Final Report

Project title: Ketamine augmentation of ECT to improve outcomes in depression

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Brief Summary

Background: Electroconvulsive therapy (ECT) is the most effective acute treatment for severe depression, but there are concerns about its adverse cognitive effects. ECT may impair cognition through stimulation of glutamate receptors and preliminary evidence has suggested that ketamine, a glutamate antagonist, may alleviate these effects. Ketamine has been shown to have a rapid, but temporary, antidepressant effect after a single infusion.

Objective: The efficacy and safety of adjunctive low-dose ketamine to reduce cognitive impairments caused by ECT, and secondarily improve symptomatic outcome.

Methods: Seventy nine severely depressed patients were randomised to ketamine (0.5mg/kg) or saline as an adjunct to their anaesthetic for their ECT course; 70 comprised the modified intention-to-treat sample. The primary outcome was delayed verbal recall on the Hopkins Verbal Learning Task-Revised (HVLT-R) after four ECT treatments (Mid-ECT), analysed using a gaussian repeated measures model. Secondary outcomes included autobiographical, working and visual memory, and verbal fluency, symptoms and quality of life; assessments occurred at Mid-ECT, End of Treatment and one and four months after the last ECT. Neuropsychological function was compared with healthy controls, and a functional near-infrared spectroscopy (fNIRS) sub-study investigated prefrontal cortex function. A patient survey of study participation was carried out.

Results: Compared with saline, adjunctive ketamine had no significant effect on HVLT-R delayed recall (treatment effect difference -0.43 [95%CI -1.73 to 0.87]), other neuropsychological outcomes, improvement in depression (difference in Montgomery-Åsberg Depression Rating Scale [MADRS] score slopes 0.46 [95%CI -0.93 to 1.84]), the number of ECT treatments to remission (MADRS≤10: 0.83 [95%CI -3.2 to 4.9]), anxiety symptoms, or quality of life. By the end of ECT treatment 37% (saline 35%, ketamine 39%) of patients had remitted. Tolerability was similar in the two treatment arms; two patients had isolated transient psychological effects attributable to ketamine. Preliminary fNIRS analysis found that patients had blunted prefrontal cortical haemodynamic responses compared with controls during a verbal fluency task at baseline; this was further diminished at Mid-ECT without modulation by ketamine. Greater haemodynamic responsivity to ECT appeared associated with a better clinical response. The majority of patients surveyed reported a positive experience with study participation.

Discussion: Although no evidence of benefit was found for ketamine, moderate benefits or harms cannot be excluded. fNIRS appeared to be a potentially feasible portable brain imaging technology in severely ill patients

Limitations: Recruitment was under 50% of that planned, limiting the power of the clinical trial. Low numbers also meant that in the fNIRS sub-study the effect of ketamine could not be assessed and the other findings must be viewed as preliminary. Included patients were younger than those not-included, and had only limited cognitive impairment with ECT, limiting generalisation to more cognitively compromised patients.

Conclusions: The results of the study do not support the use of adjunctive ketamine in routine ECT treatment in the NHS. Further research is indicated to investigate the clinical utility of fNIRS.

Report

Background

Depression is major health problem with a significant proportion of patients failing to respond adequately to treatment; about a 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 severe depression that is life threatening, 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 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. This is probably due to a number of reasons including public and professional concerns about the nature of the treatment, negative perceptions of ECT, 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 and 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. The neurotransmitter, glutamate, is involved in neuroplasticity and learning, with 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 to

healthy controls, have impaired responses during verbal fluency 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 an RCT 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 intravenous ketamine (0.5mg/kg), compared to 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 (Mid-ECT), with secondary neuropsychological measures consisting of verbal fluency, autobiographical memory, visuospatial memory and digit span. Other secondary measures were of efficacy, quality of life, and safety and tolerability, with the hypothesis that ketamine, compared to 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 follow-up at one and four months after treatment to evaluate persistence of effects. Mechanistic objectives were 1) to compare patients and healthy controls 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 to saline, would reduce the suppression caused by ECT. Give 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 or out-patients who received ECT as part of their usual clinical care. Inclusion criteria: aged 18 years or above; a DSM-IV diagnosis of a major depressive episode as part of unipolar or bipolar disorder mood disorder; had given consent to receive ECT as part of standard clinical care; able to give informed consent for the trial; sufficiently physically healthy to receive ketamine; able and willing to validly complete neuropsychological testing. Exclusion criteria: other major primary psychiatric, neurological or organic brain disorders; detention under the Mental Health Act (1983, as amended in 2007 [MHA]); ECT in the previous 3 months; known hypersensitivity to medications being used in the study or for ECT. Healthy controls (HC) were prospectively sex and

age group matched with patients, and 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 and eligibility was determined through a mixture of case-note information and a semi-structured interview to obtain demographic and background details and 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 the rest of the clinical and research teams were blind to treatment allocation.

ECT was administered according to protocols agreed between centres based on the Royal College of Psychiatrists' ECT Handbook (2005) and scheduled twice weekly. Anaesthesia consisted of propofol, with thiopental as an alternative, combined with the muscle relaxant suxamethonium. 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 requiring change 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 0.5mg/kg or an equal volume of saline given directly before the anaesthetic induction agent.

Assessments were carried out at baseline before ECT started, after four ECT treatments (Mid-ECT), at End of Treatment and at one and four months after the last ECT (Follow-ups 1 and 2). For a detailed discussion of assesssments and endpoints see Appendix. In summary neuropsychological assessments consisted of the Hopkins Verbal Learning Test-Revised (HVLT-R, anterograde verbal memory - primary outcome delayed recall), Autobiographical Memory Interview-short form (AMI-SF), Controlled Oral Word Association Test (COWAT, verbal fluency), 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), Clinical Anxiety Scale (CAS), Clinical Global Impression, Severity and Improvement (CGI-S, CGI-I), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) and EuroQol 3-level version (EQ-5D-3L). Safety was monitored by standard clinical procedures during ECT treatments, degree of re-orientation 30min after ECT, and adverse event recording.

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

For a full discussion of the formal analysis plan see Appendix. In summary the clinical trial data were analysed used a modified intention-to-treat (mITT) population which included all randomised patients who received at least one ECT treatment and the study drug, with adjustments for age at randomisation, sex, baseline degree of treatment resistance, electrode placement (bilateral or unilateral) and the 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 the available data taking account of the correlation between measures on the same subject. The weekly efficacy data were analysed using a random effects (random intercepts) analysis of covariance (ANCOVA) model with time as a quantitative explanatory variable from baseline to 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 repeated measures analysis of variance (ANOVA) for the effects of ECT treatment and ketamine.

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

Results

The first patient was recruited in December 2012 and the final assessment of the last patient occurred in June 2015. 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 due to detention under the MHA). Of the 196 potentially eligible patients, 79 (40%) were randomised and 70 (36%) formed the final mITT sample (37 in the saline arm, 33 in the ketamine arm). Retention in the study was similar in the two arms: Mid-ECT, saline - 36, ketamine - 33; End of Treatment, saline - 32, ketamine - 28; Follow-up 1 (one month post-ECT), saline - 23, ketamine - 25; Follow-up 2 (four months post-ECT), saline - 18, ketamine - 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 secondary neuropsychological measures, although for two single time points (HVLT-R retention at End of Treatment and Digit span forward at Mid-ECT) there was a significant benefit to the saline arm. There were no significant treatment difference in efficacy measures, the difference between the saline and ketamine regression slopes for the MADRS was 0.46 (95%CI -0.93 to 1.84), a slight, non-significant, benefit to saline, equivalent to a MADRS difference of 2.6 (95% CI -1.4 to 6.6) at 2 weeks and 4.4 (95%CI -3.8 to 12.6) at 6 weeks. The remission rate at End of Treatment was 35% on saline and 39% on ketamine, with the mean number of prior ECT treatments to achieve remission 7.0 (SD 3.6) and 10.0 (SD 4.7) on 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 adverse events (AEs) and ARs was non-significantly lower in the saline than ketamine groups (13 vs. 22, see Table 1 for further details), but serious AEs were numerically more common in the saline arm (5 vs. 2, Table 2).

Table 1*:* Details of adverse events or reactions with a frequency of greater than 5%.

System Organ Class*	**Number (%) of patients**	
	Ketamine group (n=33)	**Saline group (n=37)**
Infections and infestations	3 (9%)	0
Musculoskeletal & connective tissue	2 (6%)	0
Nervous system disorders	2 (6%)	1 (3%)
Psychiatric disorders	5 (15%)	7 (19%)
Skin and subcutaneous tissue disorders	2 (6%)	0

*as defined in the Medical Dictionary for Regulatory Activities (MedDRA). Patients experiencing more than one occurrence of an adverse event in a system organ class are counted once. Figures include serious adverse events and adverse reactions.

Table 2: Details of serious adverse events by treatment arm

Serious adverse event	**Allocation**
Spontaneous seizure and status epilepticus between ECT treatments	Saline
Overdose resulting in hospital admission	Saline
Suicide attempt requiring general hospital admission	Saline
Suicide attempt on in-patient ward requiring intervention	Saline
Chest pain requiring admission to hospital overnight	Saline
Clinical deterioration with suicidal ideation requiring admission to hospital	Ketamine
Overdose requiring treatment in accident and emergency department	Ketamine

Comparison of patients with 56 HC showed highly impaired neuropsychological function on all measures at baseline. Two 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 HC and 18 patients took part in the fNIRS study, with 12 patients also having 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 was further decreased after four ECT. 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 their experiences with most feeling 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, 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, while most would have preferred not to have needed it, ECT hadn't been an upsetting experience overall. Reported outcomes ranged from no benefit to feeling it had been life-saving; about half of respondents noted a temporary effect of ECT on memory, with two believing 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 associated with its use at this dose, it may cause a transient psychological reaction in a small minority of patients. The major limitation to the study is the smaller than planned sample size which reduced the power to detect an effect of ketamine therefore we cannot exclude either a moderate benefit or 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 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 to HC, and an effect of ECT consistent with our hypothesis that it further decreases prefrontal function. NIRS 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.

Appendix

Statistical analysis plan (clinical outcomes)

Version 1.1 (27/10/2015) Agreed by Data Monitoring and Ethic Committee (Chair Prof. Keith Matthews) and approved by Trial Steering Committee (Chair Prof. David Baldwin)

Brief description of the trial

The trial aims to determine whether ketamine improves cognitive outcomes after ECT. The main hypothesis is that ketamine, compared with saline, treatment will reduce ECT-induced cognitive impairments in anterograde verbal memory after the mid-course of acute ECT treatment. The main secondary hypotheses are ketamine, compared with saline, treatment will reduce ECT-induced cognitive impairments in autobiographical memory and verbal fluency after the mid-course of acute ECT treatment. The subsidiary hypotheses are that ketamine, compared with saline, treatment will reduce ECT-induced cognitive impairments at the end of acute treatment with ECT, and speed the improvement in symptoms of depression.

Study design

Randomised, placebo-controlled, parallel study with blind assessment

Trial treatments

ECT treatments are scheduled twice weekly. In a 1:1 ratio subjects will receive either intravenous ketamine 0.5mg/kg or placebo as part of the anaesthetic each time ECT is administered. The goal will be to treat patients to remission (standard Montgomery Asberg Depression Rating Scale, MADRS ≤10) in accordance with NICE guidelines.

Randomisation procedure

Patients will be randomised in a 1:1 ratio to ketamine or saline following registration and before the first ECT using permuted block randomisation (varying blocks randomly from 4 to 8), stratified by inclusion by Trust for those not undergoing MR imaging, and by scanner site (Manchester or Newcastle) for those who are receiving MR imaging. The randomisation code will be generated by the Christie CTU and provided to the local pharmacies for drug preparation when a patient is recruited. For safety reasons the anaesthetist and anaesthetic team administering the anaesthetic for ECT will not be blind, and will be aware of the randomisation by being able to identify the study drug at the time of ECT in the packaging provided by pharmacy. Once allocated, the patient will continue to receive the same experimental treatment during the study.

Baseline data

The information collected at baseline includes demographic and clinical data. The full list of baseline characteristics, including the neuropsychological tests and the efficacy ratings, is given in Section 2.2. Baseline neuropsychological and efficacy assessments will be set to missing if they are after the date/time of the first ECT. Missing baseline assessment data will not be imputed.

On-study assessments

Two ECT sessions are scheduled for each week and one to three days after every second ECT the subject should receive the efficacy rating assessments. After the fourth ECT (or if strictly necessary,

after 3 or 5 ECT sessions), neuropsychological tests are performed. This is called the mid-course ECT neuropsychological assessment and constitutes the primary outcome time point.

While receiving acute ECT efficacy assessments will be carried out on a weekly basis. After the final acute ECT the efficacy and neuropsychological assessments will be performed +1day to +5 days after the final ECT, considered as the end ECT assessment.

Approximately four weeks (ranging from 3-5 weeks) after the end of acute ECT, the first follow-up visit will be performed, collecting efficacy and neuropsychological test data. Note, a subject could be on continuation ECT at this time. These assessments will then be repeated at 16 weeks (ranging from 12-20 weeks) after the end of acute ECT.

Neuropsychological outcome measures

Primary outcome measure:

- Hopkins Verbal Learning Test – Revised (HVLT-R) delayed recall (anterograde verbal memory, Trial 4)

Secondary outcome measures

- HVLT-R total learning (sum of correct responses for trials 1,2 and 3)
- HVLT-R retention [(Trial 4 ÷ higher score of trials 2 and 3)*100]
- HVLT-R recognition (total no. of true positives) - (total no. of false positives)
- Controlled Oral Word Association Test (COWAT) category fluency
- COWAT letter fluency
- Autobiographical Memory Interview – Short Form, modified scoring method, Semkovska et al (2012, AMI-SF SM2)
- AMI-SF, standard method of scoring, (AMI-SF SM1)
- Medical College of Georgia Complex Figure Test (MCGCFT) copy score
- MCGCFT immediate recall
- MCGCFT delayed recall
- Digit span Forward Correct repeats
- Digit span Backwards Correct repeats
- Global Self Evaluation of Memory (GSE-My) (Self-Reported)

Efficacy outcome measures

Main outcome measure

Montgomery-Åsberg Depression Rating Scale (MADRS) standard, i.e., total including 4a and 5a and omitting 4b and 5b (10 items)

Secondary outcome measures

- MADRS atypical, i.e., total including 4b and 5b (10 items as a and b versions are exclusive)
- Clinical Anxiety Scale (CAS)
  Total items 1-6; Total items 1-7 (which includes panic items)
- modified BPRS (including question 19 on elevated mood)
  Psychosis items from modified BPRS (sum of qs 3,4,7,8,11,12,15,16)

Mania items from modified BPRS (sum of qs 8, 10, 17, 19)

- Remission (MADRS standard ≤10)
- Number of ECT treatments to achieve remission
- Response (≥ 50% decrease in standard MADRS from baseline)
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression - Improvement CGI-I)
- Quick Inventory of Depressive Symptomatology (QIDS-SR) (Self Report)
- From end ECT to follow up assessments: Proportion significantly worsening (MADRS increase of ≥4 points + CGI-S increase of ≥1 point to CGI-S ≥3 compared with end ECT assessment.
- EuroQol (EQ-5D)

Sample size and power calculations

Initial calculation: The study is designed to detect a standardised effect size (ES) of 0·53 between the ketamine treatment group and the placebo group in the primary outcome variable, HVLT delayed recall, after 4 ECT sessions. A sample size of 76 assessable patients per treatment group provides 90% power to detect this ES at a 5% significance level. Assuming 95% of patients can be assessed after 4 ECTs, this requires a total of 80 patients to be randomly assigned to each treatment group, or a total of 160. If only 85% of the 160 patients can be assessed then this gives 87% power to detect an ES of 0·53.

The three main cognitive interdependent measures are HVLT delayed recall, COWAT category fluency and AMI-SF. Based on a total of 76 assessable patients per group, and using a Bonferroni correction for the three outcomes, this gives 81% power to detect a standardised ES of 0·53 for all 3 outcomes assuming independence.

Revised power calculation September 2014: 90 patients (45 per treatment arm) gives 81% power to detect an ES of 0·6 for HVLT delayed recall. Depending on dropouts this will require between 90 (if 0% dropout) and 100 (if 10% dropout) patients to be recruited to achieve this at primary outcome.

Data description

Recruitment and representativeness of recruited patients

Consort chart to be added in here.

Baseline comparability of randomised groups

Patients in the two treatment groups will be described separately with respect to site, gender, age, ethnicity, marital status, occupation status, number of years in full-time education, highest academic qualification, family History of mental health, smoking and alcohol consumption. In addition, episode type, mood disorder type, co-morbid psychiatric disorders, degree of treatment resistance, age at onset of first mood episode or depression, number of prior depressive episodes, number of prior manic/hypomanic episodes, previous ECT therapy and inpatient / outpatient status will be summarised along with current physical co-morbidities (including whether due to cancer or congenital). Current psychiatric medication will be summarised. Handedness (mixed, left or right + score ratio), MMSE, and WTAR will also be summarised.

Numbers (with percentages) for binary, categorical variables and ordered categories will be presented. Means, standard deviations, and minimums and maximums for continuous variables will be presented.

Consistent with CONSORT guidance, there will be no tests of statistical significance or confidence intervals for differences between the randomised groups on any baseline variable.

All baseline neuropsychological and efficacy scales will be summarised assuming they are continuous variables (except for GSE-MY question 1 which is categorical), by treatment group. Summary statistics will be provided for each neuropsychological component captured on the CRF.

Treatment allocation questionnaire and treatment received

At the mid-course and end ECT treatment assessment the subject, ECT consultant/PI and RA are each asked which treatment they think the patient was allocated to and how certain they are about treatment allocation by choosing from one of four choices: pure guess, slight suspicion, moderately certain or very certain They also give the reason for their choice. The responses at the two time points will be tabulated by treatment arm.

A summary of how much treatment (total number of acute ECT sessions) received will be presented by treatment arm.

Treatment and trial discontinuation

The reasons for treatment discontinuation and study discontinuation / completion will be tabulated by treatment arm.

Assignment of neuropsychological assessments

As described in Section 1.6, the standard procedure is to perform two ECTs in the first week, a further 2 in the second week and then undertake the first neuropsychological assessment which is denoted as the mid-course ECT assessment which is the primary endpoint time. The Appendix illustrates rules for handling the ECT and neuropsychological data.

Neuropsychological and efficacy descriptives

The neuropsychological scales will be summarised for baseline, mid-course, end ECT and the two follow-up periods.

Efficacy scales will be summarised at baseline and then for each week while on acute treatment by arm. In addition the end ECT efficacy measure plus the two follow-up visits will be summarised.

Loss to follow-up

Selected baseline characteristics of subjects providing outcome measures after the mid-ECT session and those with missing data will be compared using a logistic regression model. Similarly, separate logistic regression models will be used to investigate patterns of failure to provide outcome measures after the final ECT and the two follow-up times, using both baseline characteristics and intermediate outcomes of treatment allocation (number of ECTs received and measures of both cognitive deficits and severity of depression). These analyses will be used to generate time-dependent inverse probability weights to evaluate the sensitivity of the formal analyses of outcomes to missing data (see below).

Formal analyses

The analyses comparing the ketamine and placebo arm will be conducted applying a modified intention to treat (ITT) approach. To be included in the modified ITT analyses a subject must have had at least 1 ECT (regardless of the quality).

If the degree of non-adherence to the ECT regime is substantial, and if failure to provide outcome data is associated with non-adherence, then the primary ITT analysis will be supplemented by estimation of the Complier-Average Causal Effect (CACE) of treatment using methods described in Dunn et al. (2005).

Differences in cognitive impairment

Cross-sectional analysis of covariance (ANCOVA) models (allowing for stratifying variables, age, sex, baseline degree of treatment resistance, electrode placement (bilateral or unilateral) and baseline values of the particular outcome being evaluated (if appropriate) will be used to evaluate the effects of treatment allocation on the neurocognitive test scores. If the subject withdraws from treatment or treatment ends after 3-5 sessions, the subsequent NP assessment will be assigned as "mid-ECT" with assignment to "end-ECT" dependent on reasons for discontinuing treatment as described in Appendix 1. If subjects are not able to be included due to lack of data inverse probability weighting adjustments will be used to assess the sensitivity of the findings to missing data (see above). All analyses will involve the use of robust standard errors and associated confidence intervals (allowing for non-normality and constraints in the ranges of some of the cognitive outcomes).

The main inference will be based on treatment effect for the HVLT cognitive assessment completed at the mid-course assessment. Statistical analysis of this outcome at the mid-course assessment will use a 5% two-sided significance level. Evaluation of treatment effects at the end of ECT and follow-up times will be regarded as secondary and the two-sided significance level for all other statistical tests will be 5%.

Differences in severity of depression

The MADRS weekly data will be analysed using a random effects (random intercepts and slopes) ANCOVA model with time (in weeks) from first ECT as a quantitative explanatory variable. The baseline variables will be the same as those for cognitive assessment. An interaction term between time and treatment allocation will also be included to assess the treatment effect. All analyses will use robust standard errors.

Note, if an end ECT efficacy measure is available then this will be assigned to a given week, yielding the last measure while on acute ECT used in the random effects analyses.

The CAS and QIDS-SR will be analysed using the same random effect modelling approach.

The binary outcomes will be analysed using longitudinal logistic regression.

Differences in number of ECT sessions provided

The number of ECT treatments to achieve remission will be analysed using a Poisson/negative binomial model for count data.

Exploratory analyses of end-ECT cognitive performance

If average cognitive impairment is less in the ketamine arm and also there have been fewer ECT sessions needed for remission in this arm this raises the question "Is impairment less in the ketamine arm because the participants have been exposed to fewer sessions of ECT (i.e. it is more effective), or is ketamine protective within each ECT session (or both)?" A simple pragmatic approach will be to stratify by the number of sessions received and to compare average cognitive performance across treatment arms within strata (testing whether there might be a dose-response effect). However here, we make the assumption that the ECT treatment has not been terminated (partly) because of the cognitive side-effects – which may not be justified – and even if it were, there is still the possibility that the effect of sessions on the difference between arms might be confounded.

ECT Treatment

All pre ECT data collected on the CRF will be summarised.

For each ECT session, means and standard deviations, plus minimums and maximums, will be presented by arm for continuous ECT treatment data i.e anaesthetic dose and units (separately for Propofol, Thiopental, Suxamethonium or other drug) and number of stimuli given. Electrode placement (bilateral vs unilateral) will be tabulated by stimulus number (1-4) by treatment group.

Post-ECT, the proportion of subjects getting 4 or more correct out of a total of 5 orientation questions at 30 and 60 minutes after first breath following ECT will be tabulated. In addition, tables showing the frequency of number correct (0-5) will be presented along with summary statistics for the number of correct items at 30 and at 60 minutes will be presented by arm.

Safety

Pre-ECT blood pressure and pulse will be summarised by treatment arm and also after each ECT treatment.

Adverse Events

To be handled by the research team in the Neuroscience and Psychiatry Unit

Statistical Analysis Plan References

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