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Oral esketamine in patients with treatment-resistant depression: a double-blind, randomized, placebo-controlled trial with open-label extension

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Abstract

About one-third of patients with depression do not achieve adequate response to current treatment options. Although intravenous and intranasal administrations of (es)ketamine have shown antidepressant properties, their accessibility and scalability are limited. We investigated the efficacy, safety, and tolerability of generic oral esketamine in patients with treatment-resistant depression (TRD) in a randomized placebo-controlled trial with open-label extension. This study consisted of 1) a six-week fixed low-dose treatment phase during which 111 participants received oral esketamine 30 mg or placebo three times a day; 2) a four-week wash-out phase; and 3) an optional six-week open-label individually titrated treatment phase during which participants received 0.5 to 3.0 mg/kg oral esketamine two times a week. The primary outcome measure was change in depressive symptom severity, assessed with the Hamilton Depression Rating Scale ($HDRS_{17}$), from baseline to 6 weeks. Fixed low-dose oral esketamine when compared to placebo had no benefit on the $HDRS_{17}$ total score (p=0.626). Except for dizziness and sleep hallucinations scores, which were higher in the esketamine arm, we found no significant difference in safety and tolerability aspects. During the open-label individually titrated treatment phase, the mean $HDRS_{17}$ score decreased from 21.0 (SD 5.09) to 15.1 (SD 7.27) (mean difference -6.0, 95% CI -7.71 to -4.29, p<0.001). Our results suggest that fixed low-dose esketamine is not effective in TRD. In contrast, individually titrated higher doses of oral esketamine might have antidepressant properties.

Introduction

Major depressive disorder (MDD) is one of the leading causes of disease burden worldwide.[1] Although MDD is responsive to pharmacotherapy and psychotherapy in most patients, one third of patients do not achieve an adequate response to these treatment options.[2] Hence, there is a pressing need to develop new treatment strategies for MDD generally, and for depression resistant to regular treatment (treatment-resistant depression; TRD) specifically.

Rapid and robust reductions in depressive symptoms have been observed following intravenous (IV) infusion of the N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine and its enantiomer esketamine, including in patients with TRD.[3,4] However, these effects are short-lived. In most patients who respond well to a single dose of IV (es)ketamine, the benefits disappear within two weeks.[3] Different strategies have been proposed to prolong these benefits, including subsequent treatment with riluzole, lithium, and repeated dosing of (es)ketamine.[4-6] Of these, the latter has emerged as most promising[6], but repeated use of IV (es)ketamine infusions has limited feasibility, accessibility, and scalability.

Alternative routes of administration of (es)ketamine have been investigated. In 2019, an intranasal (IN) application of esketamine for TRD was approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA). Its antidepressant efficacy has been shown in both short-term and longer-term studies.[6,7] However, the accessibility and scalability of the nasal spray are limited as well, as patients are required to visit the clinic for each treatment. In addition, at its current pricing the nasal spray is considered unlikely to be cost-effective for management of TRD.[8]

Most regular antidepressant medications are administered orally, having the greatest potential for accessibility and scalability as well as being the preferred route of administration for patients.[9] Therefore, if proven effective and well-tolerated, oral (es)ketamine may be an attractive alternative to the IV and IN routes. In chronic pain management, oral dosing with (es)ketamine is a well-recognised route of administration.[10] In contrast, little is known about oral (es)ketamine in patients with TRD. Although the findings of two systematic reviews suggest that oral (es)ketamine may be effective and safe in patients with TRD, most reviewed studies were uncontrolled. The two included controlled studies were small and had a high risk for bias regarding the analysis and adverse events monitoring.[10,11] Thus, carefully monitored and analysed controlled studies of oral (es)ketamine's efficacy, safety, and tolerability in larger samples of patients with TRD are needed.

We conducted a double-blind, randomized, placebo-controlled, parallel-group trial on fixed low-dose oral esketamine in patients with TRD. We primarily aimed to investigate the antidepressant efficacy of oral esketamine. Our secondary aim was to systematically assess its safety and tolerability profile. As an addition to the trial, we offered an open-label treatment with flexible higher-dose oral esketamine. This allowed for evaluation of individually titrated oral esketamine in the same subjects who participated in the fixed low-dose placebo-controlled trial.

Methods

This study was approved by the Medical Ethics Review Committee of the University Medical Center Groningen (UMCG) in the Netherlands (file number M16.198879) and registered with the

Dutch Trial Register (trial number NTR6161). An independent Clinical Research Office (CRO) and Data Safety and Monitoring Board (DSMB) oversaw the conduct of the study. A detailed study protocol has previously been published.[12]

Study design

This study featured a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial, followed by an open-label extension. It was conducted between February 2017 and February 2021 at three psychiatric institutes in the Netherlands: the University Center Psychiatry in Groningen, the Pro Persona Depression Expertise Center in Nijmegen, and the Parnassia Psychiatric Institute in The Hague. The study consisted of three phases: 1) a six-week treatment phase during which participants received fixed low-dose oral esketamine or placebo three times a day, in addition to established antidepressant medication – the double blind, randomized, placebo-controlled trial (RCT); 2) a four-week posttreatment wash-out phase; and 3) an optional six-week open-label treatment phase during which participants received individually titrated oral esketamine two times a week, in addition to established antidepressant medication (Figure 1). For the current paper, the overall effectiveness of the open-label treatment will be described for former RCT participants. Detailed analyses of the antidepressant effects and safety aspects of all participants treated in our national open-label program (i.e., including participants who did not participate in the RCT) will be published separately.

[Figure 1]

Participants

Psychiatry departments and patient and family associations throughout the Netherlands were involved in recruitment, and advertisement took place by various media. Patients were eligible if they were aged 18 to 80 years, had a current major depressive episode according to the DSM-5 as determined by the Mini International Neuropsychiatry Interview (MINI)[13], and had at least moderately severe depressive symptoms as defined by a score >18 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[14]. In addition, participants used established antidepressant medication in a stable and therapeutic dose and met the study definition of TRD, which was an insufficient lifetime response to three or more different classes of antidepressant medications, given for at least four weeks in an adequate dose. The main exclusion criteria were a lifetime history of psychotic disorder, bipolar disorder, or moderate to severe substance-use disorder, recent or current use of non-prescribed psychoactive compounds or benzodiazepines in excess of 2 mg lorazepam or an equivalent per day, and the presence of active suicidal intent. All participants provided written informed consent after receiving a complete description of the study. A full overview of the inclusion and exclusion criteria and a sample size calculation are presented in our study protocol.[12]

Randomization and masking

Participants were randomly allocated to the intervention or control arm in a 1:1 manner by a computer-generated randomization schedule. For every block of eight participants four were allocated to each arm of the trial. Placebo capsules were matched to esketamine capsules in shape, smell, and colour. They were sealed in identical blisters, which were labelled as trial medication and given a trial number by the manufacturer. Participants, clinicians, and study personnel remained blind until study completion in 2021. The success of blinding was tested by

asking participants to complete a guess form after six weeks of treatment, on which they were asked to choose “esketamine”, “placebo”, or “I don’t know”.

Procedures

Participants randomized to the intervention arm took capsules containing esketamine three times a day (8 a.m., 2 p.m., 8 p.m.) during 42 consecutive days. During the first three days, dosages were gradually increased from 30 mg a day to 90 mg a day; during the last three days, dosages were gradually decreased from 90 mg a day to 30 mg a day. For more details, including our rationale for choosing esketamine and this treatment regimen, we refer to our study protocol.[12] In short, we derived the maximum daily esketamine dose of 90 mg from previous studies on IV and oral (es)ketamine, including our pilot study.[15] To reduce the risk of side-effects and in line with findings from our systematic review about (es)ketamine dosing regimens for pain[10], daily doses were divided into three administrations a day. Participants randomized to the control arm took placebo capsules containing microcrystalline cellulose and magnesium stearate. During the first five days of treatment, all participants were hospitalized and capsules were administered by a nurse. Next, participants were allowed to go home and self-administer their capsules during the remaining 37 days of treatment. They obtained new treatment medication and were asked for compliance during every visit.

After the RCT (phase 1) and a four-week posttreatment wash-out during which esketamine and placebo were not prescribed (phase 2), participants were offered an optional six-week open-label treatment (phase 3). They could enter the open-label treatment program regardless of their allocated treatment or response in the RCT. Participants of the program received 12 doses of esketamine, administered twice weekly over a 6-week period. Esketamine was started on day 1 at

0.5 mg/kg, with the possibility, as per physician's clinical judgment of effectiveness and tolerability, of adjusting the dose to a maximum of 2.0 mg/kg (June 2017 – April 2019) or 3.0 mg/kg (May 2019 – March 2021). We increased the maximum esketamine dose during our open-label program based on clinical experience, in combination with increasing insight into the interindividual variations in oral bioavailability.[16]

Outcomes of the RCT treatment phase

The primary outcome of the RCT was change in depression symptom severity, expressed as a change in total $HDRS_{17}$ score over the course of treatment (visit 1 and visits 3 to 5). The $HDRS_{17}$ was administered by trained clinicians and researchers.

Secondary efficacy outcomes included response, defined as ≥50% decrease in total $HDRS_{17}$ score between baseline (visit 1) and end-of-treatment (visit 5); partial response, defined as 25-49% decrease in total $HDRS_{17}$ score between baseline (visit 1) and end-of-treatment (visit 5); change in the Inventory of Depressive Symptomatology – Self Report (IDS-SR)[17] total score (visit 1 and visits 3 to 5); change in the Clinical Global Impression (CGI)[18] severity score (visit 1 and visits 3 to 5); the CGI improvement score (visits 3 to 5), and; change in the EuroQol (EQ-5D-5L)[19] health-related quality of life index value (visits 1 and 5). EQ-5D-5L data were converted into index values using the Dutch tariff.[20]

General adverse events were recorded with the Systematic Assessment for Treatment Emergent Events (SAFTEE).[21] Similar to Aan het Rot et al. (2010)[22], we calculated how many participants rated a symptom as more bothersome during the RCT (visits 2 to 5) compared with the baseline

rating (visit 1). A moderate increase was defined as an increase of two degrees of severity (i.e., from “not present” to “moderate” or from “mild” to “severe”) and a severe increase as an increase of three degrees of severity (i.e., from “not present” to “severe”). Dissociative effects were assessed with the Dissociation Tension Scale (DSS)[23], psychotic experiences with the Questionnaire for Psychotic Experiences (QPE)[24], and sleep disturbances with the Iowa Sleep Disturbance Inventory (ISDI)[25]. We calculated how many participants rated a symptom (i.e., a DSS, QPE, or ISDI item) as more bothersome during the RCT (visits 2 and 5) compared with the baseline rating (visit 1).

Blood pressure (BP) was assessed daily during the first five days of the RCT and subsequently at all visits. A clinically relevant increase in systolic blood pressure (SBP) was defined as an increase of ≥30 mmHg; a clinically relevant increase in diastolic blood pressure (DBP) as an increase of ≥15 mmHg. Weight was assessed at baseline (visit 1) and after one, two, four and six weeks of blinded treatment (visits 2 to 5).

Liver enzyme levels were tested at baseline (visit 1) and at the end-of-treatment (visit 5). Abnormal results on liver function tests were defined as hepatic enzyme activity 1.5 times the upper limit of the reference range or greater, provided baseline activity was below the upper limit of the reference range, or an increase of hepatic enzyme activity of ≥100%.

Outcomes of the RCT wash-out phase

Efficacy outcomes of the posttreatment wash-out phase were sustained change in depression symptom severity, sustained response, sustained partial response, and sustained change in health-related quality of life, as measured by the $HDRS_{17,}$ IDS-SR, CGI, and EQ-5D-5L (visits 6 to 8).

The course of adverse events that had developed during the RCT treatment phase was assessed with the SAFTEE (visits 6 to 8), the DSS, QPE, and ISDI (visit 8), monitoring of BP and weight (visits 6 to 8), and monitoring of hepatic enzyme activity (visit 8). Results of the wash-out phase would be presented provided that an effect of esketamine treatment compared to placebo in the RCT was found.

Outcomes of the open-label treatment phase

Effectiveness outcomes of the open-label treatment phase were change in depression symptom severity, expressed as a change in total $HDRS_{17}$ score between open-label baseline (visit 9) and end-of-treatment (visit 10); response, defined as ≥50% decrease in total $HDRS_{17}$ score between open-label baseline (visit 9) and end-of-treatment (visit 10), and; partial response, defined as 25-49% decrease in total $HDRS_{17}$ score between open-label baseline (visit 9) and end-of-treatment (visit 10).

Statistical analysis

Baseline characteristics were compared between the two arms by using independent-samples T-Tests, Fisher's Exact Tests, or Mann-Whitney U Tests, as appropriate. Statistical analyses were performed with IBM SPSS Statistics, version 28.0 (IBM, Armonk, N.Y.). For all statistical tests, assumptions were checked, tests were two-tailed, and results were considered significant at a p-value of 0.05.

A linear mixed model (LMM) was used to analyse changes in $HDRS_{17}$ scores across the four time points from baseline to end-of-treatment in all participants who received a dose of study drug. Because a non-linear development over time was assumed, time was modelled as a

categorical variable represented by dummy variables for three of the four time points, using the baseline measurement as the reference category. To ensure that the random effects structure of the LMM had a complexity that was supported by the underlying data, we did fit random intercepts but not random slopes for the dummy variables. To adjust for baseline $HDRS_{17}$ score, the treatment variable was not part of the model, but its interaction with time was. This way the baseline values for both groups are assumed to be equal and are reflected in the intercept of the model.[26] Hence, the LMM included a random intercept and fixed effects for time and the cross-level interaction between treatment and time. The model was estimated using Restricted Maximum Likelihood Estimation (REML). Sensitivity analyses are described in the Supplement.

Proportions of participants who met response or partial response criteria after six weeks of blinded treatment were compared using Pearson Chi-Square Tests. LMMs similar to the $HDRS_{17}$ model were used to analyse change in IDS-SR and CGI scores across the four time points from baseline to end-of-treatment. CGI improvement scores and change in health-related quality of life index values were analysed with independent-samples T-tests.

Proportions of participants rating SAFTEE-items or QPE-items as more bothersome during the RCT were compared using Pearson Chi-Square Tests and Fisher's Exact Tests as appropriate. P-values were not adjusted for multiple testing. Changes in DSS total score and ISDI sub-scores between baseline and one week of treatment and between baseline and end-of-treatment were compared with independent-samples T-Tests. LMMs similar to the $HDRS_{17}$ model were used to analyse change in BP and weight scores across the nine (BP) and five (weight) time points from baseline to end-of-treatment. To analyse differences in clinically relevant increases in BP (SBP

≥30 mmHg, DBP ≥15 mmHg) and increase in liver enzyme levels above reference values, Pearson Chi-Square Tests and Fisher's Exact Tests were used as appropriate.

A paired-samples T-Test was used to evaluate change in $HDRS_{17}$ total score between open-label baseline and end-of-treatment.

Results

Of the 360 patients screened, 247 were excluded. Of these, 187 did not meet inclusion criteria, 22 declined to participate, and 38 were excluded for other reasons. Of the 113 participants randomized, 57 were allocated to the esketamine arm and 56 to the placebo arm. Two participants in the placebo arm were excluded between randomization and start of study treatment because they no longer met the inclusion criteria. Most of the 111 participants completed the 6-week RCT (87.4%) and 4-week wash-out phase (84.7%). Thirty-seven participants (77.1%) from the esketamine arm and 35 participants (76.1%) from the placebo arm subsequently entered the open-label program. Of these, 66 (91.7%) completed the open-label treatment (Figure 2). Of the 72 participants who entered the open-label treatment program, 25 entered the program between June 2017 and April 2019 (maximum esketamine dose 2.0 mg/kg) and 47 between May 2019 and March 2021 (maximum esketamine dose 3.0 mg/kg). The actual administered highest dose was below 2.0 mg/kg for 22 participants (30.6%), 2.0 mg/kg for 16 participants (22.2%), between 2.0 and 3.0 mg/kg for nine participants (12.5%), and 3.0 mg/kg for 24 participants (33.3%). Dosing data were missing for one participant (1.4%).

[Figure 2]

On average, the duration of the current depressive episode was 52.5 months (i.e., 4.4 years) and participants' depressions were non-responsive to 6.3 antidepressant medication treatments. In addition, 86 participants (77.5%) had not sufficiently improved from psychotherapy, 45 (40.9%) had received electroconvulsive therapy without sufficient response, and 72 (64.9%) had at least one comorbid axis I disorder. The treatment groups were comparable with respect to baseline demographic and clinical characteristics (Table 1). A guess form was completed by 106 (95.5%) of the participants at the end of study treatment. Of the 54 participants who received esketamine and completed the form, 30 participants (55.6%) correctly guessed esketamine, 17 (31.5%) incorrectly guessed placebo, and 7 (13.0%) checked "I don't know". Of the 52 participants who received placebo and completed the form, 30 participants (57.7%) correctly guessed placebo, 10 (19.2%) incorrectly guessed esketamine, and 12 (23.1%) checked "I don't know".

[Table 1]

RCT treatment phase. Mean total $HDRS_{17}$ score decreased from 23.2 points (SD 3.48) to 21.4 points (SD 5.79) in the fixed low-dose esketamine arm and from 23.2 points (SD 3.49) to 20.4 points (SD 6.47) in the placebo arm. The LMM revealed no significant interaction between treatment and any of the individual time-dummy variables (Supplement), nor a significant overall

effect for the treatment-by-time-interaction (F=0.65, df=4, 210, p=0.626). These results indicate no significant difference in change of depressive symptoms between the fixed low-dose esketamine arm and placebo arm. Sensitivity analyses provided results that were consistent with this finding (Supplement). After six weeks of blinded treatment, two participants (4.0%) in the fixed low-dose esketamine arm and five participants (10.4%) in the placebo arm met response criteria (X^2=1.52, p=0.264). Nine participants (18.0%) in the fixed low-dose esketamine arm and six participants (12.5%) in the placebo arm met partial response criteria (X^2=0.57, p=0.577). In line with these findings, there were no statistically significant differences between the fixed low-dose esketamine arm and placebo arm measured by the IDS-SR, CGI, or EQ-5D-5L (Supplement).

Two serious adverse events were reported. In both arms one participant committed suicide: one in the first week of treatment (placebo arm) and one in the fourth week of treatment (esketamine arm). Neither had active suicidal intent at baseline, based on item 3 (suicidality) of the $HDRS_{17}$. Six other participants experienced adverse events leading to discontinuation: four in the esketamine arm (i.e., 1) increase in depressive symptoms; 2) increase in anxiety; 3) generalized rash; and 4) a combination of adverse events, including anxiety, headache, dizziness, dry mouth, and nausea) and two in the placebo arm (i.e., 1) increase in depressive symptoms; and 2) hypertension). Three participants in the fixed low-dose esketamine arm asked for dosing reduction: one because of feeling drunk, and two because of a combination of adverse events, including headache, dizziness, dry mouth, and nausea.

Of the 55 potential adverse events measured by the SAFTEE, "dizziness or faintness" and "dizziness when standing up" were more often moderately to severely increased in the fixed low-dose esketamine arm compared to the placebo arm (Supplement). There was no significant difference between the two arms in change of dissociative symptoms (DSS), psychotic experiences (QPE), or sleep disturbances (ISDI), except for sleep hallucinations. After one week of treatment, participants in the fixed low-dose esketamine arm experienced an average increase of sleep hallucinations, while the participants in the placebo arm experienced an average decrease of sleep hallucinations. After six weeks of treatment, there was no longer a difference in report of sleep hallucinations between the two arms (Supplement). Findings regarding BP, weight, and liver enzyme levels can be found in the Supplement.

RCT wash-out phase. Two types of adverse events require course description: dizziness or faintness (SAFTEE) and dizziness when standing up (SAFTEE). Firstly, of the 12 participants in the esketamine arm who had reported moderately to severe increase of "dizziness or faintness", one (8.3%) still reported severe increase compared to baseline at the end of wash-out. Secondly, of the six participants in the esketamine arm who had reported moderately to severe increase of "dizziness when standing up" during the RCT, none reported moderate or severe increase compared to baseline at the end of wash-out.

Open-label treatment phase. $HDRS_{17}$ data were available for 59 of the 72 participants who entered the open-label program. Six participants had dropped-out before the end of treatment, of whom four because of adverse events and two because of non-response. Data were missing for seven participants. Mean total $HDRS_{17}$ score decreased from 21.0 (SD 5.09) at baseline of the

open-label treatment to 15.1 (SD 7.27) at end-of-treatment (mean difference -6.0, 95% CI -7.71 to -4.29, $p<0.001$), indicating a significant reduction of depressive symptoms. Eighteen participants (25.0% of the intention-to-treat sample of 72 participants) met response criteria and nine participants (12.5% of the intention-to-treat sample) met partial-response criteria (see Supplement for more details).

Discussion

In our randomized placebo-controlled trial in individuals with severe TRD, 30 mg of oral esketamine administered three times a day over six weeks did not lead to a higher reduction in depressive symptoms than placebo. This finding is at odds with previous studies describing antidepressant properties of fixed-dose and low-dose oral and sublingual ketamine, e.g., 10 mg sublingual ketamine multiple times per week[27], an extended-release ketamine tablet of 60 to 240 mg twice a day[28], and 25 mg oral ketamine twice a day[29]. A possible explanation for these differences in findings is that two of these studies were small and lacked a control group[27,28], possibly overestimating treatment effects. Additionally, the only larger and controlled study did not include patients with TRD[29], while participants in our trial were severely treatment resistant. With a current episode length of nearly five years, six failed antidepressant trials during this episode, insufficient response to ECT in a large proportion of participants, and high rates of psychiatric comorbidities, the chances of response to any form of subsequent treatment were already significantly reduced.[2,30] Still, both the decrease in mean depression severity (1.8 $HDRS_{17}$ points) as well as the proportion of participants meeting criteria for response (4.0%) were lower than anticipated for treatment with fixed low-dose esketamine. An explanation for this, in addition to the suggestions provided above, may be found in the treatment regimen. To reduce the

risk of side-effects and in line with findings from our systematic review about (es)ketamine dosing regimens for pain[10], daily doses were divided into three administrations a day. As a result, peak esketamine blood levels were likely much lower than after the less frequent, higher-dose (es)ketamine administrations that were generally employed in previous studies.[3,4] In addition, we did not account for interindividual variability in oral bioavailability in the RCT treatment regimen, while the optimal therapeutic oral esketamine dose might well be a range and not a single value.[16] Although we currently do not know whether the defining criterion for the efficacy of (es)ketamine is a peak blood level, it cannot be ruled out that blood levels of esketamine were too low in at least some of the patients to obtain a clinical antidepressant effect. Secondly, with regard to treatment regimen, an unresolved issue is the possible difference in efficacy between the two ketamine enantiomers. Although it has long been assumed that the majority of ketamine's antidepressant properties stem from its impact on glutamate neurotransmission through NMDA receptor binding, the concept of NMDA receptor antagonism has been challenged.[31] Various other molecular insights have been gained in the mechanistic pathways of ketamine and its enantiomers[31], which for example might imply that racemic ketamine could yield a better therapeutic effect than esketamine. Preliminary clinical data, however, indicate that esketamine may be at least as effective in reducing depressive symptoms as racemic ketamine.[32]

The suggestion that dosing of esketamine was too low to obtain a clinical antidepressant effect in the RCT, is supported by the data from our open-label treatment program. At 0.5 to 3.0 mg/kg oral esketamine administered twice a week over six weeks, $HDRS_{17}$ scores decreased on average 5.9 points, which is considered clinically meaningful.[33] Besides, the response rate of 25% at this point is substantially higher than that of the Sequenced Treatment Alternatives to Relieve

Depression (STAR*D) trial at step 3 (16.8%) and step 4 (16.3%)[2], with the participants in our trial being far beyond these regular steps in the treatment protocol.

We did not find any major safety or tolerability problems attributable to esketamine. There was no difference between the fixed low-dose esketamine arm and placebo arm in drop-out rates due to adverse events, serious adverse event rates, or any of the safety and tolerability questionnaire items, except for dizziness and sleep hallucinations.

A number of strengths and limitations of the study design merit comment. Strengths of our trial are the large sample size, randomized treatment assignment, and systematic assessment of symptomatic, functional, safety, and tolerability outcomes. In addition, many participants had remained blind to treatment condition, which is rarely mentioned in studies on psychoactive substances such as (es)ketamine, but is considered a major limitation of most previous ketamine studies.[34] Only 55.6% of the participants treated with esketamine correctly guessed their condition, which is comparable to the percentage of participants in the placebo arm who correctly guessed their condition (i.e., 57.7%) and much lower than participants in placebo controlled IV ketamine studies (i.e., 100%)[35]. In contrast, a major limitation of the open-label treatment is that it had no blinding or control. Thus, we cannot rule out the possibility that treatment expectancy led to overestimation of open-label treatment effect. Especially when considering the fact that ketamine treatment has been remarkably positively framed in the media[36], which may have increased patients' hopes and expectations of an effective treatment. On the other hand, the participants of our open-label treatment program had already had a failed trial of low dose

esketamine or placebo, on top of many steps of unsuccessful regular antidepressant treatment, so expectancy might have been limited.

In conclusion, in our RCT with open-label extension in individuals with TRD, 30 mg of oral esketamine administered three times a day over six weeks was not found to have antidepressant properties. Open-label flexible-dose oral esketamine administered twice weekly over six weeks led to clinically meaningful improvement in depressive symptoms, and may be a promising, patient-friendly, and affordable treatment for patients with very severe TRD. Overall, oral esketamine was safe and well tolerated. Future studies should focus on further assessment of efficacy, safety, and tolerability of flexible-dose oral esketamine.

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Conflict of interests

JV has received a speakers fee from Janssen Pharmaceuticals, outside the submitted work. RS has received research funding for two randomized clinical trials with generic oral esketamine from the Netherlands Organisation for Health Research & Development and the National Health Care Institute, a speakers fee and an investigator initiated research grant from Janssen

Pharmaceuticals, and consultancy fees from Clexio biosciences, GH Research, Beckley PsyTech, and QPS. All other authors declare no competing interests.

Contributors

RS obtained funding for the study and was the chief investigator. SS wrote the trial protocol with input from JV, AvA, MahR, and RS. SS, JV, and RS were responsible for general project management. SS, JV, JK, JS, AvdM, and RS were responsible for recruitment and data collection. SS conducted the statistical analysis with input from MahR. All authors contributed to the interpretation of the data. SS drafted the original manuscript, JV, JK, MahR, and RS contributed to the writing of the original manuscript, and all authors contributed to re-drafts. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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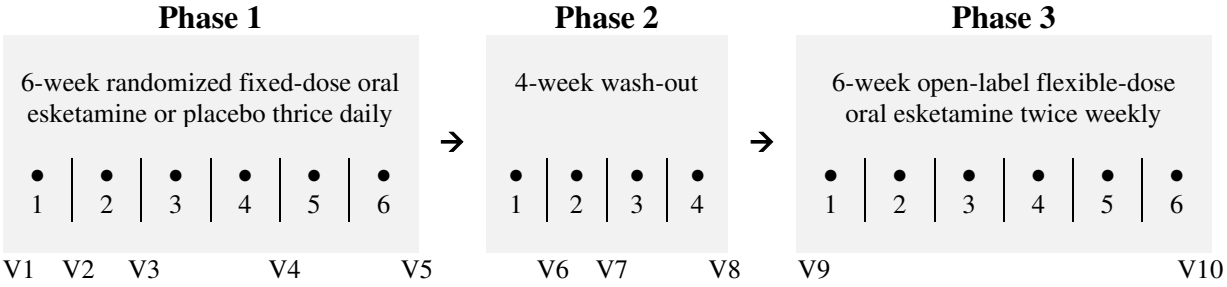
Table 1: Baseline characteristics of participants

	Total Sample (n=111)		Esketamine (n=57)		Placebo (n=54)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age, years	51.8	12.42	50.2	12.13	53.4	12.62
Number of previous antidepressant medications lifetime	8.9	2.88	8.5	2.60	9.2	3.13
Number of previous antidepressant medications in current episode	6.3	3.69	5.7	3.41	6.8	3.93
Body mass index	27.5	5.17	28.0	5.57	26.9	4.68
$HDRS_{17}$ total score	23.2	3.47	23.2	3.48	23.2	3.49
CGI severity score	5.4	0.70	5.3	0.78	5.4	0.61
IDS-SR total score	47.9	9.30	48.4	9.72	47.4	8.90
Quality of life index value	0.4	0.25	0.4	0.24	0.4	0.25
	Median	**MinMax**	**Median**	**MinMax**	**Median**	**MinMax**
Age at depression onset, years	20.0	4-70	23.0	7-66	19.0	4-70
Number of depressive episodes	2.0	1-70	2.0	1-20	3.0	1-70
Duration of current episode, months	52.5	0-560	61.0	0-394	45.0	0-560
	N	**%**	**N**	**%**	**N**	**%**
Gender assigned at birth Female Male	64	57.7	33	57.9	31	57.4
Educational level Primary education Lower vocational education Intermediate secondary ed. Intermediate vocational ed. Higher secondary education Higher vocational education University Other	 5 9 10 32 20 19 15 1	 4.5 8.1 9.0 28.8 18.0 17.1 13.5 0.9	 2 5 4 19 11 7 9 0	 3.5 8.8 7.0 33.3 19.3 12.3 15.8 0.0	 3 4 6 13 9 12 6 1	 5.6 7.4 11.1 24.1 16.7 22.2 11.1 1.9
Marital status Single Married or cohabiting Divorced Widowed	 34 65 11 1	 30.6 58.6 9.9 0.9	 19 32 5 1	 33.3 56.1 8.8 1.8	 15 33 6 0	 27.8 61.1 11.1 0.0
ECT lifetime	55	49.5	23	41.1	32	59.3
ECT in current episode	45	40.9	18	32.1	27	50.0
Psychotherapy lifetime	109	98.2	55	96.5	54	100.0
Psychotherapy in current episode	86	77.5	43	75.4	43	79.6
Concomitant treatment with psychotherapy	51	45.9	26	45.6	25	46.3
Comorbid psychiatric axis I disorder	72	64.9	38	66.7	34	63.0
Center UMC Groningen Pro Persona Nijmegen Parnassia The Hague	 66 29 16	 59.5 26.1 14.4	 34 15 8	 56.9 26.3 14.0	 32 14 8	 59.3 25.9 14.8

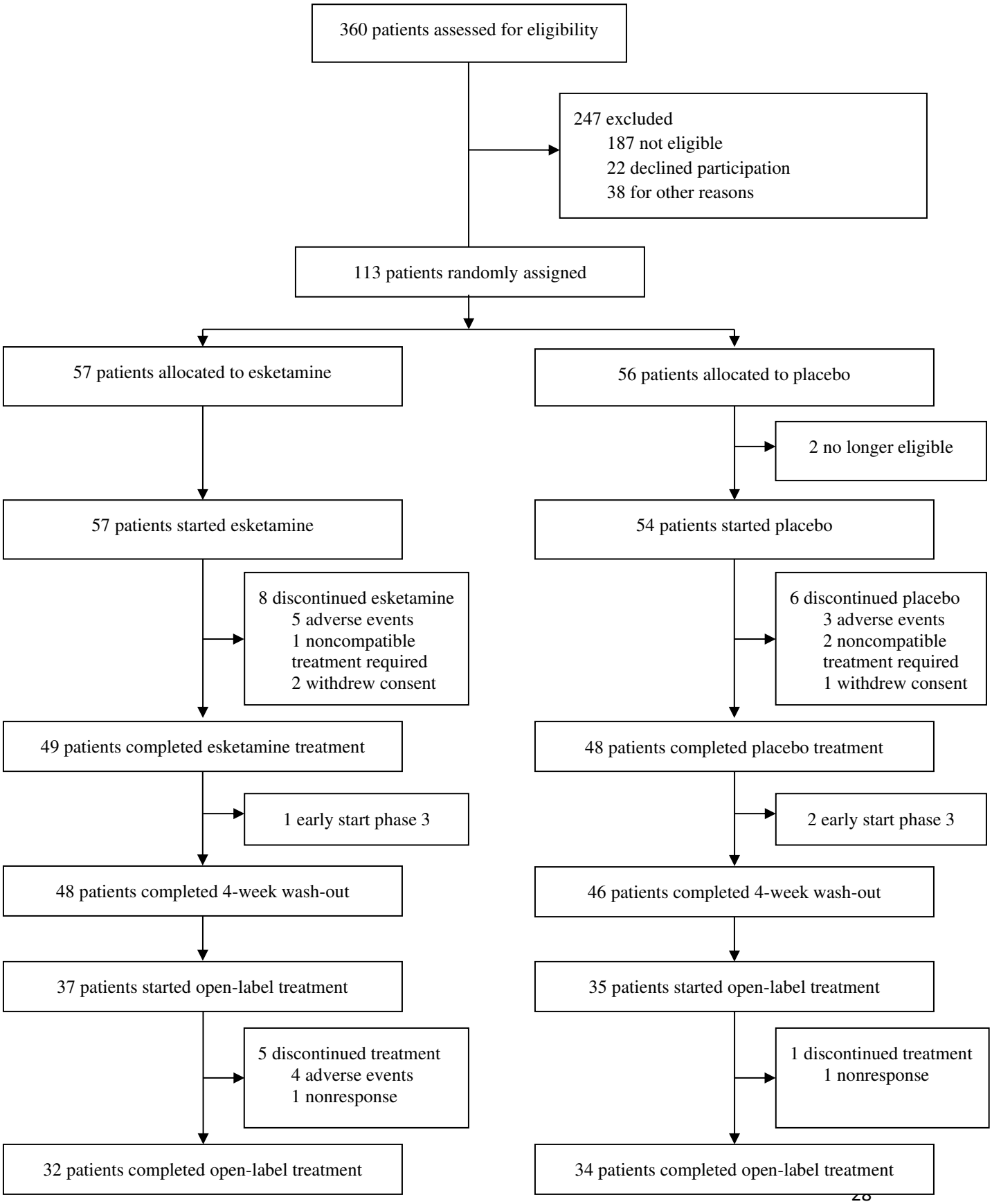
CGI = Clinical Global Impression. ECT = electroconvulsive therapy. $HDRS_{17}$ = Hamilton Depression Rating Scale – 17 items. IDS-SR = Inventory of Depressive Symptomatology – Self Report. UMC = University Medical Center.

Figure 1: Study design



V1 = visit 1, before the start of fixed low-dose oral esketamine or placebo (baseline of randomized controlled trial (RCT)). V2 = visit 2, after one week of fixed low-dose oral esketamine or placebo (RCT treatment phase week 1) - blood pressure and weight were assessed daily during the first five days of the RCT. V3 = visit 3, after two weeks of fixed low-dose oral esketamine or placebo (RCT treatment phase week 2). V4 = visit 4, after four weeks of fixed low-dose oral esketamine or placebo (RCT treatment phase week 4). V5 = visit 5, after six weeks of fixed low-dose oral esketamine or placebo (end-of-treatment of RCT). V6 = visit 6, one week after esketamine or placebo cessation (RCT wash-out phase week 1). V7 = visit 7, two weeks after esketamine or placebo cessation (RCT wash-out phase week 2). V8 = visit 8, four weeks after esketamine or placebo cessation (end-of-wash-out of RCT). V9 = visit 9, before the start of flexible higher-dose oral esketamine (baseline of open-label treatment). V10 = visit 10, after six weeks of flexible higher-dose oral esketamine (end-of-treatment of open-label treatment).

Figure 2: Trial profile



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