering Group. The Data Monitoring Committee considered efficacy data (the primary endpoint, CMAI at 12 weeks), safety data (frequency of adverse events and serious adverse events on an individual basis), and treatment compliance (dropouts and compliance with the prescribed amount of treatment medication). This consideration was done blind to subgroup but with knowledge of placebo group identity. The Data Monitoring Committee recommended discontinuation of the carbamazepine group on the basis of efficacy and safety data. The carbamazepine group was closed in August, 2018, after 40 people had been randomly allocated to the group. The data from this group are not reported here but will be presented in our final funder report, which will be published as a UK National Institute for Health Research-Health Technology Assessment monograph.

Statistical analysis

We aimed for an overall sample of 222 participants (randomly allocated 1:1) to provide 80% power using two-sided 5% significance tests to detect a drug versus placebo mean difference in CMAI scores of six points at

12-week follow-up, assuming attrition of less than 10%. Assuming a common standard deviation of 15 points, this equates to a Cohen's effect size of 0·4 or a 30% decrease in CMAI from placebo to active drug, both of which we defined as clinically significant.

The Data Monitoring Committee and the Trial Steering Group finalised and approved the statistical analysis plan. Statistical significance was set at a two-sided 5% for all analyses. Analyses were based on intention to treat (all participants were analysed according to the group to which they were randomly allocated, 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 participants with missing values). Imputation was done under the missing at random assumption. A sensitivity analysis imputed missing values using multiple imputation with chained equations approach (the mi impute chained command in Stata). The analyses of secondary outcomes 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. All analyses were completed with Stata version 16.1. This study is registered with ClinicalTrials.gov, NCT03031184, and ISRCTN17411897.

Role of the funding source
The funder (UK National Institute for Health Research) and the sponsor (University of Sussex) had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
We recruited participants between Jan 26, 2017, and Feb 6, 2020, and completed follow-up interviews by June 1, 2020. 737 participants were assessed for eligibility; after 533 participants were excluded, we randomly allocated 204 participants to the two groups, so that we had 102 participants in the mirtazapine group and 102 participants in the placebo group (figure 1). 79 participants of the mirtazapine group and 87 participants of the control group (present at the 12-week follow-up) were included in the primary analyses.

Table 1 shows baseline demographic and clinical characteristics of participants and carers. Groups were similar at baseline except for more female participants randomly allocated to receive mirtazapine (76 [75%] of 102 participants) than placebo (59 [58%] of 102 participants). In light of this difference, sex was

	Mirtazapine group (n=102)	Placebo group (n=102)
Participants		
Age (SD)	82·2 (7·8)	82·8 (7·7)
Sex	102	102
Female	76 (75%)	59 (58%)
Male	26 (25%)	43 (42%)
Residence	102	102
Own household	55 (54%)	57 (56%)
Care home	47 (46%)	45 (44%)
Agitation: CMAI score (29–203)	102 (100%); 71·1 (16·4)	102 (100%); 69·8 (17·1)
Cognition: standardised MMSE score (0–30)	52; 13·4 (8·1)	50; 16·1 (6·7)
Condition-specific quality of life: DEMQOL score (28–122)	41; 92·4 (10·8)	37; 95·8 (10·2)
DEMQOL-proxy score (31–124)	100; 92·3 (15·0)	99; 90·9 (14·4)
Generic quality of life: EQ-5D score (proxy report by carer, 0–1)	100; 0·46 (0·34)	101; 0·50 (0·32)
Neuropsychiatric symptoms	..	..
NPI total score (0–144)	98; 32·7 (16·7)	102 (100%); 34·9 (18·2)
NPI agitation or aggression subscore (0–12)	99; 5·6 (3·2)	102 (100%); 5·6 (3·4)
NPI depression or anxiety or irritability subscore (0–36)	99; 9·9 (6·2)	102 (100%); 10·5 (7·0)
Suicidality: CSSRS	102	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		
Paid carers	39 (38%)	31 (30%)
Family carers	63 (62%)	71 (70%)
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 (preretirement)		
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	61; 15·0 (5·8)	66; 14·5 (4·9)
Carer burden: Zarit Carer Burden Inventory*	58; 33·8 (15·7)	66; 34·1 (13·9)
Carer generic quality of life: EQ-5D*	61; 0·79 (0·21)	66; 0·81 (0·22)
NPI carer distress subscore (0–60)	94; 14·1 (8·6)	99; 15·5 (9·0)

Data are n, n (%), mean (SD), or n (%); mean (SD). CMAI=Cohen Mansfield Agitation Inventory. CSSRS=Columbia Suicide Severity Rating Scale. DEMQOL=disease-specific health-related quality of life. GHQ-12=12-item General Health Questionnaire. MMSE=mini-mental state examination. NPI=neuropsychiatric inventory. *Only asked of family carers.

***Table 1:* Baseline demographics and clinical characteristics of participants and carers**

included in an additional model as a sensitivity analysis. By week 12, similar numbers remained in the mirtazapine (80 [78%] of 102 participants) and the placebo group (89 [87%] of 102 participants).
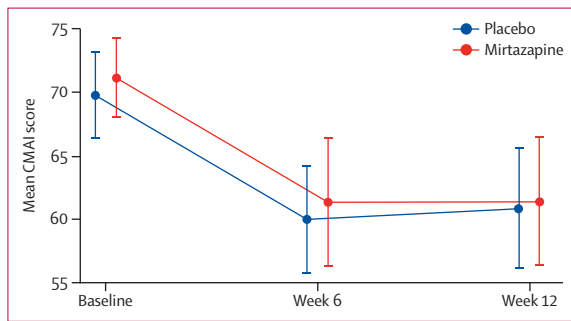
Figure 2: **Unadjusted mean CMAI scores (95% CI) by treatment group**
Please note that the y-axis does not start at 0 in this figure. CMAI=Cohen Mansfield Agitation Inventory.

Severity of agitation decreased in both groups at 6 weeks by around 10 CMAI points and continued to be lower than baseline scores at 12 weeks (figure 2); this change between baseline and 6-week 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 (table 2). Table 2 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 finding changed little with the addition of sex into the model. Table 2 shows the effect of mirtazapine compared with placebo on secondary outcomes in participants and table 3 shows this effect in carers. Again, there was no evidence of difference between the groups, apart from: a single significant difference in the Zarit Carer Burden Inventory at 12 weeks, which indicated

	Mirtazapine group (n=102)		Placebo group (n=102)		Mean difference (95% CI)	Adjusted mean difference (95% CI)*	p value
	n	Mean (SD)	n	Mean (SD)			
12-week primary outcome							
Agitation: CMAI	79	61·4 (22·6)	87	60·8 (21·8)	0·59 (−6·22 to 7·40)	−1·74 (−7·17 to 3·69)*; −0·93 (−6·42 to 4·56)†	0·530; 0·739
6-week secondary outcomes							
Agitation: CMAI	84	61·4 (23·5)	88	60·0 (19·9)	1·39 (−5·15 to 7·93)	−0·55 (−6·18 to 5·08)	0·848
Cognition: standardised MMSE	33	15·5 (7·1)	31	16·2 (7·2)	−0·68 (−4·25 to 2·89)	−0·14 (−1·17 to 1·45)	0·836
Quality of life: DEMQOL	32	95·1 (10·2)	32	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	79	96·6 (14·7)	86	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	82	0·48 (0·33)	87	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	84	27·1 (20·0)	88	24·8 (20·0)	2·29 (−3·73 to 8·31)	2·03 (−2·89 to 6·95)	0·419
Neuropsychiatric symptoms: NPI agitation and aggression subscore	84	4·0 (3·6)	88	4·2 (3·5)	−0·20 (−1·28 to 0·87)	−0·34 (−1·30 to 0·62)	0·490
Neuropsychiatric symptoms: NPI depression, anxiety, and irritability subscore	84	7·9 (7·7)	88	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: standardised MMSE	23	18·0 (6·0)	27	15·6 (7·5)	2·44 (−1·48 to 6·37)	1·45 (−0·20 to 3·10)	0·084
Quality of life: DEMQOL	24	94·3 (7·1)	24	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	71	98·4 (14·5)	82	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	77	0·46 (0·35)	84	0·50 (0·33)	−0·04 (−0·14 to 0·07)	−0·01 (−0·08 to 0·07)	0·822
Neuropsychiatric symptoms: NPI total score	75	23·9 (17·8)	84	25·7 (19·6)	−1·80 (−7·69 to 4·09)	−2·02 (−6·67 to 2·62)	0·393
Neuropsychiatric symptoms: NPI agitation and aggression subscore	76	4·1 (3·4)	84	4·5 (3·6)	−0·40 (−1·49 to 0·70)	−0·52 (−1·52 to 0·47)	0·305
Neuropsychiatric symptoms: NPI depression, anxiety, and irritability subscore	75	6·9 (6·7)	84	7·3 (8·0)	−0·44 (−2·77 to 1·88)	−0·58 (−2·43 to 1·27)	0·541

CMAI=Cohen Mansfield Agitation Inventory. DEMQOL=disease-specific health-related quality of life. EQ-5D=EuroQOL 5 dimension. MMSE=mini-mental state examination. NPI=neuropsychiatric inventory. *Adjusted for prespecified factors: baseline CMAI, household status, and centre. †Adjusted for sex and prespecified factors: baseline CMAI, household status, and centre.

Table 2: **Comparisons of participant primary outcomes at 12 weeks and secondary outcomes at 6 weeks and 12 weeks**

	Mirtazapine group (n=102)		Placebo group (n=102)		Mean difference (95% CI)	Adjusted mean difference* (95% CI)	p value
	n	Mean (SD)	n	Mean (SD)			
6-week outcomes							
Carer GHQ-12	50	12·8 (6·2)	54	12·1 (4·9)	0·69 (–1·46 to 2·85)	0·61 (–1·21 to 2·42)	0·512
Carer EQ-5D	50	0·83 (0·16)	55	0·83 (0·15)	0·00 (–0·06 to 0·06)	0·01 (–0·04 to 0·05)	0·821
Zarit Carer Burden Inventory	46	34·7 (16·3)	49	29·4 (13·9)	5·35 (0·82 to 11·53)	3·76 (–0·30 to 7·83)	0·069
NPI carer distress subscore	78	11·5 (1·1)	84	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	44	13·1 (6·0)	52	12·2 (5·4)	0·88 (–1·43 to 3·19)	0·36 (–1·58 to 2·31)	0·714
Carer EQ-5D	46	0·80 (0·16)	49	0·82 (0·19)	–0·02 (–0·09 to 0·06)	0·02 (–0·04 to 0·07)	0·561
Zarit Carer Burden Inventory†	42	35·5 (17·2)	48	29·0 (15·8)	6·48 (–0·43 to 13·39)	5·01 (0·80 to 9·23)	0·020
NPI carer distress subscore	72	10·0 (8·6)	81	10·5 (8·3)	–0·52 (–3·22 to 2·17)	–0·27 (–2·34 to 1·80)	0·798

CMAI=Cohen-Mansfield Agitation Inventory. GHQ-12=12-item General Health Questionnaire. NPI=neuropsychiatric inventory. *Adjusted for prespecified factors: baseline CMAI, household status, and centre. †Asked of family carers only.

Table 3: Comparisons of carer secondary outcomes at 6 weeks and 12 weeks

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 with higher proxy-rated EQ-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).

The mean overall dosage (including participants who withdrew from medication) was 30·5 mg per day for mirtazapine and compliance with study medication did not differ between groups (table 4). The use of permitted so-called rescue medication (lorazepam 0·5 mg or risperidone 0·5–1 mg) was similar in both groups with ten doses prescribed to nine individuals in the mirtazapine group and 18 doses to nine individuals in the placebo group.

Adverse events and severe adverse events were ascertained to 16 weeks or 4 weeks after last dose of investigational medical product; deaths were recorded up to 16 weeks after randomisation. Examining adverse events by week 16, there were 192 adverse events in 102 participants in the placebo group, with 65 (64%) individuals having at least one adverse event, compared with 225 adverse events in 102 participants in the mirtazapine group, with 67 (66%) participants having at least one adverse event. There were 35 serious adverse events in 18 individuals in the placebo group, compared with 13 in eight individuals in the mirtazapine group. The systems affected by adverse events and severe adverse events by intervention group are presented in the appendix (p 1). 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 analyses suggested weak evidence of a mortality difference between groups (Fisher's exact test p=0·065). Causes of death coded with MedDRA (Medical Dictionary

	Mirtazapine group (n=102)	Placebo group (n=102)
Dose escalation		
End of week 4	91	97
3 study medications per day	50 (55%)	59 (61%)
2 study medications per day	11 (12%)	16 (16%)
1 study medication per day	9 (10%)	8 (8%)
0 study medications per day*	19 (21%)	14 (14%)
Dose information missing or inconsistent	2 (2%)	0
End of week 6	86	95
3 study medications per day	48 (56%)	49 (52%)
2 study medications per day	10 (12%)	23 (24%)
1 study medication per day	9 (10%)	8 (8%)
0 study medications per day*	13 (15%)	7 (7%)
Dose information missing or inconsistent	1 (1%)	8 (8%)
Compliance with study medication		
In trial at 6 weeks	86	95
Compliance, mean percentage (SD)†	85 (16)	84 (16)
Compliance missing or inconsistent	44 (51%)	49 (52%)
In trial at 12 weeks	82	88
Taking trial medication at 12 weeks	68 (83%)	76 (86%)
Compliance, mean percentage (SD)†	75 (23)	74 (27)
Compliance missing or inconsistent	49 (60%)	50 (57%)

Data are n, n (%), or mean (SD). *Combining those reported on 0 tablets a day and those choosing or advised to stop. †Compliance: number of tablets taken or expected number of tablets taken x 100, with number of tablets taken being based on expected number of tablets, minus number of tablets returned at 6-week or 12-week visit; expected number of tablets calculated using prescribed number of tablets at each stage of the trial.

Table 4: Dose escalation and compliance with study medication

for 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 attributed to (1) dementia; (2) pneumonia, aspiration; (3) emphysema, dementia, pneumonia, aspiration; (4) dementia, Alzheimer's type; (5) cardiac failure; (6) pelvic fracture, osteoporosis, vascular dementia; and (7) chronic kidney disease, dementia, congestive cardiac failure.

Discussion

This study is a trial with negative findings, but these findings 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 sedative 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 because it was also seen in the placebo group. It is concerning that although the total number of adverse events did not differ between the groups, mortality did differ, with seven deaths in the mirtazapine group compared with one in the placebo group. Although we do not know whether the deaths were related to mirtazapine, in the absence of clinical benefit attributable to mirtazapine, these potential harms mean that mirtazapine cannot be recommended for the treatment of agitation in dementia.

Our study has important potential limitations. First, there was a major adjustment to the initial trial protocol. We dropped the proposed carbamazepine group 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. Stopping recruitment to this group did not affect our ability to compare the clinical effectiveness of mirtazapine with placebo. However, the data from this trial only apply to mirtazapine and it is possible that other antidepressants from other classes might have a different effect; in the CitAD trial,[17] citalopram, a selective serotonin reuptake inhibitor, was reported to have had a modest positive effect, although with concerning adverse effects.

Second, the difference in mortality observed might have been by chance. This study was not powered to investigate a mortality difference between the groups. The analysis was post-hoc and its statistical significance marginal; in our previous study of depression in dementia, there were no more deaths in 108 participants randomly allocated to mirtazapine than in 111 participants randomly allocated to placebo.[24] We therefore need to be careful in the interpretation of the mortality data in this study. Third, recruitment beyond February, 2020, was constrained by health research restrictions secondary to the COVID-19 pandemic. We only recruited 204 (92%) participants of the targeted 222 participants, 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 participants randomly allocated to the groups as planned.

Finally, there are potential limitations in generalisability because we recruited most participants from old-age psychiatry services and care homes; outcomes might have been different in those living in the community treated by primary care services alone. However, in the UK, those with substantial 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. SYMBAD was designed to match real clinical populations and interventions closely. 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 were probably others who were not referred to the trial.

The three main strengths of our study were high follow-up and compliance rates, the large sample size, and the broad nature of the study group (in terms of severity of agitation and severity and type of dementia). We were able to follow up 81 (79%) of the 102 participants in the mirtazapine group and 90 (88%) of the 102 participants in the placebo group at 12 weeks, and complete primary outcome assessment. Our data suggest that over half of the participants in each group reached the target dose of medication and that compliance was high at over 80% at 6 weeks and over 70% at 12 weeks. However, our pragmatic trial design of effectiveness, with primary analyses and inference on an intention-to-treat basis, and the relatively high level of missing data on compliance, limits any post-hoc analysis of outcome by compliance. Dropouts might have introduced bias if those not followed up had a different response to mirtazapine or placebo than those completing the trial. However, our rates of follow-up were 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 Alzheimer's disease, not just narrowly defined Alzheimer's disease; this inclusion is important because agitation can affect dementia of all causes and most people with dementia have mixed aetiology. Participants were therefore close 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 Alzheimer's disease and mixed dementia and be cautious in applying them to other subtypes (eg, vascular, Lewy body, or frontotemporal dementia).

The US National Health and Nutrition Examination Survey showed that the highest rates of antidepressant use between 2015 and 2018 were in people aged over 60, of whom 19·0% were prescribed such medication.[29] Mirtazapine is commonly prescribed for older adults. In a study of people living in long-term care facilities in Helsinki, Finland, there was a marked increase in use of mirtazapine between 2003 and 2017: from 15·7% to 22·7% in nursing homes and from 14·0% to 23·8% in assisted living facilities, both settings with high prevalence of residents with dementia.[30] In the MEDALZ cohort of 70718 community-dwelling people with Alzheimer's disease in Europe, mirtazapine was responsible for most new prescriptions (6462 [39·2%] of 16 501 prescriptions).[31] One reason for high rates of prescription of mirtazapine in later life is to avoid the use of antipsychotics.[32] 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.[19] 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 consider other medications. Sedative antidepressants such as mirtazapine, with which they are familiar, might appear an attractive and safe alternative to proscribed antipsychotics. However, there are reports that this might not be the case. Analyses of a primary care cohort showed increased all-cause mortality in people aged 20–64 who were prescribed mirtazapine.[33] Taken together, the reports of potentially serious adverse effects of citalopram in the CitAD trial,[17,18] of increased falls in trials of mixed dextromethorphan and quinidine,[34] and of potentially higher mortality in the mirtazapine than the placebo group in this trial, present growing evidence that substituting antidepressants, or other novel compounds, for antipsychotics for the treatment of agitation in dementia is not a safe alternative.

In terms of secondary outcomes, the absence of any positive effects on participant and carer quality of life, on participant cognition, or 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 study[25] 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 might be a function of the potential therapeutic value 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 where symptoms can come and go. The latter is perhaps less probable given the observed persistence of agitation.[7,35] It might also be due to artifacts such as regression to the mean, a placebo effect, or the Hawthorne effect, although the magnitude of the effect means that these artifacts 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 afterwards, 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.[36] As with our earlier study of the treatment of depression in dementia (HTA-SADD),[24] our data suggest that finding agitation in dementia could be an appropriate trigger for referral to specialist services in which detailed assessment can be completed and non-drug treatments and active monitoring done, perhaps avoiding the use of medication.

Overall, this study adds to the evidence base that shows pharmacological interventions for agitation in dementia are limited in their effectiveness[37,38] and associated with risk of harm. An important limitation in trials of drug and non-drug interventions for agitation is that the causes of agitation are heterogeneous and multifactorial. The syndrome might be caused by any combination of reasons as varied as: unmet needs (eg, hunger, thirst, pain), medical episodes (eg, infections, hypothyroidism), prescribed medication (eg, anticholinergics, steroids), and the environment (overstimulation or understimulation), as well as the illness causing dementia. Even with initial investigation of the causes of the agitation and treatment with non-drug management as in this trial, any one-size-fits-all intervention (whether a drug or non-drug intervention) for a heterogeneous syndrome such as agitation will have a high likelihood of failure due to lack of specificity. The fundamental presumption that there is a single neurobiological basis for agitation and therefore a specific drug that will target it, even in people with narrowly defined Alzheimer's disease or those with closely defined symptom clusters, seems particularly weak. Drugs for which a signal of effect has been found, such as risperidone and citalopram, appear to have achieved those effects through general sedative side-effects, which also drive much of the harm from such medication in the frail population with dementia.

We need to challenge the dominant, simple target-based framework for the development and testing of interventions for complex challenges such as agitation in dementia. Approaches that are inclusive of the heterogeneity of causation and tailor an individualised programme of investigation and management including social and psychological as well as pharmacological interventions could be of greater value. The implications of this study are not just that mirtazapine does not work and is potentially harmful. There are also reasons to be positive that treatment-as-usual by current primary and secondary health-care services could well enable people with agitation and dementia to recover from that agitation without the use of medication and its potential harms.

SYMBAD Recruitment group
Trial Investigators: Barnet Elizabeth Sampson, *Belfast* Bernadette McGuinness, *Bournemouth* Divya Tiwari, *Bradford* Sushanth Kamath, Gregor Russell, *Cambridgeshire* Catherine Hatfield, *Central and NW London* Erum Nomani, *Coventry* Demi Onalaja, *Dudley* Udaya Balakrishna, *Exeter* Carol Bannister, Joseph Butchart, Simona Brown, *Gateshead* Karen Franks, *Kings College* Adenike Dare, *Leicester* Matthew Critchfield, Matthew Noble, *Manchester* Ross Dunne, *Midlands* Rashi Negi, *Norfolk* Heather Cooke, *Northamptonshire* Paul Koranteng, *Rotherham* Oluwafemi Adio, *Sheffield* Aparna Mordekar, *SW London* Robert Lawrence, *SW Yorkshire* Suba Thiyagesh, *Surrey* Gareth O'Leary, *Sussex* Andrew Risbridger, Gosia Raczek, Richard Hoile, *Worcestershire* Dhanjeev Marrie, *2Gether* Emma Abbey. *Research Nurses, Research Workers and Clinical Research Network Staff:*
Barnet Luiza Grycuk, Tom Freeth *Birmingham* Analisa Smythe, Di Baines, Jan Wright, Jane Dyer, *Bradford* Jason Cook, Sarah Kirkland, Zarina Mirza, *Cambridgeshire Windsor Research Unit* Julie Philps Naomi Thomas, Marina Bishop, Siobhan Coleman, Gloria Calderon, *Central and NW London* Desiree Fyle, *Coventry* Emily Benson, *Dudley* Aurora Balalia, *Exeter* Amanda Henderson, Anna Grice, Olga Borejko, Sarah Brown, Stacey Horne, Sue Dyson, *Gateshead* Bryony Storey, Elaine Siddle, *Kings College* Shaula Candido, *Leicester* Iain Termie, Sarah Ballion, *Manchester* Dee Leonard, Lewis Harpin, Phillip Tinkler, Rebecca Davies, Selina Sonola, *Midlands* Paula Coventry, Susan Lavendar, *Norfolk* Caroline Sheldon, Claire Rischmiller, Kim Clipsham, Zoe Inman, *Northamptonshire* Chetan Lakhani, *North London* Liam Pikett, Narin Aker, *Rotherham* Helen Oldknow, *Sheffield* Hannah Gower, *SW London* Na'ilah Firdaws, *Surrey* George Shaya, Jessica True, Mariana Gavrilla, Sally Gosling, *Sussex* Angela Ozduran, Elise Armsby, Keren Teichmann, Marcela Carvajal, Natalie Portwine, Rachel Russell, Sam Holden, Sharne Berwald, Tamsin Eperson, *2Gether* Marelle Harvey, Sarah Little. *Norwich Clinical Trials Unit staff* Erika Sims, Estelle Payerne, Hazel Hobbs, Katharine Goodall, Lee Kitchman, Matt Hammond, Megan Jones, Nick Leavey, Veronica Bion.

References
1 Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; **390:** 2673–734.
2 Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. World Alzheimer Report 2015. The global impact of dementia. An analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International, 2015.
3 Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry* 2009; **194:** 212–19.
4 van der Linde RM, Dening T, Stephan BC, Prina AM, Evans E, Brayne C. Longitudinal course of behavioural and psychological symptoms of dementia: systematic review. *Br J Psychiatry* 2016; **209:** 366–77.
5 Cohen-Mansfield J, Billing N. Agitated behaviors in the elderly: I. A conceptual review. *J Am Geriatrics Soc* 1986; **34:** 711–21.

6   Okura T, Plassman BL, Steffens DC, Llewellyn DJ, Potter GG, Langa KM. Prevalence of neuropsychiatric symptoms and their association with functional limitations in older adults in the United States: the aging, demographics, and memory study. *J Am Geriatr Soc* 2010; **58**: 330–37.

7   Ryu S-H, Katona C, Rive B, Livingston G. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. *Am J Geriatr Psychiatry* 2005; **13**: 976–83.

8   Wetzels RB, Zuidema SU, de Jonghe JFM, Verhey FRJ, Koopmans RTCM. Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. *Am J Geriatr Psychiatry* 2010; **18**: 1054–65.

9   Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ* 2015; **350**: h369.

10   Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. Guideline Watch (October 2014): practice guideline for the treatment of patients with Alzheimer's disease and other dementias. 2014. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf (accessed Nov 15, 2020).

11   Banerjee S. The use of antipsychotic medication for people with dementia: time for action. A report. 2009. https://webarchive.nationalarchives.gov.uk/20121030234317/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_108303 (accessed Feb 15, 2021).

12   Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. *Lancet Public Health* 2017; **2**: e149–56.

13   Howard RJ, Juszczak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med* 2007; **357**: 1382–92.

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

15   Tariot PN, Schneider LS, Cummings J, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry* 2011; **68**: 853–61.

16   Defrancesco M, Marksteiner J, Fleischhacker WW, Blasko I. Use of benzodiazepines in Alzheimer's disease: a systematic review of literature. *Int J Neuropsychopharmacol* 2015; **18**: pyv055.

17   Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA* 2014; **311**: 682–91.

18   Schneider LS, Frangakis C, Drye LT, et al. Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: the CitAD randomized clinical trial. *Am J Psychiatry* 2016; **173**: 465–72.

19   UK National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. London: National Institute of Health and Care Excellence, 2018.

20   Maust DT, Kim HM, Chiang C, Kales HC. Association of the Centers for Medicare & Medicaid Services' national partnership to improve dementia care with the use of antipsychotics and other psychotropics in long-term care in the United States from 2009 to 2014. *JAMA Intern Med* 2018; **178**: 640–47.

21   Gerlach LB, Kales HC, Kim HM, et al. Trends in antipsychotic and mood stabilizer prescribing in long-term care in the US: 2011–2014. *J Am Med Dir Assoc* 2020; **21**: 1629–1635.e8.

22   Maust DT, Strominger J, Kim HM, et al. Prevalence of central nervous system-active polypharmacy among older adults with dementia in the US. *JAMA* 2021; **325**: 952–61.

23   Forns J, Pottegård A, Reinders T, et al. Antidepressant use in Denmark, Germany, Spain, and Sweden between 2009 and 2014: incidence and comorbidities of antidepressant initiators. *J Affect Disord* 2019; **249**: 242–52.

24   Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 2011; **378**: 403–11.

25   Romeo R, Knapp M, Hellier J, et al. Cost-effectiveness analyses for mirtazapine and sertraline in dementia: randomised controlled trial. *Br J Psychiatry* 2013; **202**: 121–28.

26   McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. *Neurology* 1984; **34**: 939–44.

27   Cohen-Mansfield J. Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. *Int Psychogeriatr* 1996; **8** (suppl 3)**:** 309–15.

28   Alzheimer's Society. Optimising treatment and care for people with behavioural and psychological symptoms of dementia: a best practice guide for health and social care professionals. London: Alzheimer's Society, 2011.

29   Brody DJ, Gu Q. Antidepressant use among adults: United States, 2015–2018. *NCHS Data Brief* 2020; **377**: 1–8.

30   Aalto UL, Roitto HM, Finne-Soveri H, Kautiainen H, Pitkälä KH. Temporal trends in the use of anticholinergic drugs among older people living in long-term care facilities in Helsinki. *Drugs Aging* 2020; **37**: 27–34.

31   Kettunen R, Taipale H, Tolppanen AM, et al. Duration of new antidepressant use and factors associated with discontinuation among community-dwelling persons with Alzheimer's disease. *Eur J Clin Pharmacol* 2019; **75**: 417–25.

32   Marcinkowska M, Śniecikowska J, Fajkis N, Paśko P, Franczyk W, Kołaczkowski M. Management of dementia-related psychosis, agitation and aggression: a review of the pharmacology and clinical effects of potential drug candidates. *CNS Drugs* 2020; **34**: 243–68.

33   Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in people aged 20-64 years: cohort study using a primary care database. *BMC Med* 2018; **16**: 36.

34   Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA* 2015; **314**: 1242–54. .

35   Marston L, Livingston G, Laybourne A, Cooper C. Becoming or remaining agitated: the course of agitation in people with dementia living in care homes. The English Longitudinal Managing Agitation and Raising Quality of Life (MARQUE) Study. *J Alzheimers Dis* 2020; **76**: 467–84.

36   UK National Collaborating Centre for Mental Health. Depression: the treatment and management of depression in adults (updated edition). National clinical practice guideline 90. London, UK: The British Psychological Society and The Royal College of Psychiatrists, 2020.

37   Kongpakwattana K, Sawangjit R, Tawankanjanachot I, Bell JS, Hilmer SN, Chaiyakunapruk N. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. *Br J Clin Pharmacol* 2018; **84**: 1445–56.

38   Watt JA, Goodarzi Z, Veroniki AA, et al. Comparative efficacy of interventions for aggressive and agitated behaviors in dementia: a systematic review and network meta-analysis. *Ann Intern Med* 2019; **171**: 633–42.

39   Grossberg GT, Kohegyi E, Mergel V, et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. *Am J Geriatr Psychiatry* 2020; **28**: 383–400.