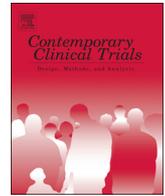




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Electroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol

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ABSTRACT

Major depressive disorder (MDD) is the most common mental illness and the leading cause of disability worldwide. Electroconvulsive therapy (ECT) is the most effective treatment for MDD and the gold-standard therapy for treatment-resistant depression (TRD), yet it remains underutilized due to factors such as limited availability, stigma, and concerns about cognitive side effects. Ketamine has emerged as the first rapid-acting antidepressant and shows robust short-term efficacy in clinical trials, but there are concerns about its long-term safety and efficacy. While response rates are similar between ECT and ketamine in clinical trials, these treatments have never been compared head-to-head in a sufficiently large, well-powered randomized study. Here we describe the study protocol for Electroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression (ELEKT-D), a non-inferiority, comparative effectiveness trial. Patients with TRD seeking clinical treatment are randomized (1:1) to receive ECT (thrice weekly) or intravenous ketamine (twice weekly) for 3–5 weeks. The primary outcome is the proportion of responders in each group at the end of study visit, as measured by a patient-reported outcome measure (Quick Inventory of Depressive Symptomatology-Self Report). The study is powered such that the non-inferiority margin allows for ketamine to retain 90% of the ECT treatment effect, with a projected sample size of 400 patients (200 per group). Secondary outcomes include remission rates, depression severity, cognitive functioning, quality of life, adverse events, and tolerability. The results of the ELEKT-D study will have important implications for patient choice, clinical practice, and health insurance policies.

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1. Introduction

1.1. Background

Major depressive disorder (MDD) is the most common mental illness and is the leading cause of disability worldwide [1]. In the United States, the total economic cost of depression in 2012 was estimated at \$188 billion [2]. Unfortunately, currently available treatments are suboptimal in approximately two-thirds of patients with MDD [3]. Treatment-resistant depression (TRD), which is commonly defined as depression that does not remit or respond to two or more adequate trials of antidepressant therapy, contributes disproportionately to the disease burden. Compared to patients with treatment-responsive depression, patients with TRD have higher rates of suicide attempts [4], higher rates of hospitalization [5,6], and higher costs of outpatient treatment [2]. Furthermore, response and remission rates for patients with TRD are only 16–17% and 13%, respectively [3,7]. Hence, there is an urgent need to identify improved treatments for MDD generally and for TRD specifically.

1.2. Electroconvulsive therapy (ECT)

Electroconvulsive therapy is the most effective treatment for MDD and the gold-standard therapy for TRD [8]. Whereas standard antidepressants achieve remission rates in only 13% of patients with TRD, ECT achieves remission rates of 50–70% in TRD [9]. The overwhelming majority of trials comparing ECT directly to a standard antidepressant have shown superior efficacy for ECT [8]. Despite the consistent evidence that ECT is an effective treatment for patients with severe mood disorders, ECT continues to be underutilized. Several factors that contribute to the underutilization of ECT in the U.S. include restricted access due to limited availability and legal restrictions in some locales [10,11]. Patient choice, stigma, and an antiquated perception of the treatment also play a role in the underutilization of ECT. Nonetheless, this treatment continues to be hailed as potentially life-saving by patients and practitioners [12–15].

1.3. Ketamine

Ketamine, an antagonist at the *N*-methyl-*D*-aspartate receptor, was approved by the U.S. Food and Drug Administration (FDA) as an anesthetic in 1970, and is classified in Schedule III, signifying abuse liability. Since 2000, several small clinical trials have shown that a single subanesthetic dose of ketamine can lead to rapid and robust antidepressant effects, with response rates of 50–71% within 24 h of exposure [16–18]. Despite the promise surrounding ketamine's potential antidepressant efficacy, several potential downsides—including abuse liability, neurotoxicity, and bladder toxicity with long-term exposure—warrant a cautious approach. Nonetheless, given the need for improved therapeutics for TRD and considering that potential benefits outweigh the risks of long-term use, a rapidly growing number of academic and private-sector practitioners have begun offering ketamine off-label for the treatment of psychiatric disorders [19].

Here we describe the study protocol for ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression (ELEKT-D) (NCT03113968). The ELEKT-D trial is a randomized, non-inferiority, comparative effectiveness trial funded by the Patient-Centered Outcomes Research Institute (Overall PI: A. Anand). The results will allow for a direct comparison of the two treatment approaches and will have important implications for patient choice, clinical practice, and health insurance policies.

2. Methods

2.1. Trial overview and management

The ELEKT-D study is a multi-site comparative effectiveness study in patients with a history of TRD, wherein treatment-seeking patients are randomly assigned (1:1 ratio) to receive ECT or ketamine. Given the nature of ketamine and ECT, treatment arms cannot be blinded at the clinician or patient level. The study was approved by local institutional review boards and is being conducted at four academic medical centers—Cleveland Clinic, Yale School of Medicine in New Haven, Baylor College of Medicine/Michael E. DeBakey VA Medical Center in Houston, and the Icahn School of Medicine at Mount Sinai in New York. A fifth site, Johns Hopkins School of Medicine, was added approximately 18 months following initiation of the study. All sites have ECT clinical programs and extensive experience with ketamine for TRD. The Cleveland Clinic site functions as the Data Coordinating Center and Clinical Coordinating Center through C5Research, an academic Contract Research Organization. An independent Data Safety and Monitoring Board oversees the conduct of the study. As per guidelines from the funding agency, a Stakeholder Council was organized, comprised of study investigators, patient advocates, insurance company representatives, and PCORI staff. The Stakeholder Council meets every 6 months to discuss study progress and give feedback to the investigators.

2.2. Recruitment and eligibility (Fig. 1)

Patients referred for ECT are approached for study enrollment. Potential study participants are approached for the trial after a psychiatrist or other clinician has evaluated them and recommended them for ECT treatment. At this time patients are informed about the study and given a thorough explanation of risks, benefits, study procedures, and expectations. After signing informed consent, patients are eligible for participation based on the following inclusion criteria: 1) Inpatients or outpatients referred by their providers for ECT treatment and eligible for ECT treatment; 2) 21–75 years old; 3) Meet DSM-5 criteria for a Major Depressive Episode as determined by both a clinician's diagnostic evaluation and confirmation with the Mini International Neuropsychiatric Interview (MINI 7.0.2); and 4) Have had 2 or more adequate trials of antidepressants/augmentation strategies during their lifetime to which they did not fully respond, as determined by the Antidepressant Treatment History Form (ATHF) [20]. The severity of depression must be such that the Montgomery-Asberg Depression Rating Scale (MADRS) [21] score is > 20 at screening. Cognitive functioning must be such that the Montreal Cognitive Assessment (MoCA) [22] is ≥ 18 at screening, which permits enrollment of severely depressed patients with pseudodementia. We note that a relatively low number of previous failed trials were allowed to enable enrollment of patients with previous favorable responses to ECT without having to prospectively undergo several rounds of medication treatment. The relatively low MADRS score was allowed because there are occasional real-world situations where a MADRS score may not accurately reflect the severity of symptoms or the urgency to treat an episode.

Exclusion criteria include the following: 1) Meet DSM-5 criteria for bipolar disorder (or has a Young Mania Rating Scale (YMRS) [23] > 5 at screening), schizophrenia, schizophreniform disorder, schizoaffective disorder, mental retardation, or pervasive development disorder; 2) Meet any exclusion criteria for ECT or ketamine treatment as described in the clinical guidelines [8,24] or according to investigator judgment; 3) The patient is pregnant or breast feeding; 4) The patient has a severe medical illness or severe neurological disorder; 5) The patient has a known ketamine allergy or is taking any medication that may interact with ketamine; 6) Diagnosis of major depressive disorder with psychotic features during the current depressive episode; and 7) Unable to give informed consent. See Table 1 for full inclusion and exclusion

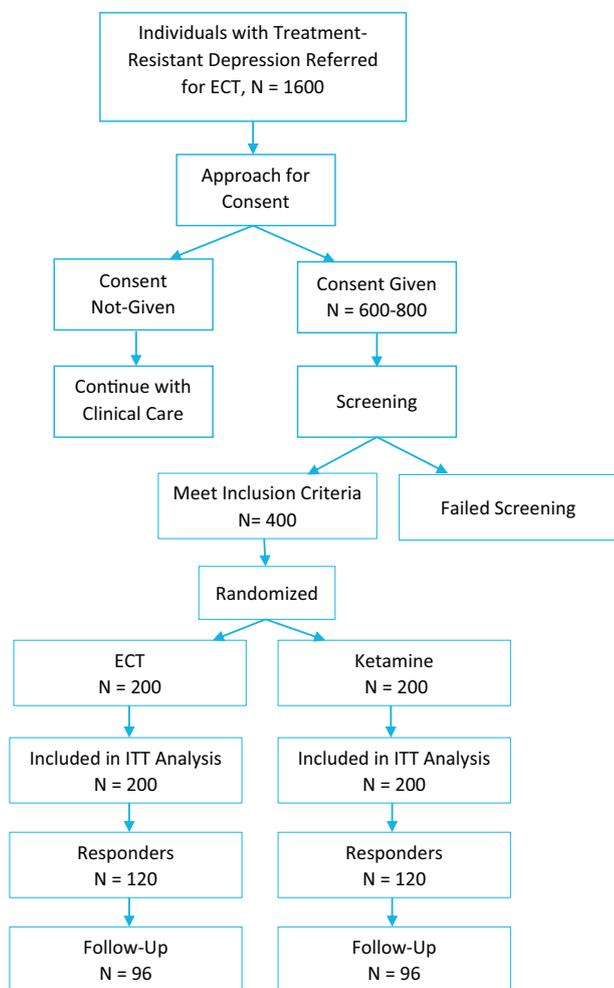


Fig. 1. Study flow diagram.

criteria. Notably, there are intentionally no absolute contraindications with respect to concomitant medications to reflect real-world practices.

2.3. Study design

2.3.1. Real world trial

As much as possible, the study has been designed as a real world, effectiveness trial so that its results have direct relevance to clinical practice for patients with TRD. ECT is administered in a standard manner three times per week. Ketamine is given two times per week, as a recent study has shown that ketamine twice weekly is as effective as thrice weekly [25]. Within this suggested framework, study clinicians have considerable flexibility. For example, clinicians would have flexibility in terms of initiating ECT treatments with right unilateral (RUL) ECT and moving to bilateral (BL) ECT if an early response is not observed. This treatment strategy is common in clinical practice in order to minimize cognitive side effects of ECT and its occurrence may be more frequent at one study site than another. Similarly, if there is no substantial change in depression severity after a reasonable number of ketamine treatments, clinicians may choose to stop treatment and terminate the study at that point. In the event that patients achieve remission before all of the study visits are complete, the clinician will also have the choice to terminate treatment before the expected three weeks of treatment have been completed. We will conduct an intention-to-treat (ITT) analysis. In addition, any patient who has received at least one treatment with ECT or ketamine and has at least one post-baseline depression rating will be included in a modified intention-to-treat (mITT) analysis, and the data will be analyzed using mixed model procedures which account for missing values (see Section 2.8 below).

2.3.2. Randomization

All patients who are eligible for the trial are randomized in a 1:1 manner to either ECT or ketamine treatment. Randomization is conducted centrally through a secure electronic data management system. Given the nature of these treatments, treatment arms cannot be blinded at the patient or clinician level.

2.3.3. Equipose between treatment arms

As this study is open-label, considerable effort is exerted by all involved in the trial to maintain therapeutic equipose. No assumptions

Table 1
Inclusion and exclusion criteria.

Subject eligibility	Patients with treatment resistant depression (TRD) who have been referred for ECT and are eligible for ECT are candidates for the study
Inclusion criteria	<ol style="list-style-type: none"> 1. Written informed consent before any study related procedures are performed 2. Inpatients or outpatients referred by their providers for ECT treatment and eligible for ECT treatment 3. Males/females at least 21 years of age, but no older than 75 years of age 4. Meet DSM-5 criteria for Major Depressive Episode as determined by both: <ol style="list-style-type: none"> A. Clinician's diagnostic evaluation and B. Confirmed with the MINI International Neuropsychiatric Interview (MINI) 5. A current depressive episode that has lasted a minimum of 4 weeks 6. Meet all of the following criteria on symptom rating scales at screening: <ol style="list-style-type: none"> C. Montgomery-Asberg Depression Rating Scale (MADRS) score > 20 D. Young Mania Rating Scale (YMRS) of ≤ 5 E. Montreal Cognitive Assessment (MoCA) of ≥ 18 7. Have had ≥ 2 adequate trials of antidepressants or augmentation strategies during their lifetime (An adequate trial is defined as 4 weeks of a medication at a minimum FDA approved dose, with a trial rating of 3 or greater) 8. In the opinion of the investigator, the patient is willing and able to comply with scheduled visits, treatment plan, and other trial procedures for the duration of the study.
Exclusion criteria	<ol style="list-style-type: none"> 1. Meet DSM-5 criteria for bipolar disorder, schizophrenia, schizophreniform disorder, schizoaffective disorder, mental retardation, or pervasive developmental disorder 2. Meets any exclusion criteria for ECT or ketamine treatment as described in the clinical guidelines or according to investigator judgment 3. The patient is pregnant or breast feeding 4. The patient has a severe medical illness or severe neurological disorder 5. The patient has a known ketamine allergy or is taking medication that may interact with ketamine 6. Diagnosis of major depressive disorder with psychotic features during the current depressive episode 7. Unable to give informed consent 8. Was previously enrolled/randomized into the trial

have been made for any of the two treatments being superior to the other at the start of the study or during the conduct of the trial. Also, the conditions and implementation of the two treatment arms were made as similar as possible.

2.3.4. Non-inferiority trial

This study is designed as a non-inferiority trial. This is the most appropriate study design to test an intervention which may have ancillary advantages beyond overall treatment effects against an ‘active control’ or gold standard treatment [26,27]. These advantages may make the treatment attractive for patients and clinicians if it can be shown that its effectiveness is not inferior to the gold standard treatment. Ketamine's potentially fewer short-term cognitive side effects, ease and safety of administration (does not require general anesthesia), and relative lack of associated social stigma makes it suitable for comparison with ECT using a non-inferiority design. If results show that ketamine is nearly the same as ECT in its efficacy for TRD, then its other advantages would likely make it attractive for both clinicians and patients.

2.4. Study treatments

2.4.1. ECT

Patients who are randomized to the ECT arm will undergo ECT as per the clinical standards at each site. The initial ECT treatment will be right unilateral (RUL) ultra-brief pulse width at 5–6 times seizure threshold determined during titration at the first treatment visit. If there is an unsatisfactory improvement with RUL, the investigator may change to bilateral (BL) electrode placement during the acute treatment course utilizing brief pulse width. The initial seizure threshold is determined by empirical titration on the first visit. The seizure threshold may increase during the course of treatment and the dose of the electrical stimulus may need to be increased incrementally [9].

Ideally, patients will receive treatments at regular intervals of three times per week for three weeks. However, patients may receive the initial course of nine treatments over three to five weeks. The expanded window up to five weeks allows for modifications based on clinician discretion and the patient's schedule. The acute arm of the study would be complete after nine treatments. Flexibility will be allowed for the ECT clinician to adjust the treatments as clinically necessary following the acute 9-treatment course.

Out of four total sites, two sites use a MECTA Spectrum 5000Q (MECTA Corp, Tualatin, Oregon) ECT machine and two sites use a Thymatron DGX ECT device (Somatics Inc., Lake Bluff, Illinois). Choice of anesthetic agents and muscle relaxants will be at the discretion of each site, although sites are instructed not to use ketamine as the anesthetic agent during ECT.

At every visit, patients are assessed by clinical providers to evaluate treatment response, appropriateness for continued treatment, and adverse events. Patients complete psychometric scales (patient-reported outcomes, PRO) and clinicians complete clinician-reported measurements at Baseline (Visit 1) as well as Visits 2, 4, 6, 7, 9 and end-of-treatment visit. Patients may remain on their concomitant psychotropic regimen throughout ECT, and standard adjustments such as lowering or discontinuing anticonvulsant medications are expected.

2.4.2. Ketamine

Patients receive up to six treatments with intravenous ketamine over three to five weeks. Ideally patients receive treatments at regular intervals of two times per week for three weeks. This schedule is based on evidence that providing ketamine thrice per week was not superior to providing ketamine twice per week [25]. The window allows for modifications based on clinician discretion and patient schedules.

Ketamine is administered according to the most commonly utilized dose in depression studies of 0.5 mg/kg infusion over a 40-min period [24]. The investigator is able to modify the dose if clinically warranted.

Treatments are given twice per week for a maximum of six treatments after which the acute arm of the study is complete. Ketamine is administered in the same physical space in the hospital as ECT for some sites, while some sites deliver ketamine in a separate suite within the hospital.

At every visit, patients are assessed by clinical providers to evaluate treatment response, appropriateness for continued treatment, and adverse events. Patients complete psychometric scales (Patient-Reported Outcomes or PROs) and clinicians complete clinician-reported measures at Baseline (Visit 1), Visits 2–6 and end-of-treatment visit. Similar to the ECT arm, patients may remain on their concomitant psychotropic regimen throughout the course of ketamine treatment. Medications which may attenuate the efficacy of ketamine such as benzodiazepines may be held at the discretion of each site's protocol.

2.5. End of treatment (EOT) visit

Patients complete an EOT visit ideally within 72 h of the final treatment. However, up to one week is allotted following the final treatment to allow for scheduling conflicts. If treatments are not stopped early, this occurs after the 9th ECT treatment or the 6th ketamine treatment. If treatments are discontinued earlier, the EOT visit occurs within one week of this final treatment. Following this visit, patients may continue to receive ECT or ketamine clinically, but the EOT visit marks the end of the acute treatment phase for the study. Patients are classified as responders or non-responders at the conclusion of the EOT visit.

2.6. Follow-up visits

Treatment responders are asked to participate in the follow-up phase of the study. Follow-up visits occur one month, three months, and six months after the EOT Visit. These visits collect all PRO, clinician-reported outcomes, cognitive outcomes, and adverse events and side effect outcome measures. Acute phase responders may receive any treatment during the follow-up period, including additional ketamine and ECT. Non-responders are exited from the study and referred back to their primary clinician for follow-up care. A follow-up telephone visit will be attempted with all non-responders to verify continuity of care as well as obtain information regarding further treatment and patient assessment regarding improvement of symptoms after EOT visit.

2.7. Psychometric measurements

2.7.1. Training and quality control of psychometric measures

The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) [28] is a 16-item self-report measure selected as the primary outcome measure. A self-report instrument was selected as the primary outcome as a stipulation of the funding agency, and is consistent with the effectiveness (and not efficacy) aim of this trial. All study coordinators are trained annually in its administration. Oral instructions for patients and appropriate answers to common questions are reviewed to ensure standardization. For clinician administered scales, all raters are required to complete training pertinent to each scale they would administer and document competence by passing quizzes. MADRS raters are also required to independently rate two full-length films of scale administration and demonstrate at least 90% reliability with the entire cohort for both films. Annual calibration exercises using audio files of novel MADRS interviews assesses ongoing reliability. All raters employed the 2011 Structured Interview Guide for the Montgomery Åsberg Depression Rating Scale (SIGMA), version 1.2 [29]. For neuropsychological testing (see Section 2.7.4), administrators were trained by a neuropsychologist (KK). Periodic reviews of administration and scoring were completed by the neuropsychologist.

2.7.2. Patient-reported outcomes

Patient-reported outcomes are critical to the central aim of the study. The PRO that will be used for Visits 1, 2, 4, 6, 7, and 9 for the ECT treatment group and for Visits 1–6 for the ketamine treatment group include the following: QIDS-SR (primary outcome), Patient Global Impression-Change (PGI-C) [30], Quality of Life Scale (QOLS) [31], and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) [32].

2.7.3. Clinician-reported outcomes

The clinician-reported outcomes that will be used for Visits 1, 2, 4, 6, 7, and 9 for the ECT treatment group and for Visits 1–6 for the ketamine treatment group include the following: MADRS, Columbia Suicide Severity Rating Scale (CSSRS) [33], the Clinician Global Impression-Severity (CGI-S) and the Clinician Global Impression-Improvement (CGI-I) [34]. In addition, changes in medical history and concomitant medications are assessed at each visit.

2.7.4. Cognitive functioning

In addition to PRO, cognitive functioning will also be evaluated via objective cognitive testing. The MOCA [22] is administered at screening as part of the inclusion criteria and at the EOT visit. These measures are also administered for eligible participants at 1 month, 3 months, and 6 months after the EOT visit. The MOCA is the primary cognitive measure for the study. The North American Adult Reading Test-35 [35] is used as an estimate of intellectual function and administered at Visit 1. Additionally, the Hopkins Verbal Learning Test-Revised [36], the Stroop Color word test [37], and the Controlled Oral Word Association Test (COWAT) [38] is administered at Baseline/Visit 1 and EOT Visit (and for responders, at 1 month, 3 months, and 6 months after EOT visit). When available, alternate forms of tests are used to minimize practice effects.

2.7.5. Adverse events and side effects

Patient-reported outcomes of adverse events and side effects include the Global Self Evaluation of Memory (GSE-My) [39], the Squires Memory Complaint Questionnaire (SMCQ) [40], and Patient Rated Inventory of Side Effects (PRISE) [41]. We opted to include these self-report measures of memory complaints as these may be valuable in understanding how patients in the two treatment arms perceive their cognition, especially with regard to anterograde memory. Clinician-reported outcomes of adverse events and side effects include the YMRS, the Clinician-Administered Dissociative State Scale (CADSS) [42], and the Brief Psychiatric Rating Scale (BPRS) psychotic subscale [43]. For practical purposes in the ECT treatment group, the CADSS and BPRS are administered after the patient re-orientes following ECT.

2.8. Statistical analysis plan and power

The primary outcome measure is a comparison of the proportion of patients in each treatment group who respond to treatment at the EOT visit. Response is defined by a 50% or greater reduction in symptom severity compared to baseline as measured by the QIDS-SR. The primary analysis will be performed on the modified intent to treat (mITT) population defined as a randomized patient having at least one treatment and one post-baseline QIDS-SR rating during the acute treatment phase. The primary outcome measure of response rate will be compared between ketamine and ECT using a chi-square test, to test the comparative effectiveness of ketamine and ECT for reduction in depressive symptoms. A multivariable logistic regression model will be constructed for the analysis, to account for potential heterogeneity of treatment effect caused by confounding variables. A similar analytic strategy will be applied to evaluate cognitive function and quality of life.

Regarding the threshold for the non-inferiority margin, consideration is given to what would be a clinically meaningful difference. In

most studies a non-inferiority margin to retain 80–85% of the clinical effect compared to the gold standard is thought to be acceptable [26,27]. In clinical terms, ketamine may provide advantages that such an inferiority margin would be acceptable. Therefore, our non-inferiority margin requirement for ketamine to retain 90% of ECT effect is conservative. We will also validate whether ketamine has ancillary advantages besides the main treatment effect, as is commonly believed; this will be done through analyses of secondary measures of patient- and clinician-rated scales for cognitive impairment, side effects and quality of life.

3. Discussion

The ELEKT-D study is the first well-powered randomized comparative effectiveness trial of ECT versus ketamine for patients with TRD. While ECT has been the gold standard therapy for treatment-resistant depression for many years, it is significantly underutilized in the U.S [44]. Only 0.26% of patients with a mood disorder diagnosis (Major Depressive Disorder or Bipolar Disorder) received ECT in 2014 among a large cohort (47 million) of privately insured Americans [10]. Given that up to one-third of patients with mood disorders have TRD [3] and that ECT is the most effective treatment for this condition [44,45], this utilization rate is inappropriately low. At the same time, the off-label use of ketamine has expanded significantly, despite a paucity of longer-term safety data and uncertainty about optimal maintenance therapy approaches. Wilkinson et al., found a rapidly growing number of physicians from a variety of geographic locations and specialties offering ketamine treatment off-label for psychiatric disorders [19]. The ELEKT-D study is therefore especially timely in its attempt to provide key stakeholders with information about outcomes of high relevance to patients and their families, which include the treatment's impact on mood, cognition, and quality of life.

Several study design considerations merit comment. First, although ECT and ketamine treatments demonstrate similar response and remission rates in the clinical trials conducted thus far, the patient samples were drawn from different contexts. Virtually all of the most recent large ECT trials have been conducted by recruiting from contexts where patients are seeking treatment [45–47]. Some ketamine trials, on the other hand, have recruited primarily using advertisements [18,48], thus it is not possible to make a true direct comparison of the two treatments from the existing literature. Importantly, prospective patients in the ELEKT-D study are approached for participation only if they have been referred for ECT and found to be suitable ECT candidates. This design feature was implemented to ensure equipoise in the randomization. The concern was that ketamine therapy is now heavily marketed by ketamine treatment centers and has received extensive coverage in the lay media (much of it positive). In contrast, most ECT facilities do not market their services, and its media profile is relatively obscure. We hypothesized that if direct-to-patient advertisements are used for recruitment purposes, some patients may prefer to be randomized to the ketamine arm, and if randomized to ECT, would withdraw from the study prior to initiating treatment, hence biasing results. The ELEKT-D strategy to recruit only among treatment-seeking patients aims to address this issue.

Second, we restricted study participation to individuals with MDD who do not have histories of bipolar disorder, although both ECT and ketamine have been used in patients with bipolar depression. In addition, patients with psychotic depression are excluded, although ECT trials often enroll a substantial portion of patients with psychotic depression who may respond particularly well to ECT [49,50]. In ketamine trials, these patients have almost been uniformly excluded due to concerns that ketamine might exacerbate psychosis [17,18,51]. Due to these same concerns, the ELEKT-D study also excludes patients with psychotic depression. This consideration should be remembered when interpreting final study results.

Third, the frequency of treatment administration is unbalanced

across the two arms in that the ECT group receives nine treatments while the ketamine group receives six treatments. Nine ECT treatments were chosen because this represents slightly above the average number of ECT treatments generally administered during an acute course of ECT in previous trials [45,47]. As noted in some of the largest ECT trials to date, the majority of patients (approximately 75%) who remit/respond to ECT do so by 3 weeks or 9 treatments [45,61,62]. Moreover, one major aim of the study is to compare both the treatment effectiveness as well as side effects burden of ECT vs. ketamine treatment. If we allow a large number of ECT treatments compared to ketamine treatments, we may have been much more likely to observe significant increase in frequency of side effects in the ECT arm. At the time of study protocol development, we did not have sufficient data to support ketamine administration beyond six infusions. Finally, as the study sponsor does not pay for the costs associated with treatment, each site had to make accommodations to ensure that all patients irrespective of financial means or insurance status would be able to receive their assigned treatment. ECT is generally covered by private and government insurance plans but ketamine is not, mandating that each site subsume the costs of ketamine treatment, and in the case of uninsured patients, the costs of ECT. While a formal cost-benefit analysis was not included in the study protocol, these issues are of major interest to the Stakeholder Council.

Finally, although we collect follow-up assessments of treatment responders for up to 6 months, the uncontrolled nature of this follow-up limits our ability to make meaningful between-group comparisons in outcomes. In many ECT treatment centers, continuation/maintenance is recommended to patients, and this strategy is becoming increasingly recognized as an optimal way to sustain response/remission [52]. With respect to ketamine, there is a paucity of long-term data [53] and at the time the protocol was designed, there was no explicit plan or means whereby ketamine would be provided on an ongoing basis following the 6 treatments. Nonetheless, this longer-term data will be useful for exploratory and within-group comparisons and for reporting naturalistic relapse rates in real-world settings. It should be noted that at the 1 month follow-up time point, for both responders and non-responders, we will collect retrospective information regarding any additional ECT, ketamine, or other treatments after the EOT visit. We will also collect patient's self-assessment of improvement at the 1 month follow-up visit.

Whether ketamine is more tolerable than ECT also remains unclear. While the most feared adverse effect from ECT is memory loss, long-term exposure to high-dose ketamine can also be associated with cognitive impairment [54,55]. Though substantial improvements in ECT treatment techniques in the past several decades have minimized the risk of memory loss [47], there is still a risk, albeit low, of significant autobiographical memory loss following ECT [56]. Notably, objective measures of memory generally show recovery or even improvements in several cognitive domains compared to baseline only a few days following the last ECT treatment during an acute course [57]. Another potential worrisome side effect that may result from long-term ketamine exposure includes bladder toxicity. Finally, ketamine is a drug of abuse and the extent to which its use as a treatment for depression may lead to an increase in rates of misuse and ketamine use disorders is unclear. Hence, even if ketamine is shown to be non-inferior to ECT, specific clinical factors in a given patient population may dictate that ECT is still the preferred treatment option.

4. Conclusions

Results of the ELEKT-D study will have important implications for patient choice, health insurance coverage policies, and clinical care for TRD. If ketamine is shown to be non-inferior to ECT in depressed patients (without psychosis), ketamine might be preferred over ECT by some patients. Given the treatment burden of ECT, including a risk of transient adverse cognitive effects, repeated exposure to general anesthesia, and the stigma and lack of access to the treatment, ketamine may represent a more tolerable intervention. However, ketamine is also

fraught with potential drawbacks, including abuse liability and the potential for bladder and neurotoxicity [58–60]. Hence, individual patient clinical factors will still have great bearing on the preferred treatment option from the perspective of the patient and the provider. While still accounting for individual patient-level clinical factors, the ELEKT-D study should help further clarify the relative positions of these two modalities in the treatment algorithm for TRD.

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