

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

Ian M Anderson,<sup>1\*</sup> Andrew Blamire,<sup>2</sup> Tim Branton,<sup>3</sup> Sabrina Brigadoi,<sup>4,5</sup> Ross Clark,<sup>6</sup> Darragh Downey,<sup>1</sup> Graham Dunn,<sup>7</sup> Andrew Easton,<sup>8</sup> Rebecca Elliott,<sup>1</sup> Clare Elwell,<sup>4</sup> Katherine Hayden,<sup>9</sup> Fiona Holland,<sup>7</sup> Salman Karim,<sup>10</sup> Jo Lowe,<sup>1</sup> Colleen Loo,<sup>11</sup> Rajesh Nair,<sup>12</sup> Timothy Oakley,<sup>13</sup> Antony Prakash,<sup>14</sup> Parveen K Sharma,<sup>15</sup> Stephen R Williams<sup>16</sup> and R Hamish McAllister-Williams<sup>13,17</sup> on behalf of the Ketamine-ECT study team

<sup>1</sup>Neuroscience and Psychiatry Unit, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

<sup>2</sup>Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

<sup>3</sup>Leeds and York Partnership NHS Foundation Trust, Leeds, UK

<sup>4</sup>Biomedical Optics Research Laboratory, University College London, London, UK

<sup>5</sup>Department of Developmental and Social Psychology, University of Padova, Padova, Italy

<sup>6</sup>Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

<sup>7</sup>Centre for Biostatistics, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

<sup>8</sup>Nuffield Health, Leeds, UK

<sup>9</sup>Pennine Care NHS Foundation Trust, Stockport, UK

<sup>10</sup>Lancashire Care NHS Foundation Trust and University of Manchester, Preston, UK

<sup>11</sup>School of Psychiatry, University of New South Wales, Black Dog Institute and St George Hospital, Sydney, NSW, Australia

<sup>12</sup>Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, UK

<sup>13</sup>Northumberland Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK

<sup>14</sup>Derbyshire Healthcare NHS Foundation Trust, Derby, UK

<sup>15</sup>Manchester Mental Health and Social Care Trust, Manchester, UK

<sup>16</sup>Centre for Imaging Science, University of Manchester, Manchester, UK

<sup>17</sup>Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

\*Corresponding author

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## Scientific summary

### Ketamine for post-ECT cognitive impairments in severe depression

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# Scientific summary

## Background

Depression is a major health problem, with a significant proportion of patients failing to respond adequately to treatment; about one-third of patients fail to remit even after four sequential drug interventions. The National Institute for Health and Care Excellence (NICE) recommends electroconvulsive therapy (ECT) as a treatment option for patients with life-threatening severe depression or for those with moderate or severe depression who have not responded to multiple drug treatments and psychological treatment. ECT involves inducing a therapeutic generalised seizure by passing an electric current across the brain and has been demonstrated to have greater acute treatment efficacy than pharmacotherapy. Despite this evidence base its use has fallen in recent decades. There are probably a number of reasons for this, including public and professional concerns about the nature of the treatment, negative perceptions of ECT, a lack of consensus on use and resource limitations; however, a major contributing factor is concern about adverse cognitive side effects following ECT. During and immediately after ECT there is significant impairment in anterograde memory, executive function and cognitive processing speed, which rapidly resolves after 1–2 weeks. An area of controversy is the frequency with which and the degree to which retrograde amnesia and loss of autobiographical memories persist, with some experiencing this as a distressing after-effect of ECT.

There is no current consensus about how far it is possible to reduce the cognitive effects of ECT while retaining its efficacy, although current brief-pulse methodology is better tolerated than historical methods of delivery. The neurotransmitter glutamate is involved in neuroplasticity and learning and there is current interest in its role in depression. Preliminary evidence has suggested that ketamine, an antagonist at *N*-methyl-D-aspartate (NMDA) glutamate receptors, may prevent the cognitive effects of ECT and it has also been shown to have rapid, although temporary, antidepressant effects.

Impaired prefrontal cortical function is related to the cognitive deficits found in depressed patients and limited evidence suggests that ECT leads to its further suppression; this is hypothesised to contribute to the acute detrimental effects of ECT on cognition. Functional near-infrared spectroscopy (fNIRS) is a portable brain imaging technique that uses the differential light absorption properties of oxyhaemoglobin (HbO) and deoxyhaemoglobin (HbR) to measure their concentrations in body tissues. Haemodynamic responses to cognitive tasks can be measured in the lateral prefrontal cortex and an expanding evidence base has shown that depressed patients, compared with healthy control subjects (HCs), have impaired responses during verbal fluency (VF) tasks, suggesting that this methodology can be used as a measure of prefrontal cortical function.

## Objectives

The primary aim of the Ketamine-ECT study was to investigate, in a randomised controlled trial, the effect of adjunctive ketamine on cognitive dysfunction caused by ECT in severely depressed patients who had consented to receive ECT as part of their usual care in NHS secondary care settings. The primary objective was to determine whether or not intravenous ketamine (0.5 mg/kg), compared with placebo (saline), given immediately before the usual anaesthetic at each ECT treatment would ameliorate anterograde amnesia caused by ECT. The primary outcome was delayed verbal recall measured by the Hopkins Verbal Learning Test – Revised (HVLT-R) at baseline and after four ECT treatments [primary assessment time point (mid-ECT)], with secondary neuropsychological measures consisting of VF, autobiographical memory, visuospatial memory and digit span. Other secondary measures were efficacy, quality of life and safety and tolerability, with the hypothesis that ketamine, compared with saline, would lead to a more rapid improvement in depressive symptoms with fewer ECT treatments needed to achieve remission.

Assessments were carried out at mid-ECT, the end of treatment and 1 and 4 months after treatment to evaluate the persistence of effects. Mechanistic objectives were (1) to compare patients and HCs on measures of neuropsychological function and prefrontal cortex haemodynamic responses to cognitive tasks using fNIRS and (2) to determine the effect of ECT on haemodynamic responses and their modulation by ketamine, with the hypothesis that ketamine, compared with saline, would reduce the suppression caused by ECT. Given the controversial nature of ECT, a patient survey was designed to explore patients' views about their participation in the study and about ECT treatment.

## Methods

The Ketamine-ECT study was a multicentre, two-arm, parallel-group, patient-randomised, placebo-controlled superiority trial of ketamine added to the standard anaesthetic for ECT in severely ill depressed hospitalised patients or outpatients who received ECT as part of their usual clinical care. Inclusion criteria were age  $\geq 18$  years; a *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) diagnosis of a major depressive episode as part of unipolar or bipolar mood disorder; consent given to receive ECT as part of standard clinical care; able to give informed consent for the trial; sufficiently physically healthy to receive ketamine; and able and willing to validly complete neuropsychological testing. Exclusion criteria were the presence of other major primary psychiatric, neurological or organic brain disorders; detention under the Mental Health Act (MHA) 1983 (as amended in 2007); ECT in the previous 3 months; and known hypersensitivity to medications being used in the study or for ECT. HCs were prospectively sex and age group matched with patients and were required to be psychiatrically well and in general good physical health, without a personal history or first-degree family history of psychiatric disorder, and to be psychotropic medication free.

Diagnoses were confirmed by the Mini International Neuropsychiatric Interview (MINI) and eligibility was determined through a mixture of case note information and a semistructured interview to obtain demographic and background details and to determine physical health. Patients were randomised in a 1 : 1 ratio to ketamine or saline using permuted block randomisation, stratified by NHS trust, by the Christie Hospital Clinical Trials Unit in Manchester. The anaesthetist administering the anaesthetic for ECT was aware of the drug being given but the patient and other members of the clinical and research teams were blind to treatment allocation.

Electroconvulsive therapy was administered in accordance with protocols agreed between centres based on the Royal College of Psychiatrists' *ECT Handbook* (2005) and scheduled twice weekly. Anaesthesia consisted of propofol, with thiopental (thiopental sodium) as an alternative, combined with the muscle relaxant suxamethonium (suxamethonium chloride). Target treatment doses were 1.5 times threshold for bilaterally administered ECT and 4–6 times threshold for right unilateral electrode placement, with these stimulus parameters maintained until after the fourth treatment unless changes were required for clinical reasons. Psychotropic medication was continued by the clinical team and remained unchanged for the first four ECT treatments and, if possible, until the end of ECT, unless changes were required for safety or clinical reasons. The goal was to treat patients to remission but the final decision to finish ECT treatment was taken by the clinical team. Study medication was intravenous ketamine 0.5 mg/kg or an equal volume of saline given directly before the anaesthetic induction agent.

Assessments were carried out at baseline before ECT started, mid-ECT, at the end of treatment and at 1 and 4 months after the last ECT (follow-ups 1 and 2). Neuropsychological assessments consisted of the HVLT-R (anterograde verbal memory – primary outcome delayed recall), the Autobiographical Memory Interview – Short Form (AMI-SF), the Controlled Oral Word Association Test (COWAT; VF), the Medical College of Georgia Complex Figure Test (MCGCFT; visual figure reproduction and memory), digit span and self-reported Global Self-Evaluation of Memory (GSE-My). Efficacy measures consisted of the Montgomery–Åsberg Depression Rating Scale (MADRS), the Clinical Anxiety Scale (CAS), Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I), the Quick Inventory of Depressive Symptomatology –

Self-Report (QIDS-SR) and the European Quality of Life-5 Dimensions three-level version (EQ-5D-3L). Safety was monitored by standard clinical procedures during ECT treatments, degree of reorientation 30 minutes after ECT and adverse event (AE) recording.

For the mechanistic studies, HCs were tested on a single occasion with the same assessments (excluding the AMI-SF). fNIRS data on both patients and HCs were acquired using a 24-channel, custom-built optode array covering the lateral prefrontal cortex on both sides of the head during a category VF task and an *n*-back working memory task.

The clinical trial data were analysed using a modified intention-to-treat (mITT) population that included all randomised patients who received at least one ECT treatment, with adjustments for age at randomisation, sex, baseline degree of treatment resistance, electrode placement (bilateral or unilateral) and baseline value of the outcome being evaluated. For neuropsychological data a Gaussian repeated measures model was applied to each of the 15 continuous outcomes using all of the available data and taking account of the correlation between measures on the same subject. The weekly efficacy data were analysed using a random-effects (random intercepts and slopes) analysis of covariance (ANCOVA) model with time from first ECT as a quantitative explanatory variable based on data up to the end-of-treatment assessment. For fNIRS data the baseline-corrected areas under the curve of the haemodynamic responses were analysed in dorsal and ventral prefrontal regions of interest by repeated measures ANCOVA covaried for age and sex for the HC–patient comparisons and by repeated measures analysis of variance (ANOVA) for the effects of ECT treatment and ketamine.

There was patient and public involvement at all stages of the study. This included the design and content of all information sheets, issues related to informed consent and the design and delivery of a survey of patient experiences of the study.

## Results

In total, 628 patients received ECT at 11 ECT suites based in seven NHS trusts in the north of England, of whom 31% were potentially eligible for the study (47% were ineligible because of detention under the MHA). Of the 196 potentially eligible patients, 79 (40%) were randomised and 70 (36%) formed the final mITT sample (saline arm, *n* = 37; ketamine arm, *n* = 33). Retention in the study was similar in the two arms [mid-ECT: saline, *n* = 36, ketamine, *n* = 33; end of treatment: saline, *n* = 32, ketamine, *n* = 28; follow-up 1 (1 month post ECT): saline, *n* = 23, ketamine, *n* = 25; follow-up 2 (4 months post ECT): saline, *n* = 18, ketamine, *n* = 19].

Patients received a mean of 11 ECT treatments in each arm. There was no significant difference between treatments in the primary outcome, HVLT-R delayed recall at mid-ECT [−0.43, 95% confidence interval (CI) −1.73 to 0.87], or in HVLT-R delayed recall at the end of treatment (−0.04, 95% CI −1.22 to 1.13); numerically, there was a slight advantage to saline. Overall, there was no consistent difference between treatment arms on the secondary neuropsychological measures, although for two single time points (HVLT-R retention at the end of treatment and digit span forward at mid-ECT) there was a significant benefit in the saline arm. There were no significant treatment differences in efficacy measures; the difference between the saline and ketamine regression slopes for the MADRS was 0.44 (95% CI −1.03 to 1.91), a slight, non-significant benefit for saline, equivalent to a MADRS difference of 2.2 (95% CI −1.3 to 5.6) at 2 weeks and 3.9 (95% CI −3.9 to 11.8) at 6 weeks. The remission rate at the end of treatment was 35% on saline and 39% on ketamine, with the mean number of prior ECT treatments to achieve remission being 7.0 [standard deviation (SD) 3.6] and 10.0 (SD 4.7) in the saline and ketamine arms, respectively. Two ketamine-treated patients had transient psychological effects after individual ECT treatments, but there were no other notable adverse reactions (ARs) to ketamine; the number of serious/non-serious AEs and ARs was non-significantly lower in the saline group than in the ketamine group (13 vs. 22), but serious AEs were numerically more common in the saline arm (5 vs. 2).

Patients, compared with 56 HCs, showed highly impaired neuropsychological function on all measures at baseline. Four months after the end of ECT (follow-up 2) patients had improved compared with baseline on most neuropsychological measures, with the pattern differing between remitted and non-remitted patients. Fifty-one HCs and 18 patients took part in the fNIRS study, with 12 patients also providing data at mid-ECT (only 11 for the VF task). On preliminary analysis patients had blunted bilateral prefrontal cortex HbO responses to the VF task, which were further decreased after four ECT treatments. No significant effect of ketamine was found but the number of patients in each arm was very small. There was a preliminary indication that patients who had a better response to ECT had more preserved haemodynamic responses in the VF task at baseline and showed more suppression after ECT.

Seventeen patients participated in the survey of patient experiences, with most feeling that the study had been explained well and that the study team had been very supportive. An altruistic motivation to take part in the research was expressed by many, with no-one expressing concern about the study procedures and assessments and, indeed, some finding them interesting. The survey highlighted the considerable emotional and practical impact of undergoing ECT and, for those having ECT for the first time, a degree of fear beforehand was common. The quality of the information given before ECT was thought to be good and, although most would have preferred not to have needed it, ECT had not been an upsetting experience overall. Reported outcomes ranged from no benefit to feeling that it had been life-saving; about half of respondents noted a temporary effect of ECT on memory, with two believing that their memory was still poorer than before ECT.

## Conclusions

The main implication of the Ketamine-ECT study is that there was no evidence of benefit in terms of cognitive and efficacy outcomes from using low-dose ketamine as an adjunctive anaesthetic agent for ECT, as currently administered in the UK. Although no serious harms appear to be associated with its use at this dose, it may cause a transient psychological reaction in a small minority of patients. The major limitation of the study is the smaller than planned sample size, which reduced the power to detect an effect of ketamine, and, therefore, we cannot exclude either a moderate benefit or a moderate harm with any confidence. Nevertheless, the best estimate of effect is for no benefit or harm, which is consistent with the evolving evidence to which this trial contributes. The included patients were not fully representative of the population of patients receiving ECT as a whole and, in particular, we cannot assume that our results would generalise to more severely ill, more cognitively compromised patients receiving ECT.

We did not have sufficient power to examine any modulatory effect of ketamine on the effect of ECT on prefrontal cortical haemodynamic responses to a VF task, but preliminary evidence showed blunted responses in patients compared with HCs and an effect of ECT consistent with our hypothesis that it further decreases prefrontal function. fNIRS is a potentially promising portable brain imaging technique that may be feasible in a seriously ill psychiatric population and could have potential as a clinical tool to guide treatment. Further research is indicated to investigate the clinical utility of fNIRS.

## Trial registration

This trial is registered as ISRCTN14689382.

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