RESEARCH ARTICLE

International Journal of
Geriatric Psychiatry WILEY

Effect of trazodone on cognitive decline in people with dementia: Cohort study using UK routinely collected data

Andrew Sommerlad[1,2] | Nomi Werbeloff[1,2,3] | Gayan Perera[4,5] | Tanya Smith[6] | Harry Costello[7] | Christoph Mueller[4,5] | Andrey Kormilitzin[8] | Matthew Broadbent[5] | Alejo Nevado-Holgado[8,9] | Simon Lovestone[9,10] | Robert Stewart[4,5] | Gill Livingston[1,2]

[1]Division of Psychiatry, University College London, London, UK

[2]Camden and Islington NHS Foundation Trust, London, UK

[3]The Louis and Gabi Weisfeld School of Social Work, Bar Ilan University, Ramat Gan, Israel

[4]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[5]South London and Maudsley NHS Foundation Trust, London, UK

[6]NIHR Biomedical Research Centre, Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

[7]Institute of Cognitive Neuroscience, University College London, London, UK

[8]Mathematical Institute, University of Oxford, Oxford, UK

[9]Department of Psychiatry, University of Oxford, Oxford, UK

[10]Johnson and Johnson Medical Ltd., Janssen-Cilag, High Wycombe, UK

Correspondence

Andrew Sommerlad, Division of Psychiatry, University College London, 6th Floor, Maple House, 149 Tottenham Court Road, London, W1T 7NF, UK.
Email: a.sommerlad@ucl.ac.uk

Abstract

Objectives: Evidence in mouse models has found that the antidepressant trazodone may be protective against neurodegeneration. We therefore aimed to compare cognitive decline of people with dementia taking trazodone with those taking other antidepressants.

Methods: Three identical naturalistic cohort studies using UK clinical registers. We included all people with dementia assessed during 2008–16 who were recorded taking trazodone, citalopram or mirtazapine for at least 6 weeks. Linear mixed models examined age, time and sex-adjusted Mini-mental state examination (MMSE) change in people with all-cause dementia taking trazodone compared with those taking citalopram and mirtazapine. In secondary analyses, we examined those with non-vascular dementia; mild dementia; and adjusted results for neuropsychiatric symptoms. We combined results from the three study sites using random-effects meta-analysis.

Results: We included 2,199 people with dementia, including 406 taking trazodone, with mean 2.2 years follow-up. There was no difference in adjusted cognitive decline in people with all-cause or non-vascular dementia taking trazodone, citalopram or mirtazapine in any of the three study sites. When data from the three sites were combined in meta-analysis, we found greater mean MMSE decline in people with all-cause dementia taking trazodone compared to those taking citalopram (0·26 points per successive MMSE measurement, 95% CI 0·03–0·49; $p = 0.03$). Results in sensitivity analyses were consistent with primary analyses.

Conclusions: There was no evidence of cognitive benefit from trazodone compared to other antidepressants in people with dementia in three naturalistic cohort studies. Despite preclinical evidence, trazodone should not be advocated for cognition in dementia.

NIHR Biomedical research Centre at Oxford Health NHS Foundation Trust

1 | INTRODUCTION

There are no successful disease modifying treatments for dementia,[1] intensifying the need for the identification of new treatment approaches. The repurposing of existing medication, which has proven effective in other diseases, has potential to bring medication more rapidly to general use; the antidepressant trazodone has been proposed to have potential for repurposing in dementia.[2] Increased protein unfolding is a pathological hallmark of many neurodegenerative diseases,[3] possibly mediated through increased activation of the pancreatic endoplasmic reticulum kinase PERK/$eIF2\alpha$-P pathway of the unfolded protein response and subsequent attenuation of protein synthesis.[4] A recent study found that trazodone has effect on $eIF2\alpha$-P in mouse models of neurodegenerative disease[2]; it restored protein synthesis, was neuroprotective, restored memory deficits, prevented neurodegeneration, and prolonged survival in these models of prion disease and frontotemporal dementia. There is potential benefit of this therapeutic approach for other forms of dementia as trazodone was linked to lower levels of phosphorylated tau, a feature of Alzheimer's disease pathology.[5]

Trazodone is an antidepressant with multiple therapeutic mechanisms; it is a serotonin 5-HT$_{2A}$ and α1-adrenergic antagonist, a serotonin reuptake inhibitor and a histamine H$_1$ inverse agonist.[6] It is licenced for major depressive disorder in the UK and US and prescribed for insomnia in depression.[7] Small studies have found it to reduce neuropsychiatric symptoms of Alzheimer's disease[8] and frontotemporal dementia[9] and because of this it is prescribed in clinical practice.[10] To explore the effect of trazodone on cognitive decline in people who develop dementia we performed naturalistic cohort studies in routinely collected secondary mental healthcare data from three large clinical services. As trazodone is prescribed for non-cognitive symptoms of dementia which may reflect more rapidly progressive dementia,[11] we compared trazodone with citalopram and mirtazapine; antidepressant drugs which do not have effect on $eIF2\alpha$-P[2] but are prescribed for similar indications. While there has been no evidence that mirtazapine or citalopram improve cognitive trajectory, we hypothesised that trazodone may do so. As trazodone may be used as a treatment for depression or other neuropsychiatric symptoms, and these symptoms may be risk factors for or symptoms of worse dementia trajectory,[12] we also aimed to take into account the potential confounding effect of neuropsychiatric symptoms. Our specific objectives were to:

- compare the cognitive trajectory of people with dementia who were prescribed trazodone with those prescribed citalopram or mirtazapine
- examine these associations in people with non-vascular dementia subtypes because the PERK/$eIF2\alpha$-P pathway is not pathogenic in vascular dementias

2 | MATERIALS AND METHODS

2.1 | Study setting and data source

We conducted three cohort studies using data from three separate datasets of routinely collected clinical data from large mental health trusts in North London (Camden and Islington NHS Foundation Trust), South London (South London and Maudsley NHS Foundation Trust) and Oxford (Oxford Health NHS Foundation Trust), UK. We used these services' case register Clinical Record Interactive Search (CRIS) data tools, which provide pseudonymised electronic medical records for research purposes.[13,14] These healthcare providers deliver a range of psychiatric services, including dementia assessment and management, to geographic catchment areas containing 1.2 million residents in south London; 480,000 residents in north London; and 1.9 million residents in Oxfordshire, Buckinghamshire, Swindon and Wiltshire, thereby covering around 5% of the UK population. CRIS allows data to be extracted from structured fields in patients' electronic clinical records and, to enhance recognition of relevant information, unstructured text (including correspondence, discharge summaries and clinical notes). Information from the unstructured text is extracted using General Architecture for Text Engineering (GATE), a language processing software[15]; use of GATE in the CRIS resource is detailed in the description of the data resource.[13,14] CRIS has previously been used to examine a variety of dementia-related research questions[13,16] and data from more than one database has previously been combined to allow more diverse and generalizable samples.[17] GATE software has previously been shown to have precision (akin to positive predictive value) of between 94% and 96% for correct identification of psychotropic drugs in these data.[18,19]

2.2 | Ethical approval

Approval to use CRIS was received from the Oxfordshire Research Ethics Committee C (08/H0606/71 + 5) for South London; the National Research Ethics Service Committee East of England—Cambridge Central (14/EE/0177) for North London; the National Research Ethics Service Committee South Central—Oxford C (15/SC/0247) for Oxford. The terms of the ethical approval do not require consent to be provided, but all participants have the right to opt out of data use at any time.

2.3 | Study window

For North London we used all available clinical records from patients seen between 1 January 2008 and 30 September 2016; for South London from 1 January 2006 until 31 March 2016; and for Oxford from 1 June 2008 to 31 March 2016. Cohort entry was the time of last mini-mental state examination (MMSE) assessment before trazodone, citalopram or mirtazapine initiation or, if no MMSE record prior to drug initiation, the time of drug initiation.

2.4 | Study participants

2.4.1 | Inclusion criteria

We retrieved records from the three databases for eligible study participants of any age who had:

- received diagnosis of dementia during the study window (defined as ICD-10[20] code of F01-03 or G30 entered in the structured field of the electronic medical record).
- been recorded in electronic medical record as taking trazodone, citalopram or mirtazapine at any time before or after dementia diagnosis (derived from GATE 'medication' application).
- ≥2 recorded cognitive test scores, with at least one after the initiation of trazodone.
- ≥6 weeks recorded exposure to the drug of interest: drug initiation could precede dementia diagnosis if exposure continued after diagnosis, or it could follow dementia diagnosis.

2.5 | Exposure

We ascertained exposure status by extracting information from CRIS using GATE. This bespoke application is designed to identify medications that are currently prescribed to the patient and was developed through expert annotation, which means that domain experts coded whether the medication prescription was present in a particular document based on pre-defined coding rules and/or their expert experience.[21] This searched for any reference to trazodone (and common mis-spellings or molipaxin, the UK trade name) and

comparator drugs, citalopram or mirtazapine, and extracted the date of the record. Any relevant record of the drugs of interest during the study window would be detected by the GATE algorithm so drug exposure was measured longitudinally. The index date was the first record of the drug starting or continuing and participants were considered as being exposed until the date of the last record of the drug, the date of death, or the end of the study window.

Individuals recorded taking trazodone and citalopram or mirtazapine during the study window, either in combination or succession, were categorised as in the trazodone exposure group, because of our hypothesis that trazodone may benefit cognitive trajectory while mirtazapine or citalopram have not been reported do so. Those who switched medication, for example took trazodone and later took mirtazapine would have been included in the trazodone group with exposure to trazodone defined as from the first to last relevant record of trazodone. Those recorded as taking both mirtazapine and citalopram during the study window were excluded from either control groups.

2.6 | Outcomes

We extracted all MMSE[22] dates and numerator and denominator scores from included patients before and after drug prescription at any time during study window, drawn from a structured field in the source record and a further GATE information extraction. For analysis, we used up to 10 MMSE records for each participant, the baseline record being the last MMSE record before drug initiation or, if no MMSE before initiation, the first MMSE following initiation. MMSE is a 30-point scale assessing global cognitive function regularly recorded by clinicians, has good psychometric properties for determining disease severity,[23] and has been used as a cognitive outcome measure in trials.[24] MMSE has shown validity in differentiating people with and without dementia in previous studies using this datasource.[25]

2.7 | Covariates

We derived data on:

- Sociodemographic factors, as recorded at start of exposure: age, sex, ethnicity, marital status, and socioeconomic status based on area-level deprivation using the 2010 Index of Multiple Deprivation.[26]
- Last-recorded dementia subtype (Alzheimer's disease; vascular dementia; dementia with Lewy bodies, including dementia in Parkinson's disease); other dementia (encompassing any other specified dementia type); and unspecified dementia, where dementia aetiology was not recorded.
- From the South London research site, we extracted data on clinician-rated severity of agitation and depression symptom severity at the start of exposure using the Health of the Nation Outcome Scale (HoNOS).[27] HoNOS is a clinician-rated scale with

acceptable psychometric properties which is usually completed at regular clinical assessments; depression, which may take into account symptoms of loneliness as a symptom of depression, and agitation are rated on a scale from 0 (no symptoms) to 4 (severe symptoms).

We also derived data on date of death for deceased patients from the Office of National Statistics mortality database and the NHS national spine linked using NHS national patient record numbers and additional sociodemographic data. These data have been shown to have accuracy of 94%.[28]

2.8 | Analytic approach

We first examined the baseline demographic and clinical characteristics of the cohort according to drug status. To compare clinical practice in use of trazodone across the three study sites, a psychiatrist manually reviewed the clinical notes for the time of drug initiation to identify the indication for trazodone use and trazodone daily dose in a randomly selected 20 patients for each site.

We compared rate of MMSE change between drug groups using linear mixed models[29] as this approach uses all available outcome data and takes account of individuals' repeated MMSE measurements being correlated. For these analyses, both the intercept and slope were fitted as random effects as individuals had different cognitive scores at baseline and different rates of cognitive change over time. Because less than 10% of our study participants had more than 10 MMSE scores, we only used up to 10 MMSE records in our analysis, with the index MMSE being the final before drug initiation or, if none was available, the first MMSE after drug initiation, and up to nine subsequent MMSEs, until the last recorded documentation of the medication.

Our pre-specified main analysis was adjusted for age, sex and the length of time (as a continuous variable) between first and last MMSE scores. We repeated our main analysis excluding those who had been diagnosed with vascular dementia, as it is not considered to be neurodegenerative,[30] so we hypothesised it as less likely to be affected by trazodone treatment.

Due to data security and governance regulations, only aggregated data could be shared across sites. We conducted meta-analysis of effect estimates from the three sites using random effects models of the weighted mean difference.[31] Data were analysed using STATA (version 12) for mixed models analysis and Comprehensive Meta-analysis (version 3) for meta-analysis.

2.8.1 | Sensitivity analyses

In post-hoc sensitivity analyses, we examined whether confounding by indication affected our results, by (1) conducting our primary analysis with additional adjustment for neuropsychiatric symptom severity using data from the South London site—the largest of our

research sites—with HoNOS agitation and depressed mood domains included as two separate continuous variables; and (2) repeating our analysis only including people with mild dementia (MMSE ≥20), adjusted for age, time and sex and, in a separate model, additionally for agitation and depressed mood.

2.9 | Role of the funding source

Funders had no role in the study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication.

3 | RESULTS

The baseline characteristics according to site and drug groups are detailed in Table 1 and study flow is in Figure 1 We included 2,199 people with dementia, of whom 406 were prescribed trazodone, 702 mirtazapine and 1,091 citalopram; 455 participants were from North London, 1,263 from South London; and 481 from Oxford. The mean follow-up was 2.2 years duration (standard deviation (sd) 1.4 years) and the mean time between each MMSE assessment was between 4 and 7 months in the drug groups. Participants were 79.3 (3.0) years old on average and 1,435 (65.3%) were female. Most were white ethnicity (79.8%), 34.2% were married and 32.7% widowed. Mean baseline MMSE in the total sample was 18.8 (2.6) and 1,733 (78.8%) had a neurodegenerative non-vascular dementia. The primary indication for use of trazodone in a sample of 55 participants was depression, agitation or insomnia (Table 2) and mean daily dose was 101.8 mg (range 50–300 mg); for one patient, trazodone was marked as to be given 'PRN' (when necessary.)

3.1 | Comparison of trazodone to mirtazapine or citalopram in three research sites

Mean unadjusted MMSE change (Table 3) for people with all-cause dementia taking trazodone was −0.86 points per assessment (standard error (se) 0.49) in North London, −1.03 (0.12) in South London and −0.96 (0.14) in Oxford. In the adjusted model (Table 3, Figure 2) for people with all-cause dementia, there were no significant differences in MMSE change between the trazodone and other drug groups. MMSE decline per assessment in people taking trazodone was 0.01 (95% confidence interval −1.33, 1.35) points more than those taking mirtazapine in North London, 0.22 more (−0.06, 0.51) in South London and 0.40 more (−0.21, 1.01) in Oxford. For people taking trazodone compared to citalopram, MMSE decline was 0.08 points (−1.24, 1.40) more per assessment in North London, 0.27 (0.00, 0.54) more in South London and 0.26 points more (−0.21, 0.73) in Oxford.

For people with non-vascular dementia type, MMSE change did not differ between those taking trazodone and mirtazapine or

TABLE 1 Baseline patient demographic and clinical characteristics for three research sites

		Trazodone		Mirtazapine		Citalopram		
		n	%	n	%	n	%	p-value[a]
North London								
Number of patients		16		158		281		
Mean years follow-up (sd)		2.7 (2.6)		2.5 (2.3)		2.3 (1.8)		0.44
Age at drug initiation (y ± sd)		74.4 (9.6)		78.6 (8.9)		78.9 (8.7)		0.15
Sex	Female	9	56.3	109	69.0	180	64.1	0.42
	Missing	0	0	0	0	0	0	
Ethnicity	White	12	75.0	130	82.3	229	81.5	0.54
	Black	1	6.3	9	5.7	21	7.5	
	Asian	3	18.8	9	5.7	16	5.7	
	Other	0	0	4	2.5	9	3.2	
	Missing	0	0	6	3.8	6	2.1	
Marital status	Married	4	25.0	44	27.8	79	28.1	0.63
	Missing	0	0	10	6.3	16	5.7	
Mean baseline MMSE score (sd)		18.1 (5.0)		21.1 (6.4)		21.5 (6.2)		0.10
Vascular dementia		5	31.3	27	17.1	33	11.7	0.04
South London								
Number of patients		190		451		622		
Mean years follow-up (sd)		2.6 (2.7)		2.5 (2.3)		2.3 (1.8)		0.38
Age at drug initiation (y ± sd)		78.3 (8.3)		79.3 (9.5)		79.1 (9.6)		0.22
Sex	Female	99	52.1	308	68.3	415	66.7	0.05
	Missing	0	0	4	0.9	3	0.5	
Ethnicity	White	147	77.4	342	75.8	475	76.4	<0.001
	Black	36	19.0	58	12.9	97	15.6	
	Asian	4	2.1	27	6.0	33	5.3	
	Other	2	1.1	20	2.1	13	4.4	
	Missing	1	0.5	4	0.9	4	0.6	
Marital status	Married	74	39.5	150	33.3	193	31.0	<0.001
	Missing	4	2.1	7	1.6	20	3.5	
Mean baseline MMSE score (sd)		13.7 (8.0)		18.0 (7.1)		18.7 (6.6)		<0.001
Vascular dementia		58	30.5	110	24.4	184	29.6	<0.001
Oxford								
Number of patients		200		93		188		
Mean years follow-up (sd)		1.2 (0.9)		1.2 (1.0)		1.3 (1.0)		0.40
Age at drug initiation (y ± sd)		81.1 (7.7)		79.7 (7.3)		80.6 (7.2)		0.35
Sex	Female	113	46.5	66	71.0	136	72.3	0.002
	Missing	0	0	0	0	0	0	
Ethnicity	White	177	88.5	71	76.3	171	91.0	<0.001
	Black	3	1.5	0	0	0	0	
	Asian	0	0	3	3.2	1	0.5	

(Continues)

T A B L E 1 (Continued)

		Trazodone		Mirtazapine		Citalopram		
		n	%	n	%	n	%	*p*-value[a]
	Other	3	1.5	0	0	1	0.5	
	Missing	17	8.5	19	20.4	15	8.0	
Marital status	Married	98	49.0	34	36.6	77	41.0	0.07
	Missing	32	16.0	29	31.2	36	19.2	
Mean baseline MMSE score (sd)		17.7 (6.2)		20.9 (5.7)		20.4 (6.3)		<0.001
Vascular dementia		23	11.5	13	14.0	13	6.9	0.13

Abbreviation: MMSE, mini-mental state examination.

[a]*p*-values were derived from ANOVA for continuous variables and Pearson's chi square for categorical variables.
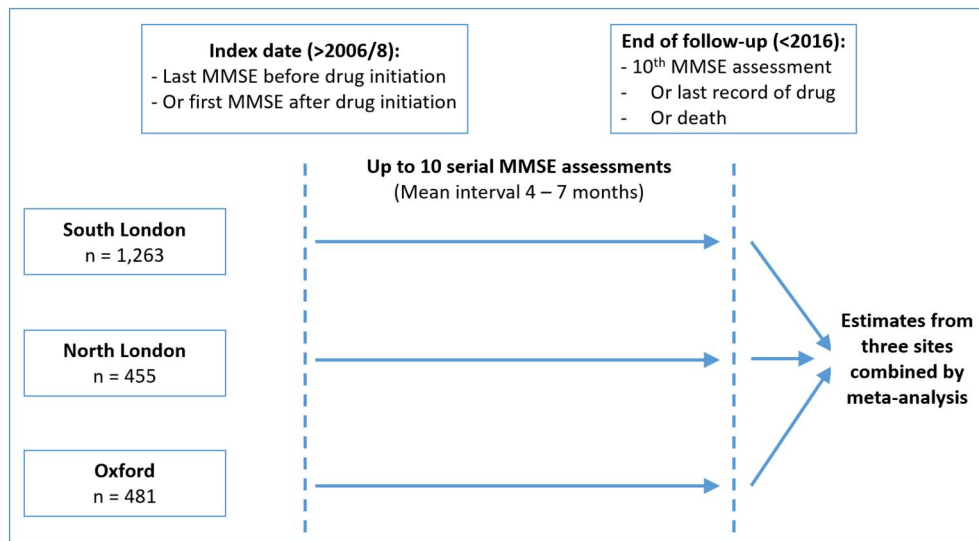
F I G U R E 1 Study flow

	North London (n = 16[a])	South London (n = 20)	Oxford (n = 20)
Symptom	**n (%)**		
Agitation	6 (37.5)	12 (60)	14 (70)
Depression	7 (43.8)	3 (15)	2 (10)
Insomnia	3 (18.8)	5 (25)	4 (20)
Mean daily dose (mg)	93.8	130	80[b,c]
Range	50, 200	50, 300	50, 200

T A B L E 2 Indication for trazodone in a sample of 20 participants in each sites

[a]16 people with dementia taking trazodone in North London site.

[b]Dose information only available for 19 of the 20 patient notes screened in Oxford site.

[c]One of 19 patients recorded as having trazodone prescribed 'PRN'.

citalopram in the North London or Oxford sites and there was a marginally faster rate of MMSE decline in the South London site for people taking trazodone compared to mirtazapine (0.31 (0.00, 0.62) points more per MMSE assessment) and citalopram (0.35 (0.05, 0.65) points per MMSE assessment.)

3.2 | Pooled results from research sites

In pooled results from random-effects meta-analysis, there was no difference between MMSE change for people taking trazodone v mirtazapine (0.24 (−0.01, 0.50), $p = 0.06$, $I^2 = 0\%$ for

TABLE 3 Mixed models examining cognitive change over time for three sites

North London				
			Difference from trazodone group	
		Change in MMSE per assessment (S.E.)	**Mean change (95% CI)**	**p-value**
All-cause dementia unadjusted model	Trazodone	−0.86 (0.49)	Reference	
	Mirtazapine	−0.73 (0.50)	0.12 (−0.86; 1.10)	0.81
	Citalopram	−0.64 (0.49)	0.21 (−0.76; 1.18)	0.67
All-cause dementia adjusted model[a]	Trazodone	−0.84 (0.66)	Reference	
	Mirtazapine	−0.83 (0.68)	0.01 (−1.33; 1.35)	0.99
	Citalopram	−0.75 (0.67)	0.08 (−1.24; 1.40)	0.90
Non-vascular dementia adjusted model[a]	Trazodone	−0.26 (0.56)	Reference	
	Mirtazapine	−0.77 (0.58)	−0.50 (−1.64; 0.63)	0.38
	Citalopram	−0.68 (0.57)	−0.41 (−1.54; 0.71)	0.47
South London				
			Difference from trazodone group	
		Change in MMSE per assessment (S.E.)	**Mean change (95% CI)**	**p-value**
All-cause dementia unadjusted model	Trazodone	−1.03 (0.12)	Reference	
	Mirtazapine	−0.83 (0.14)	0.20 (−0.08; 0.48)	0.16
	Citalopram	−0.80 (0.14)	0.23 (−0.04; 0.49)	0.09
All-cause dementia adjusted model[a]	Trazodone	−1.09 (0.12)	Reference	
	Mirtazapine	−0.86 (0.14)	0.22 (−0.06; 0.51)	0.12
	Citalopram	−0.82 (0.14)	0.27 (0.00; 0.54)	0.05*
Non-vascular dementia adjusted model[a]	Trazodone	−1.17 (0.14)	Reference	
	Mirtazapine	−0.87 (0.16)	0.31 (0.00; 0.62)	0.05*
	Citalopram	−0.83 (0.15)	0.35 (0.05; 0.65)	0.02*
Oxford				
			Difference from trazodone group	
		Change in MMSE per assessment (S.E.)	**Mean change (95% CI)**	**p-value**
All-cause dementia unadjusted model	Trazodone	−0.96 (0.14)	Reference	
	Mirtazapine	−0.54 (0.25)	0.42 (−0.08; 0.92)	0.10
	Citalopram	−0.67 (0.19)	0.29 (−0.09; 0.67)	0.13
All-cause dementia adjusted model[a]	Trazodone	−0.97 (0.16)	Reference	
	Mirtazapine	−0.57 (0.28)	0.40 (−0.21; 1.01)	0.18
	Citalopram	−0.71 (0.22)	0.26 (−0.21; 0.73)	0.26
Non-vascular dementia adjusted model[a]	Trazodone	−1.13 (0.18)	Reference	
	Mirtazapine	−0.61 (0.32)	0.52 (−0.13; 1.17)	0.12
	Citalopram	−0.76 (0.25)	0.37 (−0.13; 0.87)	0.15

Abbreviation: MMSE, mini-mental state examination.

[a]adjusted for age, sex and time between first and last MMSE scores.

*indicates p value < 0.05.

all-cause dementia (Figure 2); 0.29 (−0.05, 0.63), $p = 0.10$, $I^2 = 16.3\%$ for non-vascular dementia (Figure 3)). MMSE decline was 0.26 points greater ((0.03, 0.49), $p = 0.03$, $I^2 = 0\%$) per MMSE assessment more for people with all-cause dementia taking trazodone compared to citalopram (Figure 2) and 0.32 points more ((0.07, 0.57), $p = 0.01$, $I^2 = 0\%$) for those with
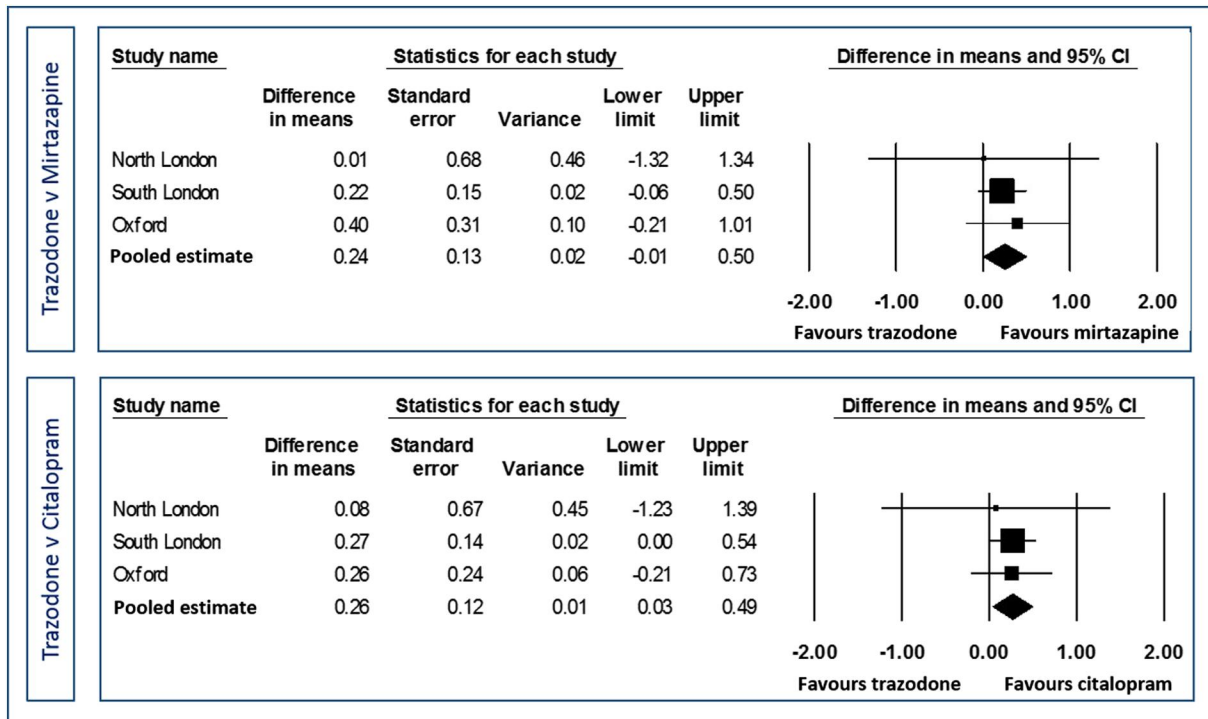
FIGURE 2 Forest plots of difference in mini-mental state examination change for people with all-cause dementia taking trazodone v citalopram and mirtazapine
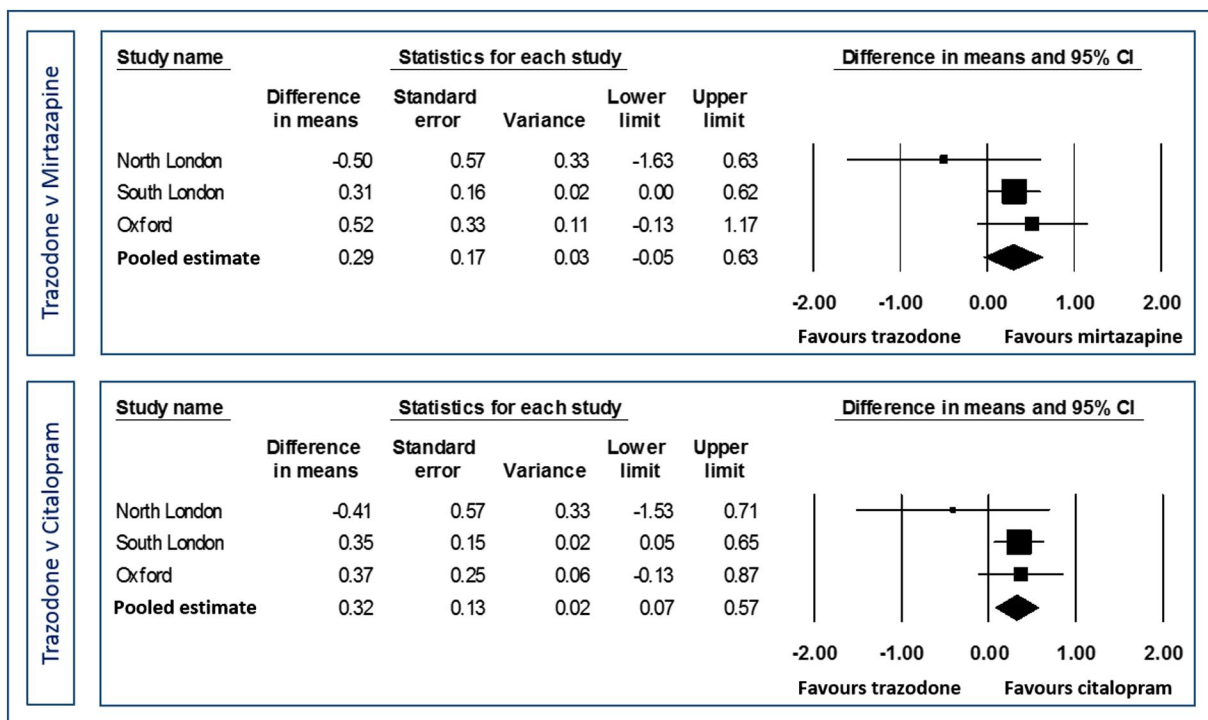

FIGURE 3 Forest plots of difference in mini-mental state examination change for people with non-vascular dementia taking trazodone v citalopram and mirtazapine

non-vascular dementia taking trazodone compared to citalopram (Figure 3).

3.3 | Sensitivity analyses

We included 1,236 people with all-cause dementia in South London (188 trazodone, 446 mirtazapine, 602 citalopram) with rating of depressed mood and agitation (Appendix 1a) in analysis adjusted for neuropsychiatric symptoms severity. Results were similar to primary analyses (Appendix 1b) with no difference in cognitive decline between those taking trazodone and mirtazapine (0.21 (−0.08, 0.49)) or citalopram (0.25 (−0.02, 0.52)).

When we included only the 660 of 1,263 patients in South London with mild all-cause dementia at baseline (61 trazodone, 248 mirtazapine, 351 citalopram) we found that people taking trazodone had faster cognitive decline than those taking mirtazapine (0.45 MMSE difference per assessment (0.02; 0.88), $p = 0.04$) and citalopram (0.53 (0.12; 0.94), $p = 0.01$) (Appendix 1b). In models adjusted for agitation and depressed mood, people with mild dementia taking trazodone performed worse on successive MMSE assessments than those taking mirtazapine (0.43 (0.00; 0.86), $p = 0.05$) and citalopram (0.52 (0.10; 0.93), $p = 0.01$).

4 | DISCUSSION

In this naturalistic cohort study in people with clinically diagnosed dementia who were prescribed one of three antidepressants, we found no evidence of cognitive benefit of trazodone in either all-cause dementia or non-vascular dementias. Overall, people taking trazodone had a slightly worse cognitive trajectory than those taking citalopram and there was a similar pattern in the comparison between trazodone and mirtazapine although the smaller numbers in these groups meant that the result was not significant. We found an absence of cognitive benefit from trazodone in all three clinical sites, as well as when combined in meta-analysis. The consistent absence of positive findings in our sensitivity analyses adjusted for severity of neuropsychiatric symptoms and in people with mild dementia at baseline adds to the strength of our conclusions.

This study suggests that there is no modification of cognitive trajectory associated with trazodone in people with established dementia. This supports evidence from small randomised controlled trials (sample sizes between 15 and 37) which have examined the cognitive effect of trazodone as secondary outcomes. One of these found worse MMSE function in people with AD taking trazodone compared to those who received behavioural management techniques for agitation[32] (mean baseline MMSE 14) another trial of trazodone for neuropsychiatric symptoms in FTD found no effect on MMSE[9] (mean baseline MMSE 20.8). Trazodone for sleep disturbance in AD had no effect on cognition or general function[33] (mean baseline MMSE 11.4). Other associated outcomes also support no disease-modifying benefit of trazodone in established dementia; a Cochrane review of pharmacological interventions for agitation in dementia found no difference in global impression or trial withdrawal rates between trazodone and typical antipsychotics or placebo.[34] There is mixed literature on the cognitive effect of citalopram and mirtazapine in dementia, including early preclinical evidence of neuro-protective effects.[35,36] However citalopram and mirtazapine appeared to worsen cognition in the multicentre randomised, double-blinded, placebo-controlled trials CitAD[37] and HTA-SADD[38] respectively and there is no consistent evidence of cognitive benefit for these medications. The worse cognitive performance for patients taking trazodone compared to citalopram in our study suggests it is unlikely that there is cognitive benefit from trazodone.

Patients in our study had moderately severe dementia at baseline (mean MMSE in the three sites 13.7 to 18.1), reflecting the use of trazodone in these patients for non-cognitive symptoms of dementia which are less common in mild dementia.[39] To consider whether benefit from trazodone would only be seen in earlier disease when medication is hypothesised to be more effective as neuropathological damage is less severe,[40] we analysed only those with mild dementia. We found those with mild dementia taking trazodone declined faster than comparators, suggesting trazodone does not confer cognitive benefit early in the illness. Three other studies support our finding as they did not find cognitive benefit or reduced dementia incidence in people without dementia. Firstly, a cohort study using UK general practice data reported higher incidence of dementia in 4,596 people aged over 50 years without dementia at baseline who were prescribed trazodone compared to those taking other antidepressants.[41] Secondly, a cross-sectional observational study examining the cognitive effects of a range of medications in participants without dementia in the UK Biobank found no cognitive benefit associated with trazodone and instead a slowing of reaction time,[42] and thirdly a small study of non-demented people found three-fold increase in incident dementia in the 15 people taking trazodone compared to non-users.[43]

The coefficients for MMSE change were summarised across the whole follow-up period and show mean decline in cognitive function of between 0.5 and 1 point per successive MMSE assessment, which took place at an interval of between 4 and 7 months. The people in each of the three drug groups showed an initial improvement from the first to second assessment and this is consistent with other naturalistic studies examining cognitive function in routine practice.[16] This improvement may reflect the combined effect of simultaneous initiation of pharmacological or psycho-social cognition-enhancing treatments, improvement of cognition as a result of the antidepressants alleviating neuropsychiatric symptoms, or practice effect in MMSE performance.[44] As expected, cognitive decline was subsequently seen in all drug groups.

4.1 | Strengths and limitations

This is the largest study to examine the effect of trazodone on cognition with any comparator and with the longest follow-up,

providing strong evidence as to the absence of cognitive benefit of trazodone in its current routine clinical use. Our use of data from three different services covering around 5% of the UK's population, as well as the inclusion of almost all eligible people in this naturalistic study, ensures that our findings are generalizable and avoids the selection bias common in randomised controlled trials.[45,46] Our use of mixed linear models is a strong analytic approach as it uses every cognitive assessment to reduce measurement error. Although duration of drug exposure was variable, this was accounted for in our analysis.

Our study has limitations. Firstly, our observational, non-randomised study design meant that there were baseline differences between the groups which may suggest confounding by indication. Patients in the trazodone groups had lower MMSE scores at baseline and more neuropsychiatric symptoms than the comparator groups. People taking trazodone therefore may have had more advanced dementia with more severe neuropsychiatric symptoms. In addition, the drugs may have been used differentially for depression meaning that trazodone may have been used for people with treatment resistance which could have ameliorated the drug's potential cognitive benefit. In our sensitivity analyses, we found consistent results when we adjusted for neuropsychiatric symptom severity and when we only analysed those with mild dementia at baseline, although these analyses may still have had residual confounding. In addition, our cohort's derivation of patients from secondary mental healthcare services meant that data was only available for those continuing to receive follow-up from these services, with potential for bias. Patients with continuing clinical concerns, and likely worse disease course, may be more likely to receive follow-up and cognitive assessment. However, the custom in these clinical settings is to follow patients receiving active intervention and the consistent results between these settings lends support to our conclusions.

Unlike studies which use pharmacy data and scrutinise drug use, we could not derive reliable data on concordance with prescribed medication, nor dose, which may modulate any cognitive effect of trazodone. We therefore manually reviewed the notes of 55 randomly-selected patients, finding a range of daily doses (50 to 300 mg) and one patient marked as receiving the medication 'PRN'. The dose used in the mouse-model study was equivalent to 194 mg daily in humans so some in our study may have received a lower or higher dose than the experimental study. However, our sample consisted of older people for whom a smaller dose is required to achieve the same plasma level, and clinicians were likely to have prescribed sufficient doses targeting clinical effect. Furthermore, the indication for trazodone differed between sites suggesting that clinical use of the medication may be different but nonetheless we found consistent results from the three sites. We lacked other information of interest including as we were not able to derive data on comorbid medications, hospitalisations, physical health or activity of daily living performance although these factors are unlikely to have confounded our main analyses as they would not have affected the decision about prescribing of trazodone. Finally, MMSE assessments were unblinded meaning that there could be patient or observer bias if clinicians were expecting different cognitive benefit from the drugs of interest, but such effect is unlikely as, at the time of these observations, it was not widely thought that these drugs were of cognitive benefit.

4.2 | Clinical implications and future research

This study provides naturalistic evidence of the lack of effect of trazodone on cognitive decline, compared to other antidepressants. While randomised controlled trials of trazodone are the gold-standard evaluation of a medication, these are costly and time-consuming and as not all drugs can be examined, it is important to pick the drugs examined with care as those most likely to lead to benefit and less likely to cause harm. Our research is evidence of the potential utility of large scale routinely collected research data for the rapid examination of research hypotheses to guide future experimental studies. There are several potential limitations of these data resources, including non-representative patient populations, misclassification bias or confounding by indication,[45] meaning that conclusions using such data should be cautious. Antidepressants are commonly used for neuropsychiatric symptoms in dementia. For example a study of UK primary care data indicated that 37% of people with recorded dementia in 2015 had a prescription for an antidepressant,[47] and this has increased from 28% in 2005, and an examination of 2007 UK general practice data found that 5.4% of people with dementia had a prescription for trazodone.[10] Despite the preliminary evidence from animal models, evidence from our study and others suggests there is no current justification to advocate trazodone use for cognition in dementia.

design, data collection and analysis, decision to publish, or preparation of the manuscript.

ORCID

Andrew Sommerlad https://orcid.org/0000-0002-8895-7055
Gayan Perera https://orcid.org/0000-0002-3414-303X
Christoph Mueller https://orcid.org/0000-0001-9816-1686
Robert Stewart https://orcid.org/0000-0002-4435-6397

REFERENCES

1. Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades? *Alzheimer's Dement: J Alzheimer's Assoc.* 2016;12(1):60-64.
2. Halliday M, Radford H, Zents KA, et al. Repurposed drugs targeting eIF2α-P-mediated translational repression prevent neurodegeneration in mice. *Brain.* 2017;140(6):1768-1783.
3. Halliday M, Mallucci GR. Modulating the unfolded protein response to prevent neurodegeneration and enhance memory. *Neuropathology Appl Neurobiol.* 2015;41(4):414-427.
4. Smith HL, Mallucci GR. The unfolded protein response: mechanisms and therapy of neurodegeneration. *Brain.* 2016;139(8):2113-2121.
5. Reddy PH. Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. *Brain Res.* 2011;1415:136-148.
6. Stahl SM. Mechanism of action of trazodone: a multifunctional drug. *CNS Spectr.* 2009;14(10):536-546.
7. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin psychiatry.* 2005;66(4):469-476.
8. López-Pousa S, Garre-Olmo J, Vilalta-Franch J, Turon-Estrada A, Pericot-Nierga I. Trazodone for Alzheimer's disease: a naturalistic follow-up study. *Arch Gerontol Geriatr.* 2008;47(2):207-215.
9. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dementia geriatric cognitive Disord.* 2004;17(4):355-359.
10. Guthrie B, Clark SA, McCowan C. The burden of psychotropic drug prescribing in people with dementia: a population database study. *Age Ageing.* 2010;39(5):637-642.
11. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. *Am J Psychiatry.* 2015;172(5):460-465.
12. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390(10113):2673-2734.
13. Perera G, Broadbent M, Callard F, et al. Cohort profile of the South London and Maudsley NHS foundation trust biomedical research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. *BMJ open.* 2016;6(3):e008721.
14. Werbeloff N, Osborn DPJ, Patel R, et al. The Camden & Islington Research Database: using electronic mental health records for research. *PLOS One.* 2018;13(1):e0190703.
15. Cunningham H. GATE, a general architecture for text engineering. *Comput Humanit.* 2002;36(2):223-254.
16. Perera G, Khondoker M, Broadbent M, Breen G, Stewart R. Factors associated with response to acetylcholinesterase inhibition in dementia: a cohort study from a secondary mental health care case register in London. *PloS One.* 2014;9(11):e109484.
17. Werbeloff N, Chang C-K, Broadbent M, Hayes JF, Stewart R, Osborn DP. Admission to acute mental health services after contact with crisis resolution and home treatment teams: an investigation in two large mental health-care providers. *Lancet Psychiatry.* 2017;4(1):49-56.
18. Hayes RD, Downs J, Chang C-K, et al. The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. *Schizophr Bull.* 2015;41(3):644-655.
19. NIHR Maudsley Biomedical Research Centre. *CRIS Natural Language Processing (NLP) Service*; 2021. https://www.maudsleybrc.nihr.ac.uk/facilities/clinical-record-interactive-search-cris/cris-natural-language-processing/
20. World Health Organization. International statistical classification of diseases and health related problems (The) ICD-10. World Health Organization; 2004.
21. Mueller C, John C, Perera G, Aarsland D, Ballard C, Stewart R. Antipsychotic use in dementia: the relationship between neuropsychiatric symptom profiles and adverse outcomes. *Eur J Epidemiol.* 2021;36(1):89-101.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
23. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry.* 2006;14(2):139-144.

24. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med.* 2012;366(10):893-903.

25. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016. *Alzheimer's Dementia.* 2018;14(7):933-943.

26. Jordan H, Roderick P, Martin D. The Index of Multiple Deprivation 2000 and accessibility effects on health. *J Epidemiol Community Health.* 2004;58(3):250-257.

27. Pirkis JE, Burgess PM, Kirk PK, Dodson S, Coombs TJ, Williamson MK. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS) family of measures. *Health Qual Life Outcomes.* 2005;3(1):76.

28. Jewell A, Broadbent M, Hayes RD, Gilbert R, Stewart R, Downs J. Impact of matching error on linked mortality outcome in a data linkage of secondary mental health data with Hospital Episode Statistics (HES) and mortality records in South East London: a cross-sectional study. *BMJ Open.* 2020;10(7):e035884.

29. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics.* 1982;38(4):963-974.

30. Schneider JA, Bennett DA. Where vascular meets neurodegenerative disease. *Stroke.* 2010;41(10 suppl 1):S144-S6.

31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials.* 1986;7(3):177-188.

32. Teri L, Logsdon R, Peskind E, et al. Treatment of agitation in AD A randomized, placebo-controlled clinical trial. *Neurology.* 2000;55(9):1271-1278.

33. Camargos EF, Louzada LL, Quintas JL, Naves JO, Louzada FM, Nóbrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. *Am J Geriatr Psychiatr.* 2014; 22(12):1565-1574.

34. Martinón-Torres G, Fioravanti M, Evans JG. Trazodone for agitation in dementia. *Cochrane Database Syst Rev.* 2004;(3):CD004990.

35. Ramon-Duaso C, Rodríguez-Morató J, Selma-Soriano E, et al. Protective effects of mirtazapine in mice lacking the Mbnl2 gene in forebrain glutamatergic neurons: relevance for myotonic dystrophy 1. *Neuropharmacology.* 2020;170:108030.

36. Reddy AP, Yin X, Sawant N, Reddy PH. Protective effects of antidepressant citalopram against abnormal APP processing and amyloid beta-induced mitochondrial dynamics, biogenesis, mitophagy and synaptic toxicities in Alzheimer's disease. *Hum Mol Genet.* 2021;30(10):847-864.

37. Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA.* 2014;311(7):682-691.

38. Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multi-centre, double-blind, placebo-controlled trial. *Lancet.* 2011;378(9789):403-411.

39. Livingston G, Barber J, Marston L, et al. Prevalence of and associations with agitation in residents with dementia living in care homes: MARQUE cross-sectional study. *BJPsych Open.* 2017;3(4):171-178.

40. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med.* 2014;275(3):251-283.

41. Brauer R, Lau WC, Hayes JF, et al. Trazodone use and risk of dementia: a population-based cohort study. *PLoS Med.* 2019;16(2):e1002728.

42. Nevado-Holgado AJ, Kim C-H, Winchester L, Gallacher J, Lovestone S. Commonly prescribed drugs associate with cognitive function: a cross-sectional study in UK Biobank. *BMJ Open.* 2016;6(11):e012177.

43. Leng Y, Diem SJ, Stone KL, Yaffe K. Antidepressant use and cognitive outcomes in very old women. *J Gerontol A Biol Sci Med Sci.* 2017;73(10):1390-1395.

44. Galasko D, Abramson I, Corey-Bloom J, Thal LJ. Repeated exposure to the mini-mental state examination and the information-memory-concentration test results in a practice effect in Alzheimer's disease. *Neurology.* 1993;43(8):1559-1563.

45. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Routinely collected data and comparative effectiveness evidence: promises and limitations. *Can Med Assoc J.* 2016;188(8):E158-E164.

46. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials.* 2015;16(1):495.

47. 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(3):e149-e156.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.