

Project Title:	Ketamine augmentation of electroconvulsive therapy to improve outcomes in depression
Project Ref:	10-90-04
Cost:	£1,002,385
Lead Applicant & Institution:	Professor Ian Muir Anderson University of Manchester
Start Date:	1 April 2012
Plain English Summary:	<p>Depression is a major cause of disability with many patients failing to recover with current drug and psychological treatments. Electroconvulsive Therapy (ECT), the most effective treatment known for severe depression, can be life-saving but remains controversial. The most serious concern is impairment in memory and other cognitive (thinking) abilities. This can lead to patients stopping ECT before it has improved their mood, and many people report distressing long-term loss of past memories. If these memory and cognitive effects could be prevented, and fewer ECT treatments were needed, this would represent an important advance and would change clinical practice. Ketamine is an anaesthetic drug that blocks the effects of a major brain chemical, glutamate, involved in memory and mood. Preliminary research has found that ketamine protects against the adverse effects of ECT on memory and makes it work more quickly. The proposed study will investigate the benefit of adding ketamine to the usual anaesthetic used for ECT. It will involve enough patients receiving ECT in an NHS setting to be able to assess whether it would be a useful routine treatment. In order to do this 160 patients due to receive ECT in 6 NHS Trusts in the North of England, who give informed consent, will be randomised to either receive ketamine injection or saline placebo during ECT. The effects of the treatment will be assessed using validated measures of memory, cognitive function and mood improvement during, at the end of and one and four months after treatment.</p> <p>In depression there are changes in nerve cell connections (neural networks) between brain areas responsible for mood and cognitive function; glutamate is involved in these. We will use brain imaging to investigate whether ketamine a) prevents the ECT-induced impaired working of the front part of the brain (frontal cortex) believed to contribute to cognitive adverse effects, and b) reduces disruption in connections between the frontal cortex and an important memory area of the brain (hippocampus). Given the difficulty in studying severely ill people we will use magnetic resonance imaging (MRI) in a small subgroup to look at the network connections and brain glutamate levels. We will relate this to</p>

	<p>results obtained in a majority of patients from a simple, portable, imaging technology, near infrared spectroscopy (NIRS).</p> <p>The research team has expertise in carrying out clinical trials, in the relevant areas of brain imaging and neuropsychology. There is extensive clinical expertise in ECT and anaesthesia, the capacity to recruit patients and links with user organisations.</p>
<p>Abstract:</p>	<p><u>AIMS:</u></p> <p>To determine i) the size of clinical benefit of adjunctive ketamine given during electroconvulsive therapy (ECT) in preventing cognitive deficits and in speeding clinical response and ii) whether ketamine protects against ECT's deleterious effects on frontal cortex function and its disruption of fronto-hippocampal connectivity using functional near-infrared spectroscopy (fNIRS) and functional magnetic resonance imaging (fMRI).</p> <p><u>PRIMARY OUTCOME PREDICTIONS AND MECHANISTIC HYPOTHESES:</u></p> <p>1) Ketamine will prevent ECT-induced cognitive impairment and speed up the clinical response to ECT;</p> <p>2) Ketamine will act by a) attenuating ECT-induced impairment of frontal cortex reactivity, b) preventing ECT-induced disruption of fronto-hippocampal connectivity.</p> <p><u>DESIGN:</u></p> <p>A 3-year prospective, randomised placebo-controlled trial of ketamine augmentation of standard ECT treatment in patients with severe depression. ECT treatment, clinical and mechanistic outcomes will be assessed double-blind (ketamine administration will be by unblinded anaesthetist for safety reasons).</p> <p><u>INTERVENTION:</u></p> <p>Ketamine (0.5mg/kg) or saline given during anaesthesia for each standard ECT treatment.</p>

	<p><u>OUTCOMES:</u></p> <p>1) verbal episodic memory, autobiographical memory (AM) and verbal fluency (VF) after last ECT treatment (primary outcome);</p> <p>2) reduction in MADRS score after 4 treatments;</p> <p>3) frontal cortex activation to a VF task (increased activation ketamine>saline related to improved cognitive function) using fNIRS;</p> <p>4) fronto-hippocampal connectivity (disruption ketamine<saline) using fMRI. Subsidiary outcomes: number of ECT treatments to remission, persistence of AM impairment after 1 and 4 months, glutamate increases with magnetic resonance spectroscopy.</p> <p><u>POPULATION AND SAMPLE SIZE:</u></p> <p>160 patients with major depression due to have ECT recruited over 2 years in 6 NHS Trusts.</p> <p><u>ANALYSIS:</u></p> <p>Intention-to-treat analysis allowing for missing outcome data, using variations on analysis of covariance adjusting for treatment site, and important baseline covariates. Mediation mechanisms will be evaluated using recent approaches based on instrumental variable methods to allow for hidden confounding between putative mediator and clinical outcome.</p> <p><u>EXPERTISE:</u></p> <p>The investigators have expertise in clinical trials and experimental research including neuropsychological testing and brain imaging as well as clinical experience in delivering ECT treatment.</p>
ISRCTN: (if applicable)	To follow
Project Protocol:	To follow
Project website: (if applicable)	To follow
URL of this Page:	www.eme.ac.uk/projectfiles/109004info.pdf