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

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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 prescribed for agitation in dementia.

Methods: Parallel-group, double-blind, placebo-controlled trial, the Study of Mirtazapine for Agitated Behaviours in Dementia trial (SYMBAD) 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 ≥ 45. They were randomly allocated 1:1 to mirtazapine titrated to 45 mg or placebo. The primary outcome was reduction in CMAI score at 12 weeks. ISRCTN17411897, ClinicalTrials.gov NCT03031184.

Findings: Between January 2017 and February 2020, 204 participants were recruited and randomised. Mean CMAI scores at 12 weeks were not significantly different between participants allocated to receive mirtazapine and placebo (adjusted mean difference -1.74, 95% CI -7.17 to 3.69, p=0.53). The number of controls with adverse events (65/102 [64%]) was similar to that in 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), with post-hoc analysis suggesting this 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.

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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 commonest cause of dementia is Alzheimer's disease, it 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.[3] These are common, occurring in up to 90% of people with dementia, with agitation, 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 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 will have them six 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. 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.[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 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 2009, in the UK there were an estimated 1,800 deaths and 1,620 cerebrovascular adverse events attributable to the use of antipsychotics in dementia.[11] While 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 license 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 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]".

Other drug treatments considered for agitation in dementia, such as the acetylcholinesterase donepezil[13] and the NMDA inhibitor memantine[14] they have been tested in randomised controlled trials and not demonstrated efficacy. In a large multicentre trial, the anticonvulsant sodium valproate did not delay or prevent NPS 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 citalopram 30mg 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 as a treatment of agitation in dementia. This substitution strategy to avoid antipsychotic prescription was reported in a large US nursing homes study where 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 2009-2014, 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, there was a possible positive effect of mirtazapine on decreasing NPS (Neuropsychiatric 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 13.2 between mirtazapine and sertraline (95%CI 4.47 to 21.95; p=0.003).[25] Mirtazapine is a centrally active presynaptic a2-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 NPS. 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 that it may not have the safety concerns associated with other compounds.

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

Trial design and participants

We undertook a multicentre, parallel-group, double blind, placebo-controlled, randomised trial of participants recruited from 26 UK National Health Service clinical centres with six and 12-week follow-up, with the 12-week data the primary outcome. Assessments were carried out in-person by research workers in participants' own homes or other agreed setting, except for the very last individuals followed up in the COVID-19 lockdown who were assessed by telephone. Inclusion criteria mirrored clinical practice. Eligible participants met National Institute of Neurological and Communicative Diseases and Stroke (NINCDS) – Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for probable or possible Alzheimer's disease[26] (ascertained by referring psychiatrist) and co-existing agitation defined as a Cohen Mansfield Agitation Inventory[27] (CMAI) score of 45 or more. This was chosen as 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/Department of Health algorithm.[28] Participants were ineligible for inclusion if they were considered clinically too critically unwell for participation (e.g., 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, women under the age of 55 of childbearing potential, or had no family or professional carer informant available. Further safety data were collected at 16 weeks. 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 study is registered, ISRCTN17411897, ClinicalTrials.gov NCT03031184.

Randomisation and masking

After baseline assessment and consent, participants were allocated in a 1:1 ratio to receive placebo or mirtazapine, together with treatment as usual. Random allocation was block stratified by centre and type of residence (care home versus 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 at two weeks, and three at four weeks. The research worker telephoned carers at weeks two and four and completed questionnaires concerning adverse effects and adherence. Those 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.

The primary outcome was clinical effectiveness of mirtazapine in terms of reduction of agitation, measured by CMAI score at 12 weeks. Secondary outcomes (for references see Supplementary Information) were: CMAI score at six 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 (General Health Questionnaire, GHQ-12); carer burden (Zarit Carer Burden Inventory, CBI); cognition (standardised mini-mental state examination, sMMSE). Safety outcomes included death, withdrawal, drug adherence, adverse events, and Columbia Suicide Severity Rating Scale (C-SSRS) score. The cost-effectiveness of the intervention, using data collected with the Client Service Receipt Inventory (CSRI), will be reported elsewhere. All outcomes were assessed at six and 12 weeks. Adverse events were recorded up to four weeks after the last dose of medication. Percentage compliance was estimated as the proportion of tablets taken compared with number of tablets returned at six

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 and mirtazapine arms 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 (drop outs and compliance with the prescribed amount of treatment medication). This was done subgroup-blind but with knowledge of placebo arm identity. They recommended discontinuation of the carbamazepine arm on the basis of efficacy and safety data. It was closed in August 2018 after 40 randomisations to it. The data from this arm are not reported here but will be presented in our final funder report which will be published as an NIHR-HTA monograph.

Statistical analysis

We aimed for an overall sample of 222 (randomised 1:1) to provide 80% power using two-sided 5% significance tests to detect a drug versus placebo mean difference in CMAI score at 12 weeks of six points, 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 trial Steering and the Data Monitoring Committees 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 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 versus 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). Analysis 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.

Role of the funding source

The funder (NIHR) and the sponsor (University of Sussex) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the study data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We recruited participants between January 2017 and February 2020 and completed follow up interviews by May 2020. Table 1 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=60, 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%).

Severity of agitation decreased in both groups at six weeks by around 10 points and continued to be lower than baseline scores at 12 weeks (Figure 2), this change between baseline and six 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 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 in carers. Again, there was no evidence of difference between the groups, apart from: a single statistically significant difference in the Zarit CBI 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 six 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 six 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 “rescue medication” (lorazepam 0.5mg or risperidone 0.5-1mg) was similar in both groups with 10 doses prescribed to 9 individuals in the mirtazapine group and 18 to 9 in the placebo group.

Adverse events and severe adverse events were ascertained to 16 weeks or four weeks after last dose of IMP; deaths were recorded up to 16 weeks after randomisation. Examining adverse events by week 16, there were 192 in 102 participants in the placebo group, of whom 65 (64%) individuals had at least one adverse event, compared with 225 events in 102 participants in the mirtazapine group of whom 67 (66%) had at least one. There were 35 serious adverse events in 18 individuals in the placebo group, compared with 13 in eight 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 Regulatory Activities) terms showed no consistent pattern with the one death in the placebo group attributed to (i) 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,

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 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 six weeks of treatment, which was then maintained from six to 12 weeks; however, this drop was not attributable to mirtazapine since it was also seen in the placebo group. It is concerning that while the total number of adverse events did not differ between the groups, mortality *did*, with seven deaths in the mirtazapine group compared with one in the placebo group. While we do not know whether the deaths were mirtazapine-related, 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 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. 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[17] citalopram, an SSRI, was reported to have had a modest positive effect, though with concerning adverse effects.

Second, the difference in mortality observed may 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 randomisations to mirtazapine than in 111 randomised 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%) 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.

Finally, 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. However, 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. 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 will have been others who were not referred to the trial.

The three main strengths of our study were high follow-up and compliance rates, 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 mirtazapine group and 90 (88%) of the placebo group at 12 weeks and complete primary outcome assessment. Our data suggest that over half of each group reached the target dose of medication and that compliance was high at over 80% at six 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 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 Alzheimer's disease, not just narrowly defined Alzheimer's disease; this is important since 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 (e.g., 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, where 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, 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 assistive living facilities, both settings with very high prevalence of residents with dementia.[30] In the MEDALZ cohort of 70,718 community dwelling people with Alzheimer's disease in Europe, mirtazapine was responsible for most new prescriptions (n=6,462, 39.2%).[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, 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.[33] Taken together, the reports of potentially serious adverse effects of citalopram in the CitAD trial,[17,18] of increased falls in trials of dextromethorphan-quinidine,[34] and the potentially higher mortality in the mirtazapine group in this trial, present growing evidence that substituting antidepressants, or other novel compounds, for antipsychotics for the treatment 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[25] 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 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 may wax and wane. The latter is perhaps less likely given the observed persistence of agitation.[7,35] It might also be due to artefacts such as regression to the mean, a placebo effect, 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 six-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.[36] As with our earlier study of the treatment of depression in dementia (HTA-SADD),[24] 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.

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 significant 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 may be caused by any combination of reasons as varied as: unmet needs (e.g., hunger, thirst, pain); medical episodes (e.g., infections, hypothyroidism); prescribed medication (e.g., anticholinergics, steroids); and the environment (over- or under-stimulation), 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 drug or non-drug for a heterogeneous syndrome like 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. Those drugs where there has been a signal of effect, such as risperidone and citalopram, appear to have done so 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 paradigm 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 may 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 may well enable people with agitation and dementia to recover from that agitation without the use of medication and its potential harms.

Panel: Research in context

Systematic review

We searched PubMed and the Cochrane Library databases up to 19 February 2021, using the following 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 was no restriction on the language. A systematic review investigating pharmacological treatments of agitation in people with dementia included 36 RCTs (5,585 participants).[37] Dextromethorphan/quinidine [OR 3.04; 95% CI, 1.63 to 5.66], risperidone (1.96; 1.49 to 2.59) and selective serotonin reuptake inhibitor antidepressants (SSRIs, 1.61; 1.02 to 2.53) were found to be more efficacious than placebo. However, both antipsychotics and SSRIs are associated with serious potential harms and the dextromethorphan/quinidine data are derived from a single study. Subsequently a single paper describing two trials of the atypical antipsychotic brexpiprazole has reported mixed results.[39]

Added value of this study

This paper demonstrates 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 observation of potentially higher mortality in the group prescribed mirtazapine compared with placebo, while not definitive, provides further reason for caution in its use for this indication.

Implication 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 since such approaches have been shown to be at least as effective as drug treatment.[38] 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 sedative antidepressant mirtazapine in order to avoid such harms is not a clinically effective strategy.

Contributors

SB was the chief investigator for the study and designed and managed the study with input from the group. SS and LS carried out the statistical analyses. All authors had access to data and participated in data interpretation. JH, SS, LS, CH and SB have verified the underlying data. SB drafted the first and subsequent versions of this paper with input and key revisions by all authors, who reviewed and approved the final submitted paper.

Declaration of interests

SB reports personal fees and non-financial support from Lilly, personal fees from Boehringer-Ingelheim, personal fees from Axovant, personal fees from Lundbeck, personal fees from Nutricia, and honoraria from the Hamad Medical Service for lectures and talks, outside the submitted work; he is a Trustee of the Alzheimer's Society and has research grants from NIHR, ESRC, and ESPRC. AB reports being National Clinical Director for Dementia at NHS England and receiving professional fees from NHS England, personal fees from International Journal of Geriatric Psychiatry, personal fees from lectures and talks, personal fees from medico-legal reports, and the Driver and Vehicle Licensing Authority, outside the submitted work. CB reports grants and personal fees from Acadia pharmaceutical company, grants and personal fees from Lundbeck, personal fees from Roche, personal fees from Otsuka, personal fees from Novartis, personal fees from Eli Lilly, personal fees from Suven, personal fees from Sunovion, personal fees from ADDEX, personal fees from Exciva, personal fees and other from Synexus, personal fees and other from Novo Nordisk, other from Biogen, outside the submitted work. PB reports work as a paid Consultant for TauRx Therapeutics outside the submitted work. RH reported grant support from NIHR and being a Trustee of Alzheimer's Research UK. J O'B reports personal fees from TauRX, personal fees from Axon, personal fees from GE Healthcare, personal fees from Eisai, non-financial support from Alliance Medical, personal fees from Roche, grants from Merck outside the submitted work. NT reports grant support from Avenir Pharma and NIHR ARC and CRN leadership roles. AT reports grants from NIHR HTA, during the conduct of the study. All other authors report no relevant interests other than NIHR funding for investigator time on this grant.

Data sharing

Deidentified participant data will be available with investigator support from nine months after publication of the final project reports via sube.banerjee@plymouth.ac.uk by researchers whose proposed use of the data has been approved by the Trial Management Committee for

meta-analyses or analyses that have been approved. The trial protocol will be available as a supporting document.

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