Minocycline 200 mg or 400 mg versus placebo for mild Alzheimer's disease: the MADE Phase II, three-arm RCT

Robert Howard,[1*] Olga Zubko,[2] Richard Gray,[3] Rosie Bradley,[4] Emma Harper,[4] Linda Kelly,[4] Lynn Pank,[4] John O'Brien,[5] Chris Fox,[6] Naji Tabet,[7] Gill Livingston,[1] Peter Bentham,[8] Rupert McShane,[9] Alistair Burns,[10] Craig Ritchie,[11] Suzanne Reeves,[1] Simon Lovestone,[9] Clive Ballard,[12] Wendy Noble,[13] Gordon Wilcock[14] and Ramin Nilforooshan[15]

[1]Division of Psychiatry, University College London, London, UK
[2]Department of Old Age Psychiatry, King's College London, London, UK
[3]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[4]Medical Research Council Population Health Research Unit, University of Oxford, Oxford, UK
[5]Department of Psychiatry, University of Cambridge, Cambridge, UK
[6]Norwich Medical School, University of East Anglia, Norwich, UK
[7]Department of Old Age Psychiatry, University of Sussex, Brighton, UK
[8]The Barberry Centre, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK
[9]Department of Psychiatry, University of Oxford, Oxford, UK
[10]Department of Old Age Psychiatry, University of Manchester, Manchester, UK
[11]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[12]Medical School, University of Exeter, Exeter, UK
[13]Department of Basic and Clinical Neuroscience, King's College London, London, UK
[14]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[15]Abraham Cowley Unit, Surrey and Borders Partnership NHS Foundation Trust, Redhill, UK

*Corresponding author robert.howard@ucl.ac.uk

Declared competing interests of authors: Robert Howard reports membership of the Health Technology Assessment (HTA) Commissioning Board between 2013 and 2018. John O'Brien reports personal fees from TauRx Pharmaceuticals Ltd (Singapore) and GE Healthcare (Chicago, IL, USA), Eli Lilly and Company (Indianapolis, IN, USA) and Eisai Co., Ltd (Tokyo, Japan), outside the submitted work. Gill Livingston reports membership of the HTA Clinical Trials Board Associate from 2007 to 2010. Peter Bentham reports personal fees from TauRx Pharmaceuticals Ltd outside the submitted work. Craig Ritchie reports other payments from Roche Holding AG (Basel, Switzerland), Nutricia International B.V. (Zoetermeer, the Netherlands), Actinogen Medical (Sydney, NSW, Australia), Kyowa Hakko Kirin Co., Ltd (Singapore), Biogen Inc. (Cambridge, MA, USA) and Merck Sharp & Dohme Corp. (Kenilworth, NJ, USA) and grants from Janssen Pharmaceutica (Beerse, Belgium) outside the

submitted work. Simon Lovestone reports other from Janssen-Cilag Ltd (High Wycombe, UK) and grants from AstraZeneca plc (Cambridge, UK) and European Federation of Pharmaceutical Industries and Associations (Brussels, Belgium) outside the submitted work. In addition, Simon Lovestone has patents issued and pending related to biomarkers for Alzheimer's disease. He also reports membership of the Efficacy and Mechanism Evaluation Strategy Group from 2015 to 2019 and of the Medical Advisory Board of SomaLogic (Boulder, CO, USA) up to 2019 and other consultancy for Merck Sharp & Dohme Corp., Eli Lilly and Company and Optum, Inc. (Eden Prairie, MN, USA). Clive Ballard reports grants and personal fees from Acadia Pharmaceutical Company (San Diego, CA, USA) and Lundbeck A/S (Copenhagen, Denmark) and personal fees from Roche Holding AG, Otusaka Pharmaceutical Co., Ltd (Tokyo, Japan), Novartis International AG (Basel Switzerland), Eli Lilly and Company and Pfizer Inc. (New York, NY, USA) outside the submitted work.

Published April 2020
DOI: 10.3310/eme07020

Plain English summary

The MADE RCT

Efficacy and Mechanism Evaluation 2020; Vol. 7: No. 2
DOI: 10.3310/eme07020

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

Plain English summary

Alzheimer's disease affects about 700,000 people in the UK and, although there are drug treatments that can modestly improve some of the symptoms, we do not yet have any treatments that slow down the progression of dementia.

Minocycline is an antibiotic that has been shown to protect brain cells in a number of experimental and animal models of Alzheimer's disease. Minocycline is cheap and well tolerated. If it could significantly slow down the course of Alzheimer's disease, it could quickly be made available to large numbers of people with Alzheimer's disease worldwide. Although minocycline is probably one of the best current candidates for Alzheimer's disease modification, the current evidence can only suggest a potential benefit.

A clinical trial was conducted to determine definitively whether or not minocycline is effective in slowing the decline in Alzheimer's disease. Long-term treatment effects of minocycline were investigated, with two doses of minocycline, on decline in cognitive function, including memory, attention and language, and ability to carry out essential functions of daily living, such as getting dressed, grooming and eating.

Unfortunately, the study found that minocycline treatment did not have any measurable effect in slowing down the progression of Alzheimer's disease. Participants who took minocycline showed exactly the same worsening of their cognitive functioning and activities of daily living as those who were allocated to placebo treatment. The trial also established that minocycline at the high dose is poorly tolerated in patients with Alzheimer's disease, whereas the low dose of minocycline is well tolerated, with participants being no more likely to withdraw from trial medication than those taking placebo.

One limitation of the study is that biomarkers were not used to confirm Alzheimer's disease diagnosis, as tests for biomarkers are not routinely available within the NHS. Compliance with medication was also worse than expected, with few patients in the high-dose arm completing 2 years' treatment and only moderate compliance in the low-dose and placebo treatment arms. It was difficult to obtain outcome assessments that resulted in unequal numbers of completed assessments across treatment arms, which could have biased the study's results. Having said that, additional analyses investigating potential bias have, reassuringly, shown the same pattern of results.

Although disappointing, these results are important because they will guide further research into the search for a treatment. There is currently much interest in treating inflammatory changes in the brain in Alzheimer's disease and, as minocycline is a potent anti-inflammatory drug, the study's results will show researchers which pathways they should focus on.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

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 EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal

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

EME programme

The Efficacy and Mechanism Evaluation (EME) programme funds ambitious studies evaluating interventions that have the potential to make a step-change in the promotion of health, treatment of disease and improvement of rehabilitation or long-term care. Within these studies, EME supports research to improve the understanding of the mechanisms of both diseases and treatments.

The programme support translational research into a wide range of new or repurposed interventions. These may include diagnostic or prognostic tests and decision-making tools, therapeutics or psychological treatments, medical devices, and public health initiatives delivered in the NHS.

The EME programme supports clinical trials and studies with other robust designs, which test the efficacy of interventions, and which may use clinical or well-validated surrogate outcomes. It only supports studies in man and where there is adequate proof of concept. The programme encourages hypothesis-driven mechanistic studies, integrated within the efficacy study, that explore the mechanisms of action of the intervention or the disease, the cause of differing responses, or improve the understanding of adverse effects. It funds similar mechanistic studies linked to studies funded by any NIHR programme.

The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 11/47/01. The contractual start date was in June 2013. The final report began editorial review in April 2019 and was accepted for publication in November 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. 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 MRC, NETSCC, the EME 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, NETSCC, the EME programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).