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

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

[1]Faculty of Health, University of Plymouth, Plymouth, UK
[2]Centre for Dementia Studies, Brighton and Sussex Medical School, University of Sussex, Brighton and Hove, UK
[3]Care Policy and Evaluation Centre, London School of Economics and Political Science, London, UK
[4]Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, Norfolk, UK
[5]Coordinator for Service User and Carer Involvement in Research, Sussex Partnership NHS Foundation Trust, Brighton and Hove, UK
[6]College of Medicine and Health, University of Exeter, Exeter, UK
[7]Birmingham and Solihull Mental Health Foundation NHS Trust, Birmingham, UK
[8]Department of Psychiatry, University of Manchester, Manchester, UK
[9]Division of Psychiatry, University College London, London, UK
[10]Department of Psychiatry, Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland
[11]Research and Development, Surrey and Borders Partnership NHS Foundation Trust, Leatherhead, UK
[12]Former Carer, Alzheimer's Society Research Network, London, UK
[13]Department of Psychiatry, University of Cambridge School of Medicine, Cambridge, UK
[14]Cambridgeshire and Peterborough Foundation Trust, Cambridge, UK
[15]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[16]Joint Clinical Research Office, University of Sussex, Brighton, UK

[*]Corresponding author sube.banerjee@plymouth.ac.uk

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/VPDT7105.

Primary conflicts of interest: Sube Banerjee 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. Alistair Burns 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 medicolegal reports and the Driver and Vehicle Licensing Authority, outside the submitted work. Clive Ballard 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. Peter Bentham reports work as a paid Consultant for TauRx Therapeutics outside the submitted work. Robert Howard reported grant support from NIHR and being a Trustee of Alzheimer's Research UK, member HTA Commissioning sub-board 2016–17 and HTA Commissioning Committee 2013–18. John O'Brien 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 and NIHR Dementia lead. Lee Shepstone was EME Funding Committee member 2010–15. Ann Marie Swart NCTU is funded by NIHR; member HTA Efficient Designs 2 2015–16, HTA Efficient Study Designs Board 2014 and NIHR CTU Standing Advisory Committee 2016–22. Naji Tabet reports grant support from Avenir Pharma and NIHR ARC and CRN leadership roles. Alan Thomas 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.

Published October 2023
DOI: 10.3310/VPDT7105

Scientific summary

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

Health Technology Assessment 2023; Vol. 27: No. 23
DOI: 10.3310/VPDT7105

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

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

Aim

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

Primary objectives

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

Methods

Design

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

Intervention

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

Inclusion and exclusion criteria

Patients were eligible if the following criteria were met:

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

Exclusion criteria included:

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

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

Setting

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

Consent

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

Randomisation and blinding

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

Outcomes

Primary outcome

CMAI score (Long Form) at 12 weeks.

Secondary outcomes

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

Sample size and statistical analysis

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

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

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

Economic evaluation

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

Patient and public involvement

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

Protocol change

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

Results

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

Conclusions

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

Trial registration

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

Funding

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

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.6

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2021 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), Embase (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/115/76. The contractual start date was in December 2015. The draft report began editorial review in July 2021 and was accepted for publication in September 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).