The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 22, 2023 VOL. 388 NO. 25

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

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ABSTRACT

BACKGROUND

Electroconvulsive therapy (ECT) and subanesthetic intravenous ketamine are both currently used for treatment-resistant major depression, but the comparative effectiveness of the two treatments remains uncertain.

METHODS

We conducted an open-label, randomized, noninferiority trial involving patients referred to ECT clinics for treatment-resistant major depression. Patients with treatment-resistant major depression without psychosis were recruited and assigned in a 1:1 ratio to receive ketamine or ECT. During an initial 3-week treatment phase, patients received either ECT three times per week or ketamine (0.5 mg per kilogram of body weight over 40 minutes) twice per week. The primary outcome was a response to treatment (i.e., a decrease of ≥50% from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report; scores range from 0 to 27, with higher scores indicating greater depression). The noninferiority margin was –10 percentage points. Secondary outcomes included scores on memory tests and patient-reported quality of life. After the initial treatment phase, the patients who had a response were followed over a 6-month period.

RESULTS

A total of 403 patients underwent randomization at five clinical sites; 200 patients were assigned to the ketamine group and 203 to the ECT group. After 38 patients had withdrawn before initiation of the assigned treatment, ketamine was administered to 195 patients and ECT to 170 patients. A total of 55.4% of the patients in the ketamine group and 41.2% of those in the ECT group had a response (difference, 14.2 percentage points; 95% confidence interval, 3.9 to 24.2; P<0.001 for the noninferiority of ketamine to ECT). ECT appeared to be associated with a decrease in memory recall after 3 weeks of treatment (mean [±SE] decrease in the T-score for delayed recall on the Hopkins Verbal Learning Test–Revised, –0.9±1.1 in the ketamine group vs. –9.7±1.2 in the ECT group; scores range from –300 to 200, with higher scores indicating better function) with gradual recovery during follow-up. Improvement in patient-reported quality-of-life was similar in the two trial groups. ECT was associated with musculoskeletal adverse effects, whereas ketamine was associated with dissociation.

CONCLUSIONS

Ketamine was noninferior to ECT as therapy for treatment-resistant major depression without psychosis. (Funded by the Patient-Centered Outcomes Research Institute; ELEKT-D ClinicalTrials.gov number, NCT03113968.)

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This article was published on May 24, 2023, and updated on June 22, 2023, at NEJM.org.

N Engl J Med 2023;388:2315-25.
DOI: 10.1056/NEJMoa2302399

A Quick Take is available at NEJM.org

Major depressive disorder is a leading cause of disability worldwide and is estimated to affect 21 million adults in the United States.[1] Although antidepressants are widely available, the effectiveness of antidepressants is suboptimal in more than a third of patients.[2] Treatment-resistant major depression is commonly defined as depression with an unsatisfactory response to two or more adequate trials of antidepressants.[3]

Electroconvulsive therapy (ECT) has a track record of nearly 80 years as one of the most effective and rapid strategies for treatment-resistant major depression.[4-6] Advancements in ECT, including administration while the patient is under brief general anesthesia, unilateral electrode placement, and refined techniques for seizure elicitation such as ultrabrief pulse stimulation, have enabled it to be more commonly performed as an outpatient procedure.[7,8] However, ECT remains underused owing to limited availability, social stigma, and concerns regarding the adverse effect of cognitive impairment.[4,5]

Ketamine, an N-methyl-D-aspartate receptor antagonist, has been approved by the Food and Drug Administration as a sedative, analgesic, and general anesthetic. Over the past two decades, ketamine, administered intravenously at subanesthetic doses of 0.5 mg per kilogram of body weight, was noted to have a rapid antidepressant effect in patients with major depressive disorder[9] and treatment-resistant major depression.[10] Ketamine, in single or multiple doses, is increasingly being used for treatment-resistant major depression.[11] Ketamine is an attractive alternative for patients because it does not require general anesthesia and is not associated with clinically significant memory impairment.[12] However, ketamine is a schedule III medication with liability for potential abuse.[13,14] Because treatment with ketamine can lead to transient changes in perception and thinking,[15] it is mainly used in patients with treatment-resistant major depression without psychotic features. There is also concern about whether ketamine is as effective as ECT.[16] To address these concerns and the current gap in evidence, we conducted a pragmatic comparative-effectiveness trial of ketamine and ECT for treatment-resistant major depression (the ELEKT-D trial). The trial aimed to determine whether ketamine was noninferior to ECT in the treatment of nonpsychotic treatment-resistant major depression.

Methods

Trial Design and Oversight

This trial was a prospective, open-label, randomized, noninferiority trial that was conducted at five sites: an urban community hospital (Lutheran Hospital, Cleveland Clinic), a Veterans Administration hospital (Baylor College of Medicine), and three university hospital–based centers (Yale University School of Medicine, Johns Hopkins Medical Institute, and Mount Sinai School of Medicine). The trial protocol, with the statistical analysis plan, is available with the full text of this article at NEJM.org. The trial consisted of a 3-week initial treatment phase with either ketamine (administered twice per week)[18] or ECT (administered 3 times per week)[4,17] to determine a response to treatment, defined as a decrease of at least 50% in the score on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; scores range from 0 to 27, with higher scores indicating greater depression).[19] After the initial 3-week treatment phase, the patients who had a response were followed for a 6-month period, during which they received treatment, which could include ketamine or ECT, as prescribed by their clinical providers; follow-up visits were conducted at months 1, 3, and 6. Trial participation ended for the patients who did not have a response after 3 weeks, except for a follow-up telephone call that was made after 1 month to ensure that continuity of care was maintained and to assess safety.

Our trial was funded by the Patient-Centered Outcomes Research Institute (PCORI) under a contract with the Cleveland Clinic Foundation (the sponsor). The institutional review board at each trial site approved a standard protocol and consent form. All the patients provided written informed consent. The trial was designed and supervised by an executive committee consisting of the first author and site principal investigators. The first and last author and the site principal investigators vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. A data and safety monitoring board monitored the trial. A stakeholder committee met regularly and provided input for the ongoing trial. Data coordination and project management were conducted by the Cleveland Clinic Center for Clinical Research (C5Research). Statistical analysis was conducted by the last au-

thor. The first author wrote the manuscript with contributions from all the authors, and the publication committee approved the manuscript that was submitted.

TRIAL POPULATION

From March 2017 through September 2022, outpatients or inpatients referred for treatment by their clinical providers to an ECT service at a trial site were invited to participate in the trial. Patients with treatment-resistant major depression who were interested in participation were enrolled after providing written informed consent. Patients 21 to 75 years of age were eligible if they met the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5), criteria for major depressive disorder without psychotic features and reported having had an unsatisfactory response to at least two adequate trials of antidepressant treatment in their lifetime. Verification of treatment resistance was done with the use of information from the referring provider, the Antidepressant Treatment History Form guidelines,[20] and clinical interview. Patients were also required to have a score greater than 20 (indicating moderate or more severe depression) on the Montgomery–Åsberg Depression Rating Scale (MADRS) (scores range from 0 to 60, with higher scores indicating greater depression)[21] as well as no contraindications to ketamine or ECT. The full inclusion and exclusion criteria are described in the trial protocol.

RANDOMIZATION AND TREATMENT

After screening, eligible patients were randomly assigned in a 1:1 ratio to receive ketamine or ECT. Randomization was performed with the use of a secure electronic data-management system and was stratified according to trial site. Owing to the different nature of the two treatments, patients, attending physicians, and research staff were aware of the treatment-group assignments.

Ketamine (twice per week for 3 weeks)[18] was administered intravenously at the accepted subanesthetic dose of 0.5 mg per kilogram of body weight over a 40-minute period, with allowance for dose modification if clinically indicated. The recommended starting procedure in the patients assigned to receive ECT (three times per week for 3 weeks) was specified as right unilateral ultrabrief pulse at six times the seizure threshold that was determined during titration at the first visit, with allowance for subsequent modification of settings and electrode placement.[4] Treatment could end early, according to the clinical judgment of the investigator. Patients could discontinue treatment for any reason. In the event of early completion of the initial treatment phase, patients were encouraged to complete an end-of-treatment visit. In both trial groups, patients were allowed to continue treatment with their previously prescribed medications during the initial treatment phase and follow-up. Dosages of psychotropic medications, durations of treatments at the time of enrollment, and subsequent changes to such treatments during the course of the trial were recorded.

TRIAL OUTCOMES

The primary outcome was a response according to the QIDS-SR-16, defined as a decrease from baseline (the first treatment visit) of at least 50% in the score on the QIDS-SR-16 at the end-of-treatment visit, which occurred within 3 days after the last treatment session at the end of the initial 3-week period. The QIDS-SR-16 is a validated patient-rated measure that has been used in other large trials of depression treatment.[2]

Secondary outcomes were a response according to the MADRS, defined as a decrease from baseline of at least 50% in the score on the clinician-rated MADRS[21]; measures of remission according to the QIDS-SR-16 (i.e., a score of ≤5) and the MADRS (i.e., a score of ≤10); and response and remission according to the Clinical Global Impression–Improvement (CGI-I) and Patient Global Impression–Improvement (PGI-I) scales. Other secondary outcomes were the changes in scores from baseline to the end-of-treatment visit on the QIDS-SR-16 and the MADRS; scores at the end-of-treatment visit on the Global Self-Evaluation of Memory (GSE-My), a patient-rated scale of memory function (scores range from 1 to 7, with higher scores indicating better memory function),[22] and the Squire Memory Complaint Questionnaire (SMCQ), a patient-rated scale of cognitive symptoms (scores range from –72 to 72, with higher scores indicating better memory function)[23]; changes in scores from baseline to the end-of-treatment visit on the Hopkins Verbal Learning Test–Revised (HVLT-R), a rater-administered test of memory function,[24] and the 16-item Quality-of-Life Scale, a patient-rated questionnaire that measures quality of life in six

Table 1. Trial Sites and Characteristics of the Patients in the Intention-to-Treat Population at Randomization.*

Variable	Ketamine (N=200)	ECT (N=203)
Trial site — no. (%)		
Baylor College of Medicine	47 (23.5)	48 (23.6)
Johns Hopkins Medical Institute	23 (11.5)	24 (11.8)
Lutheran Hospital, Cleveland Clinic	56 (28.0)	58 (28.6)
Mount Sinai School of Medicine	35 (17.5)	34 (16.7)
Yale University School of Medicine	39 (19.5)	39 (19.2)
Female sex — no. (%)	106 (53.0)	100 (49.3)
Age — yr	45.6±14.8	47.1±14.1
White race — no. (%)†	173 (86.5)	182 (89.7)
Hispanic or Latino ethnic group — no. (%)†	24 (12.0)	11 (5.4)
Body-mass index‡	29.5±7.4	30.4±7.9
Inpatient at time of randomization — no. (%)	23 (11.5)	21 (10.3)
Psychiatric history		
Age at onset of first episode of major depression — yr	19.7±11.5	19.4±11.0
Median no. of previous episodes of major depression (IQR)	5 (2–16)	5 (2–18)
Median duration of current episode of major depression (IQR) — mo	24 (12–75)	24 (10–72)
Family history of depression — no. (%)	154 (77.0)	160 (79.2)§
Attempted suicide — no. (%)	73 (36.5)	84 (41.4)
Previous ECT — no. (%)	23 (11.5)	21 (10.3)
Previous ketamine treatment — no. (%)	14 (7.0)	8 (3.9)
Depression severity		
CGI-S score¶	5.0±0.6	5.2±0.6
MADRS score‖	32.3±6.2	32.6±6.0
QIDS-SR-16 score**	17.9±4.1	18.2±4.2
Subtype of depression — no. (%)		
Anxious features	111 (55.5)	110 (54.2)
Atypical features	9 (4.5)	9 (4.4)
Melancholic features	28 (14.0)	31 (15.3)
Diagnosis of coexisting condition — no. (%)		
Antisocial personality disorder	4 (2.0)	6 (3.0)
Alcohol use disorder	8 (4.0)	11 (5.4)
GAD	113 (56.5)	113 (55.7)
OCD	9 (4.5)	18 (8.9)
Panic disorder	33 (16.5)	42 (20.7)
PTSD	38 (19.0)	50 (24.6)
Social phobia	56 (28.0)	57 (28.1)
Moderate-to-severe substance use	10 (5.0)	13 (6.4)
Use of psychiatric medication at enrollment — no. (%)		
Anticonvulsants	54 (27.0)	51 (25.1)
Atypical antidepressants	90 (45.0)	92 (45.3)

Table 1. (Continued.)

Variable	Ketamine (N = 200)	ECT (N = 203)
Atypical antipsychotics	59 (29.5)	58 (28.6)
Augmentation medications	31 (15.5)	40 (19.7)
Benzodiazepines	60 (30.0)	63 (31.0)
Serotonin-reuptake inhibitors	58 (29.0)	75 (36.9)
Serotonin- or norepinephrine-reuptake inhibitors	67 (33.5)	70 (34.5)
Tricyclic antidepressants	13 (6.5)	10 (4.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ECT denotes electroconvulsive therapy, IQR interquartile range, GAD generalized anxiety disorder, OCD obsessive–compulsive disorder, and PTSD post-traumatic stress disorder.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data were missing for 1 patient.
¶ Scores on the Clinical Global Impression–Severity (CGI-S) scale range from 1 to 7, with higher scores indicating more severe depression.
‖ Scores on the Montgomery–Åsberg Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater depression.
** Scores on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) range from 0 to 27, with higher scores indicating greater depression.

domains[25]; and scores on the Clinician-Administered Dissociative States Scale (CADSS)[26] and other rating scales. A complete list of trial outcomes, score ranges, and time points of treatment is provided in the Supplementary Appendix, available at NEJM.org.

STATISTICAL ANALYSIS

The trial was powered to detect noninferiority of ketamine to ECT. With a noninferiority margin of –10 percentage points (i.e., the percentage of patients with a response to ketamine would be no more than 10 percentage points less than the percentage with a response to ECT), we calculated that a total of 346 participants would provide the trial with 80% power to detect the noninferiority of ketamine according to the Farrington–Manning score statistic[27] (one-sided alpha of 0.025), assuming that 50% of the patients would have a response to ECT and that the actual between-group difference in response would be 5 percentage points (details are provided in the Supplementary Appendix). To account for 15% attrition, we planned to recruit 400 patients (200 per group).

Patient characteristics were summarized with the use of descriptive statistics. The principal analysis of the primary outcome was performed in the modified intention-to-treat population, which included the patients who had completed at least one treatment session and had at least one QIDS-SR-16 measurement during the initial treatment phase. The Farrington–Manning test was used to assess the noninferiority of ketamine. Sensitivity analyses were performed in the intention-to-treat population and were conducted by imputing the missing primary outcome values for the patients who were not included in the modified intention-to-treat population (details are provided in the Supplementary Appendix). Linear mixed-effects models were used to model the longitudinal QIDS-SR-16 scores during the initial treatment phase and included treatment, assessment, treatment-by-assessment interaction, and trial site as fixed terms and a random intercept at the patient level. Least-squares estimates were derived according to treatment and assessment.

The analysis of the secondary outcomes was also performed in the modified intention-to-treat population (see the Supplementary Appendix). The widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Adverse events were reported according to the proportions of patients in each group with an event. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and RStudio software, version 2023.03.0.

RESULTS

PATIENTS

A total of 403 patients underwent randomization; 200 were assigned to the ketamine group and 203 to the ECT group. Of the these, 35 patients (4 in the ketamine group and 31 in the ECT group) did not start the initial treatment phase, and another 3 (1 in the ketamine group and 2 in the ECT group) had no post-treatment QIDS-SR-16 rating assessment. Thus, the modified intention-to-treat population comprised 365 patients (195 in the ketamine group and 170 in the ECT group) (Fig. S1 in the Supplementary Appendix).

The demographic and clinical characteristics of the intention-to-treat population were summarized according to trial group (Table 1). The patients in the intention-to-treat population were representative of those with treatment-resistant major depression referred for ECT treatment (Table S1). Among the 403 patients, the mean age was 46 years, 206 (51.1%) were women, and 355 (88.1%) were White, and most (359 [89.1%]) were outpatients at the time of randomization. The severity of the current depression episode was moderate to severe with a median duration of 2.0 years (interquartile range, 0.8 to 6.0). Most patients (314 [77.9%]) had a family history of depression, and 157 (39.0%) had attempted suicide. The characteristics of the patients in the modified intention-to-treat population were similar to the those of the dropouts (Table S2).

PRIMARY OUTCOME

A response according to the QIDS-SR-16 occurred in 108 of 195 patients (55.4%) in the ketamine group and in 70 of 170 patients (41.2%) in the ECT group (difference, 14.2 percentage points; 95% confidence interval [CI], 3.9 to 24.2; Farrington–Manning score statistic, 4.64; P<0.001 for the noninferiority of ketamine to ECT) (Fig. 1A). The results of the sensitivity analysis that was performed in the intention-to-treat population with the use of multiple imputation were consistent with those of the primary analysis, with a response of 55.4% with ketamine and 41.6% with ECT (difference, 13.8 percentage points; 95% CI, 3.9 to 23.8; P<0.001 for the noninferiority of ketamine) (Fig. S2). Other sensitivity analyses that used different imputation scenarios also showed the noninferiority of ketamine. The results of the subgroup analyses are provided in Table S3.

SECONDARY OUTCOMES

Depression

A response according to the MADRS occurred in 99 of 195 patients (50.8%) in the ketamine group and in 70 of 169 patients (41.4%) in the ECT group (difference, 9.3 percentage points; 95% CI, −0.9 to 19.4) (Fig. 1B and Table 2). Both QIDS-SR-16 and MADRS scores gradually declined during the initial treatment phase (Fig. 1C and 1D). The least-squares mean (±SE) change from baseline in the score on the QIDS-SR-16 at the end-of-treatment visit was −9.0±0.4 in the ketamine group and −7.2±0.4 in the ECT group (difference, −1.8 points; 95% CI, −2.8 to −0.8) (Table S4). The least-squares mean change from baseline in the score on the MADRS was −15.3±0.7 in the ketamine group and −13.1±0.7 in the ECT group (difference, −2.2 points; 95% CI, −4.1 to −0.3).

Remission according to the QIDS-SR-16 occurred in 63 of 195 patients (32.3%) in the ketamine group and in 34 of 170 patients (20.0%) in the ECT group. Remission according to the MADRS occurred in 74 of 195 patients (37.9%) in the ketamine group and in 37 of 170 patients (21.8%) in the ECT group (Table 2).

Cognitive Impairment and Quality of Life

The mean (±SE) score on the GSE-My for patient-reported memory function at the end-of-treatment visit was lower in the ECT group than in the ketamine group (3.2±0.1 vs. 4.2±0.1; difference, 1.1 points; 95% CI, 0.9 to 1.2) (Table 2). The scores on the SMCQ at the end-of-treatment visit indicated that there were fewer patient reports of cognitive symptoms in the ketamine group than in the ECT group, with a between-group difference in the mean score of 9.0 points (95% CI, 5.1 to 13.0) (Table 2).

At the end-of-treatment visit, the decline from baseline in the T-score on the delayed-recall component of the HVLT-R was greater in the ECT group than in the ketamine group (−9.7±1.2 vs. −0.9±1.1; difference, 8.8 points; 95% CI, 5.7 to 11.9). The results for the changes from baseline in the T-scores on the total score and discrimination index component of the HVLT-R were in the same direction as those for the delayed-recall

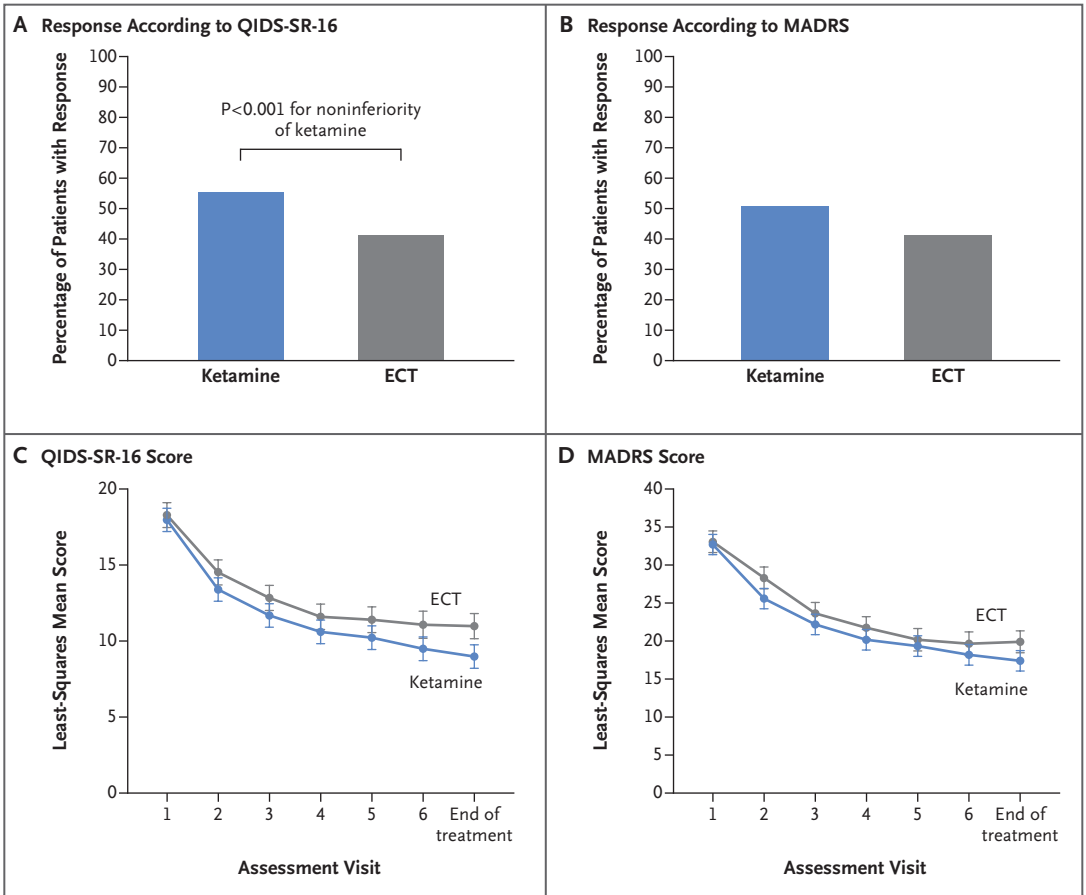

Figure 1. Response to Ketamine and ECT According to the QIDS-SR-16 and MADRS during the Initial 3-Week Treatment Phase.

Shown are the percentages of patients who had a response to ketamine or electroconvulsive therapy (ECT) according to the scores on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16, Panel A) and the Montgomery–Åsberg Depression Rating Scale (MADRS, Panel B) at the end-of-treatment visit, as well as the least-squares mean QIDS-SR-16 scores (Panel C) and the mean MADRS scores (Panel D) at the assessment visits during the initial 3-week treatment phase. Analyses were performed in the modified intention-to-treat population, which included all the patients who had completed at least one treatment session and had at least one QIDS-SR-16 measurement. Scores on the QIDS-SR-16 range from 0 to 27, with higher scores indicating greater depression. Scores on the MADRS range from 0 to 60, with higher scores indicating greater depression. The I bars in Panels C and D represent 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

component (Table 2). Scores on the 16-item Quality-of-Life Scale increased from baseline to the end-of-treatment visit in both trial groups, with changes of 12.3 in the ketamine group and 12.9 points in the ECT group (difference, −0.6 points; 95% CI, −3.4 to 2.1) (Table 2).

TREATMENT SESSIONS

In each trial group, the number of treatment sessions did not differ substantially between the patients who had a response and those who did not (Table S5). In the ketamine group, 180 of 195 patients (92.3%) completed all six treatment sessions, and in the ECT group, 158 of 170 patients (92.9%) completed six to nine treatment sessions. ECT was changed from right unilateral to bilateral treatment in 39% of the patients (Table S6), whereas the ketamine dose was kept constant in nearly all patients (Table S7).

Table 2. Primary and Secondary Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Ketamine (N=195)	ECT (N=170)	Difference (95% CI)†
Primary outcome			
QIDS-SR-16–based response — no./total no. (%)‡	108/195 (55.4)	70/170 (41.2)	14.2 (3.9 to 24.2)
Secondary outcomes			
Effectiveness outcomes — no./total no. (%)			
MADRS-based response‡	99/195 (50.8)	70/169 (41.4)	9.3 (–0.9 to 19.4)‡
Remission§			
QIDS-SR-16–based	63/195 (32.3)	34/170 (20.0)	12.3 (3.4 to 21.2)
MADRS-based	74/195 (37.9)	37/170 (21.8)	16.2 (7.0 to 25.4)
CGI-I score¶			
Much improved or better rating	99/189 (52.4)	78/164 (47.6)	4.8 (–5.6 to 15.3)
Very much improved rating	59/189 (31.2)	35/164 (21.3)	9.9 (0.8 to 19.0)
PGI-I score‖			
Much improved or better rating	84/190 (44.2)	60/164 (36.6)	7.6 (–2.6 to 17.8)
Very much improved rating	37/190 (19.5)	18/164 (11.0)	8.5 (1.1 to 15.9)
Cognitive and behavioral outcomes			
GSE-My score at end-of-treatment visit**	4.2±0.1	3.2±0.1	1.1 (0.9 to 1.2)
SMCQ score at end-of-treatment visit††	0.2±1.4	–8.8±1.5	9.0 (5.1 to 13.0)
Change from baseline in HVLT-R T-score‡‡			
Total	3.2±0.8	–2.1±0.8	5.3 (3.1 to 7.4)
Delayed recall	–0.9±1.1	–9.7±1.2	8.8 (5.7 to 11.9)
Discrimination index	–1.5±1.1	–9.7±1.2	8.2 (5.2 to 11.3)
Change from baseline in the 16-item Quality-of-Life Scale score§§	12.3±1.0	12.9±1.1	–0.6 (–3.4 to 2.1)

* Plus–minus values are means ±SE. The modified intention-to-treat population included the patients who had completed at least one treatment session and had at least one QIDS-SR-16 measurement.

† The differences in the categorical outcomes are reported in percentage points, and the differences in the continuous outcomes are reported in the respective unit of measure. All confidence intervals are two-sided, and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

‡ A QIDS-SR-16–based response and a MADRS-based response were defined as a decrease from baseline in the respective score of at least 50% at the end-of-treatment visit. The Farrington–Manning score statistic was used to assess the noninferiority of ketamine, with a noninferiority margin of –10 percentage points (i.e., the percentage of patients with a response to ketamine would be no more than 10 percentage points less than the percentage with a response to ECT).

§ Remission according to the QIDS-SR-16 was defined as score of 5 or lower, and remission according to the MADRS was defined as a score of 10 or lower.

¶ Scores on the CGI–Improvement (CGI-I) scale range from 1 to 7, with higher scores indicating less improvement. A much improved or better rating was defined as a score lower than 2, and a very much improved rating as a score of 1.

‖ Scores on the Patient Global Impression–Improvement (PGI-I) scale range from 1 to 7, with higher scores indicating less improvement. A much improved or better rating was defined as a score lower than 2, and a very much improved rating as a score of 1.

** Scores on the Global Self-Evaluation of Memory (GSE-My) range from 1 to 7, with higher scores indicating better memory function.

†† Scores on the Squire Memory Complaint Questionnaire (SMCQ) range from –72 to 72, with higher scores indicating better memory function.

‡‡ T-scores on the Hopkins Verbal Learning Test–Revised (HVLT-R) range from 0 to 100 for total, from –300 to 200 for the delayed-recall component, and from –300 to 200 for the discrimination index, with higher scores indicating better cognitive function. A negative HVLT-R result indicates a decrease in score from baseline to the end-of-treatment visit. Aged-corrected norms were used.

§§ Scores on the 16-item Quality-of-Life Scale range from 16 to 112, with higher scores indicating better quality of life.

ADVERSE EVENTS

Adverse events are reported in Table 3 and Table S8. No deaths occurred during the trial. During the initial treatment phase, 49 of 195 patients (25.1%) in the ketamine group and 55 of 170 patients (32.4%) in the ECT group had at least one moderate or severe adverse event (Table 3). The scores of dissociative symptoms as measured with the CADSS were higher in the ketamine group than in the ECT group on all treatment days (Fig. S3). The percentage of patients with musculoskeletal adverse events was higher in the ECT group than in the ketamine group (5.3% vs. 0.5%). Six patients (4 in the ketamine group and 2 in the ECT group) reported new suicidal ideation, and in the follow-up period, 1 patient in the ketamine group had a suicide attempt (Table 3).

Table 3. Moderate and Severe Adverse Events in the Modified Intention-to-Treat Population.*

Adverse Event	Ketamine	ECT
	no. of patients/total no. (%)	
Initial treatment phase		
≥1 Adverse event	49/195 (25.1)	55/170 (32.4)
Gastrointestinal adverse event	13/195 (6.7)	9/170 (5.3)
Muscle pain or weakness	1/195 (0.5)	9/170 (5.3)
Headache	16/195 (8.2)	12/170 (7.1)
Severe or prolonged hypertension	6/195 (3.1)	4/170 (2.4)
Suicidal ideation	4/195 (2.1)	2/170 (1.2)
Suicide attempt	0/195	0/170
Follow-up period		
≥1 Adverse event	17/108 (15.7)	10/70 (14.3)
Severe or prolonged hypertension	2/108 (1.9)	0/70
Suicidal ideation	4/108 (3.7)	1/70 (1.4)
Suicide attempt	1/108 (0.9)	0/70

* P>0.05 for all adverse events except muscle pain or weakness (P=0.01).

FOLLOW-UP

During the follow-up period in which the patients received treatment as prescribed by their clinical providers, depression scores increased (Fig. S4). Relapse, defined as a QIDS-SR-16 score greater than 11, occurred in 19.0% of the patients in the ketamine group and in 35.4% of those in the ECT group at month 1; in 25.0% and 50.9%, respectively, at month 3; and in 34.5% and 56.3%, respectively, at month 6 (Table S9). Among the patients who had a response in the ECT group, the SMCQ scores indicated gradual recovery over 6 months; however, GSE-My scores remained lower than those in the ketamine group through the end of follow-up (Table S9). The scores for memory function in all aspects of HVLT-R that were observed to be lower in the ECT group than in the ketamine group at the end-of-treatment visit had returned to similar levels by the 1-month follow-up visit and remained stable over 6 months. The improvement in quality of life that was observed in both trial groups at the end-of-treatment visit was maintained during the follow-up period (Table S9). The proportions of patients who continued to receive the randomly assigned treatment and of those who started new treatments during the follow-up period are provided in Tables S9 and S10, respectively.

DISCUSSION

This randomized trial evaluating the comparative effectiveness of ketamine and ECT in patients with treatment-resistant depression without psychosis showed noninferiority of ketamine to ECT with respect to the primary outcome of treatment response according to the QIDS-SR-16. The decline in memory performance appeared to be greater with ECT than with ketamine at the end-of-treatment visit, but the results were similar in the two trial groups at the 1-month follow-up visit. Both ketamine and ECT appeared to be associated with improved quality of life immediately after the initial treatment phase.

The percentage of patients who withdrew from the trial after randomization but before treatment was started was higher in the ECT group than in the ketamine group, a finding that reflects patient preferences and logistic issues. In the three different imputation analyses, the results of the sensitivity analyses that were performed with the use of multiple imputation in the intention-to-treat population supported the noninferiority of ketamine to ECT.

Our trial results differ from those of a recent European trial[28] and a meta-analysis that included several small trials and the larger European ketECT trial.[29] These trials showed that remission with ketamine was inferior to that with ECT. Our trial differs from these reports in that it included only patients with major depressive disorder without psychosis (those with psychosis were excluded), had a larger sample size, and

was performed in a primarily outpatient population (89% of patients).

In the current trial, the percentages of patients who had a response or remission with ECT were lower than those in other reports.[4] ECT has been shown to be more effective among older adults, among patients with major depressive disorder with psychosis, and in inpatient and research settings.[17,30,31] The results of our pragmatic trial are more similar to the reports of lower rates of remission with ECT in community[31] and outpatient settings[17,30] than to reports of higher rates in inpatient and research settings. The current trend in the United States is for ECT to be administered on an outpatient basis to patients with treatment-resistant major depression.[32] ECT is recommended as being highly effective for rapid treatment of late-life, catatonic, and suicidal depression.[33,34] Future studies will need to be conducted to determine the comparative effectiveness of ketamine and ECT in older patients, patients with bipolar depression, and in emergency inpatient settings.[35]

Our trial has several limitations. ECT was started with right unilateral placement and was then switched to bilateral placement in the event of inadequate response. If ECT was started with bilateral placement, a higher percentage of patients with a response might have been observed.[4] It is also possible that more sessions of ECT would have led to a higher percentage of patients with a response. However, most patients in the ECT group received six to nine ECT sessions, a number that had been shown to result in an adequate treatment effect.[4,17] Both bilateral ECT and a greater number of ECT sessions would also have been associated with more adverse events, possibly diminishing the advantage for increased effectiveness. The open-label design of our trial could have influenced response. Maintenance treatment was not studied. Other limitations of our trial include a lack of placebo, the flexibility of treatment methods, and a follow-up period during which the patients received treatment as prescribed by their clinical providers. However, the design of the current trial is also its strength, because the results are easily translated to day-to-day clinical practice.

In this trial, subanesthetic intravenous ketamine was noninferior to ECT for the treatment of nonpsychotic treatment-resistant major depression.

The views in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its board of governors, or its methodology committee.

Supported by an award (TRD-1511-33648, to Dr. Anand) from PCORI.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the patients who participated in the trial; the members of the data and safety monitoring board (Lawrence H. Price, M.D. [chair], Deepak L. Bhatt, M.D., M.P.H., Kathryn R. Cullen, M.D., Anantha Shekhar, M.D., Ph.D., and Daniel Kerzner, M.D.); Kelly Brezina, B.S.N., and Susan Gailey, B.A., M.H.A., from C5Research, Cleveland Clinic, for project management; Deborah Gladish, B.A., from C5Research for data management; the members of the stakeholder committee who provided their input for the trial; and the PCORI staff who were involved in the trial.

APPENDIX

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REFERENCES

1. Substance Abuse and Mental Health Services Administration. 2020 National Survey of Drug Use and Health (NSDUH) releases. 2021 (https://www.samhsa.gov/data/release/2020-national-survey-drug-use-and-health-nsduh-releases).
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
3. Gaynes BN, Lux L, Gartlehner G, et al. Defining treatment-resistant depression. Depress Anxiety 2020;37:134-45.
4. Espinoza RT, Kellner CH. Electroconvulsive therapy. N Engl J Med 2022;386:667-72.
5. Lisanby SH. Electroconvulsive therapy for depression. N Engl J Med 2007;357:1939-45.
6. Ross EL, Zivin K, Maixner DF. Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA Psychiatry 2018;75:713-22.
7. Sackeim HA. Modern electroconvulsive therapy: vastly improved yet greatly underused. JAMA Psychiatry 2017;74:779-80.
8. Hermida AP, Glass OM, Shafi H, McDonald WM. Electroconvulsive therapy in depression: current practice and future direction. Psychiatr Clin North Am 2018;41:341-53.
9. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351-4.
10. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63:856-64.
11. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am J Psychiatry 2021;178:383-99.
12. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol 2013;27:444-50.
13. Freedman R, Brown AS, Cannon TD, et al. Can a framework be established for the safe use of ketamine? Am J Psychiatry 2018;175:587-9.
14. Singh I, Morgan C, Curran V, Nutt D, Schlag A, McShane R. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. Lancet Psychiatry 2017;4:419-26.
15. Anand A, Charney DS, Oren DA, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 2000;57:270-6.
16. Kellner CH, Greenberg RM, Ahle GM, Liebman LS. Electroconvulsive therapy is a standard treatment; ketamine is not (yet). Am J Psychiatry 2014;171:796.
17. Brus O, Cao Y, Gustafsson E, et al. Self-assessed remission rates after electroconvulsive therapy of depressive disorders. Eur Psychiatry 2017;45:154-60.
18. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry 2016;173:816-26.
19. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54:573-83.
20. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62:Suppl 16:10-7.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
22. Berman RM, Prudic J, Brakemeier E-L, Olfson M, Sackeim HA. Subjective evaluation of the therapeutic and cognitive effects of electroconvulsive therapy. Brain Stimul 2008;1:16-26.
23. Squire LR, Wetzel CD, Slater PC. Memory complaint after electroconvulsive therapy: assessment with a new self-rating instrument. Biol Psychiatry 1979;14:791-801.
24. Belkonen S. Hopkins verbal learning test. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of clinical neuropsychology. New York: Springer, 2011:1264-5.
25. Flanagan JC. Measurement of quality of life: current state of the art. Arch Phys Med Rehabil 1982;63:56-9.
26. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 1998;11:125-36.
27. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9:1447-54.
28. Ekstrand J, Fattah C, Persson M, et al. Racemic ketamine as an alternative to electroconvulsive therapy for unipolar depression: a randomized, open-label, non-inferiority trial (KetECT). Int J Neuropsychopharmacol 2022;25:339-49.
29. Rhee TG, Shim SR, Forester BP, et al. Efficacy and safety of ketamine vs electroconvulsive therapy among patients with major depressive episode: a systematic review and meta-analysis. JAMA Psychiatry 2022;79:1162-72.
30. Nordenskjöld A, von Knorring L, Engström I. Predictors of the short-term responder rate of electroconvulsive therapy in depressive disorders — a population based study. BMC Psychiatry 2012;12:115.
31. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. Biol Psychiatry 2004;55:301-12.
32. Rosenbach ML, Hermann RC, Dorwart RA. Use of electroconvulsive therapy in the Medicare population between 1987 and 1992. Psychiatr Serv 1997;48:1537-42.
33. American Psychiatric Association Committee on Electroconvulsive Therapy. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging: a task force report of the American Psychiatric Association. 2nd ed. Washington, DC: American Psychiatric Association Publishing, 2001.
34. Food and Drug Administration, HHS. Neurological devices; reclassification of electroconvulsive therapy devices; effective date of requirement for premarket approval for electroconvulsive therapy devices for certain specified intended uses: final order. Fed Regist. 2018;83:66103-24.
35. Rapid reversal of acute suicidal depression across the lifespan: a pragmatic comparative effectiveness trial of electroconvulsive therapy vs. intravenous ketamine treatment. 2022 (https://www.pcori.org/research-results/2022/rapid-reversal-acute-suicidal-depression-across-lifespan-pragmatic-comparative-effectiveness-trial-electroconvulsive-therapy-vs-intravenous-ketamine-treatment).