Randomised controlled trial of ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (Ketamine-ECT study)

Ian M Anderson,¹* Andrew Blamire,² Tim Branton,³ Sabrina Brigadoi,^{4,5} Ross Clark,⁶ Darragh Downey,¹ Graham Dunn,⁷ Andrew Easton,⁸ Rebecca Elliott,¹ Clare Elwell,⁴ Katherine Hayden,⁹ Fiona Holland,⁷ Salman Karim,¹⁰ Jo Lowe,¹ Colleen Loo,¹¹ Rajesh Nair,¹² Timothy Oakley,¹³ Antony Prakash,¹⁴ Parveen K Sharma,¹⁵ Stephen R Williams¹⁶ and R Hamish McAllister-Williams^{13,17} on behalf of the Ketamine-ECT study team

- ¹Neuroscience and Psychiatry Unit, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
- ²Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK ³Leeds and York Partnership NHS Foundation Trust, Leeds, UK
- ⁴Biomedical Optics Research Laboratory, University College London, London, UK ⁵Department of Developmental and Social Psychology, University of Padova, Padova, Italy

⁶Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK ⁷Centre for Biostatistics, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

⁸Nuffield Health, Leeds, UK

⁹Pennine Care NHS Foundation Trust, Stockport, UK

- ¹⁰Lancashire Care NHS Foundation Trust and University of Manchester, Preston, UK
- ¹¹School of Psychiatry, University of New South Wales, Black Dog Institute and St George Hospital, Sydney, NSW, Australia
- ¹²Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, UK
- ¹³Northumberland Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK ¹⁴Derbyshire Healthcare NHS Foundation Trust, Derby, UK
- ¹⁵Manchester Mental Health and Social Care Trust, Manchester, UK
- ¹⁶Centre for Imaging Science, University of Manchester, Manchester, UK
- ¹⁷Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

*Corresponding author

Declared competing interests of authors: Ian M Anderson reports personal fees from Alkermes, Janssen, Lundbeck-Otsuka and Takeda, outside the submitted work. Rebecca Elliot reports grant support from Genzyme Therapeutics, Pfizer and Johnson & Johnson and personal fees from P1vital, all outside the submitted work. Colleen Loo reports lecture fees from MECTA Corporation, outside the submitted work. Rajesh Nair reports personal fees from Lundbeck and Sunovion, outside the submitted work. R Hamish McAllister-Williams reports personal fees from Roche, Ferro Group, Sunovion, Pulse, Janssen, My Tomorrows, Lundbeck, AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Servier, Saudi Pharmaceutical Industries & Medical Appliances Corporation, Otsuka and Pfizer, outside the submitted work.

Published March 2017 DOI: 10.3310/eme04020

Plain English summary

Ketamine for post-ECT cognitive impairments in severe depression Efficacy and Mechanism Evaluation 2017; Vol. 4: No. 2 DOI: 10.3310/eme04020

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

Plain English summary

lectroconvulsive therapy (ECT) is the most effective short-term treatment for depression but there are concerns about it causing memory difficulties. ECT may affect memory through a brain chemical called glutamate. Small studies had suggested that ketamine, an anaesthetic drug that blocks some of alutamate's effects, might prevent the memory problems seen after ECT and speed clinical response. We tested whether a low dose of ketamine, compared with a placebo (salt solution) injection, given with the anaesthetic used for ECT would reduce the impairment in memory and other cognitive tasks caused by ECT given for depression and whether depression would get better faster. We found no differences between ketamine- and placebo-treated patients in any of the measures but we could not exclude modest degrees of harms or benefits. Ketamine did not cause serious side effects, although two people had short-lived vivid dreams or altered sensations. The results do not support ketamine being useful for improving the outcome of ECT treatment. Some patients received near-infrared spectroscopy to measure activity in the brain. Preliminary findings showed that people with depression had lower activation in the front of the brain, which ECT further reduced, with ketamine having no apparent effect. People who benefited more from treatment had greater suppression by ECT, but further research is needed before we can be sure of whether this is a real effect or whether it could be useful in guiding treatment. Some of the patients were surveyed after the trial and they were mostly positive about their participation and about their ECT treatment.

© Queen's Printer and Controller of HMSO 2017. This work was produced by Anderson *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

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 was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report

The research reported in this issue of the journal was funded by the EME programme as project number 10/90/04. The contractual start date was in April 2012. The final report began editorial review in February 2016 and was accepted for publication in August 2016. 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. 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.

© Queen's Printer and Controller of HMSO 2017. This work was produced by Anderson *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

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

Efficacy and Mechanism Evaluation Editor-in-Chief

Professor David Crossman Bute Professor of Medicine and Dean and Head of Faculty of Medicine, University of St Andrews, and Honorary Consultant Cardiologist, NHS Fife Health Board, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Health Sciences Research, Health and Wellbeing Research Group, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

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