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Esketamine use in real-world clinical practice in patients with treatment-resistant depression

Short Title: Real-world use of esketamine in depression

Ismael Conejero[1,2], Raquel Alvarez García[3], Alejandro Porras-Segovia[1,3], Ana María De Granda Beltrán[1], Sergio Benavente López[4], Ezequiel Di Stasio[5], Lucía Albarracín-García[1], Jorge Lopez-Castroman[2,6], Philippe Courtet[7], Enrique Baca-Garcia[2,3,5,8-10] and Memind Group[+]

Affiliations:

1. Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain; Universidad Autónoma de Madrid, Madrid, Spain; Department of Psychiatry, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

2. Department of Psychiatry, CHU Nîmes, IGF, INSERM, University of Montpellier, Nîmes, France.

3. Departamento de Psiquiatría, Hospital Rey Juan Carlos Móstoles, Madrid, Spain

4. Departamento de Psiquiatría, Hospital Universitario Infanta Elena Valdemoro, Madrid, Spain

5. Departamento de Psiquiatría, Hospital Universitario General de Villalba, Madrid, Spain

6. Department of Psychiatry, Radiology, Public Health, Nursing and Medicine; University of Santiago de Compostela, A Coruña, Spain

7. Department of Emergency Psychiatry and Acute Care, Centre Hospitalier Universitaire Montpellier, University of Montpellier, Montpellier, France

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8. Departamento de Psiquiatría, Universidad Autónoma de Madrid, Madrid, Spain

9. Universidad Católica del Maule, Talca, Chile

10. Centro de Investigación Biomédica en Red de Salud Mental, Madrid, Spain; CIBERSAM, Research Group CB/07/09/0025, Madrid, Spain

[+]Memind Group

María Luisa Barrigón, Jorge Lopez-Castroman, Phillippe Courtet, Antonio Artés-Rodriguez, Enrique Baca-Garcia, Fuensanta Aroca Bisquert,Ana De Granda-Beltrán, José Luis Palomo, Elizabeth Madridejos, Lucía Albarracín García, Carmen Aguilar Castillo, Laura Jiménez-Muñoz, Sofía Abascal-Peiró, Ana Pérez-Balaguer

Corresponding Author:

Ismael Conejero, ismael.conejero@gmail.com

Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain

Department of Psychiatry, CHU Nîmes

Place du Professeur Robert Debré, 30900 Nîmes, France.

Tel +33466683426/+33770216238

Fax number: +33466683865

E-mail: ismael.conejero@gmail.com

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Abstract:

Background: Esketamine has been shown to produce a major antidepressant response in patients with treatment-resistant depression (TRD). We aimed to evaluate the factors associated with achieving remission in these individuals.

Methods: The study was carried out across four psychiatry departments in Madrid, Spain. Patients aged over 18 years were included if they received esketamine as an augmentation treatment for TRD. Standard esketamine protocol included an induction phase (2 administrations per week for 4 weeks) and a maintenance phase (1 administration per week for 5 to 8 weeks). A subsequent treatment continuation phase was also proposed. Clinical data and scores at the Clinical Global Impression scales were measured following each esketamine administration.

Results: Sixty-five patients initiated the treatment, and 45 patients (69.2%) completed the standard protocol. The median number of esketamine administrations was 19. The mean age of the sample was 53.09 and 52.3% of the patients were females. Out of the whole sample, 36 (55%) of the patients achieved remission over the follow-up. Remission rates elevated to 67% in those who completed the standard protocol, and to 70% in those having received more than 19 esketamine administrations. Achieving remission over the follow-up was associated with the absence of dissociative symptoms, and with completing the standard esketamine protocol (OR=0.229, p=0.045; and OR=4.538, p=0.025, respectively). Receiving more than 19 esketamine administrations was associated with remission over the follow-up (OR=6.513, p=0.006).

Conclusions: Our results suggest that extending the numbers of esketamine administration may increase the chances to obtain remission. Adverse effects did not impact the treatment course.

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Keywords: treatment resistant depression; esketamine; augmentation treatment; naturalistic study

INTRODUCTION

Depression is a common mental disorder with the highest prevalence in Europe reaching 11.32% lifetime, and 10.3 % in the Spanish population [1]. While Major Depressive Disorder (MDD) has been often considered as a transient condition, epidemiological data suggest that more than 30% of depressed individuals do not achieve remission following antidepressant treatment [2; 3]. In addition, MDD is a risk factor for suicide with a relative risk exceeding 7.6 compared to general population [4], especially in individuals suffering from treatment-resistant depression (TRD) [5]. Despite the lack of consensus, the European Medicines Agency and the US Food and Drug Administration defined TRD in patients failing to achieve response to at least two antidepressant trials of different classes despite adequate dose, duration and adherence to treatment [6]. Patients with TRD show lower quality of life, as well as increased work disability and utilization of health resources.

The clinical guidelines offer a range of recommendations for the treatment of TRD, including psychotherapeutic approaches, pharmacological alternatives, and especially the combination of both. Treatments currently available have limited effectiveness and clinical response is often delayed. Intranasal esketamine (Spravato®), a new antidepressant treatment increases response rates in patients with a TRD [7]. In 2022, the Spanish Agency for Medicines and Health Products (AEMPS) authorized esketamine in combination with an oral antidepressant drug for the treatment of TRD in adults who did not respond to at least two different antidepressant treatments [8].

Trials have evidenced rapid efficacy of esketamine as an augmentation treatment for major depression [9]; [10], and also as a treatment for TRD [11]. In particular, the results of a prior

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real-world Italian study supported the safety and tolerability of the treatment [12], and showed a response rate of 76 % at 6 months to follow-up [13]. Furthermore, esketamine showed effectiveness in various patients subsamples, including individuals with bipolar TRD [14] and in those with comorbid substance use disorders [15]. The combination of esketamine with vortioxetine was linked with an increased reduction of emotional blunting and better tolerance as compared with other antidepressant augmentation strategies [16]. Younger age, being employed and low number of prior antidepressant trials were identified as predictors of response and remission over one month [17]. However, its therapeutic effect and long-term safety need to be further investigated.

While the response to antidepressants is measured through the Montgomery-Åsberg Depression Rating Scale (MADRS) in research [18; 9], clinical changes in patients receiving treatment for TRD in routine care are easy to investigate using the Clinical Global Impressions-Severity (CGI-S) that assesses severity at the time of the evaluation, and using the Clinical Global Impressions-Improvement scales (CGI-I) which investigates the evolution of the severity since last visit [19].

Hence, in this real-world naturalistic cohort study we aimed at evaluating the factors associated with achieving remission during esketamine augmentation treatment measured through the CGI-S and through the CGI-I. We also assessed the factors associated with the premature interruption of treatment in patients with TRD.

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MATERIALS AND METHODS

Setting and design

This observational study was carried out across four psychiatry departments: Rey Juan Carlos University Hospital, Fundación Jiménez Díaz, Infanta Elena Hospital, and General University Hospital of Villalba. All of them are part of Spain's National Health Services and affiliated with the Fundación Jiménez Díaz. The study was approved by the Hospital Fundación Jiménez Díaz Ethics Committee (CEIm-FJD) on 18th March 2024, and patients' information was handled as stated in Spanish and European regulations on data protection and patients' digital rights. All the participants provided written informed consent before entering the study.

Sample

The patients aged 18 years and older were included in the analysis if they filled the European Medicine Agency's criteria for a diagnosis of TRD – i.e failure to achieve response to at least two prior antidepressant trials despite adequate dose, duration and adherence to treatment – [6; 20], and if they received esketamine as an augmentation treatment for TRD. The use of esketamine in routine care started in January 2023 in the four centres. Patients with a TRD were proposed intranasal administration of flexible doses of esketamine (28 mg, 56 mg or 84 mg/administration) according to clinical judgement for augmenting antidepressant treatment according to the following sequences:

- Standard esketamine protocol including an induction phase (2 administrations per week for 4 weeks, 8 in total), and a maintenance phase (1 administration per week for 5 to 8 weeks, 5-8 in total).
- Treatment continuation (1 weekly administration or every 2 weeks) according to clinician's judgement and patient's choice.

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All the patients received concomitant standard clinical care for TRD involving at least one antidepressant (Selective Serotonin Reuptake Inhibitor/ Serotonine-Norepinephrine Reuptake Inhibitor or other antidepressant), and eventual psychotherapy as recommanded [6]. Current antidepressant medication was unchanged at esketamine initiation.

The routine sociodemographic and clinical data from 75 patients recorded in the electronic medical records at baseline and after each esketamine administration were anonymized and extracted in compliance with Spanish laws on the Protection of Personal Data.

Variables and measures

The following information was drawn from structured fields in electronic health records: baseline sociodemographic data, psychiatric diagnosis, comorbidities and depression subtype according to the International Statistical Classification of Diseases and Related Health Problems 10th (ICD-10) criteria (single episode (F32.x), or recurrent depressive disorder (F33.x)). After each esketamine administration, clinicians assessed the occurrence of suicidal ideation and attempts, treatment dosage, and the CGI level. The occurrence of dissociative symptoms, headache, hypertension, anxiety and drowsiness were systematically assessed after treatment intake. The CGI-S scale includes items concerning psychosocial aspects, behavior, symptoms and the impact of depression on daily life. It allows to establish different levels of disease based on the physician's clinical experience. The CGI-I is measured by comparing the patient's baseline symptom severity with its state following treatment administration. According to Morrens et al (2022), remission was defined in patients with a decrease of ≥ 2 points from the baseline CGI-S value or a CGI-S score of ≤ 3 points over the follow-up (from slightly depressed to normal) [19].

During the last visit of the follow-up, physicians assessed the general clinical improvement. All the data were retrieved from the electronic health records (HER).

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Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 29. First, we provided descriptive statistics of the whole population and performed univariate analyses to compare the clinical characteristics of patients receiving esketamine according to the occurrence of remission and premature interruption of treatment. The univariate analyses were performed using F-exact test, chi-square, or ANOVA.

Then we used logistic regression models to assess the multivariate relationship between the outcomes (the occurrence of remission and premature interruption of treatment), and the clinical factors associated in the univariate analysis with $p<0.1$. Overall, the significance level was set at $p < 0.05$, using 2-sided tests and 95% confidence intervals.

RESULTS

Baseline characteristics of the sample

Out of the 75 candidate patients screened for esketamine, 65 initiated the treatment and were evaluated through the CGI measures over the standard protocol. Out of them, 45 patients (69.2%) completed the standard protocol (i.e., received esketamine at least during the induction and the 5 weeks maintenance phases). The median number of esketamine administrations per subject was 19. The mean esketamine dosage was 66.04 mg [SD=15.39] per administration in the patient sample. The figure 1 shows the study flow chart.

The baseline clinical characteristics of the patients are reported in Table 1. The mean age of the sample was 53.09 [SD=10.15] and 52.3% of the patients were females (N=34). The mean number of esketamine administrations was 20.42 [SD=14.60]. Overall, 4.6% of the patients were diagnosed with bipolar disorder, 60% had recurrent depressive disorder, 12.3% were diagnosed with comorbid substance use disorder, 36.9% with a comorbid personality disorder, and 58.5% with a comorbid anxiety disorder. Over the follow-up, 32.3% reported suicidal

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ideation. In terms of esketamine-related adverse effects, 26.6% of patients experienced a dissociative episode, 9.4% reported headaches, 21.9% had hypertensive episodes, and 10.9% experienced drowsiness.

Factors associated with achieving remission

Remission was assessed using CGI-S measurement and defined according to Morrens' criteria at each clinical visit. Out of the whole sample, 36 (55%) of the patients achieved remission over the follow-up. Overall remission rates elevated to 67% in those who completed the standard protocol, and to 70% in those having received more than 19 esketamine administrations, (i.e., the median number; figure 1). Figure 2A shows the clinical improvement according to the CGI-I scale over the follow-up.

The occurrence of remission measured during follow-up was significantly associated with a higher mean number of esketamine administration (25.11 [SD=16.46] vs 14.97 [SD=9.65] in patients remitted and not remitted respectively, p=0.005); with completing the standard esketamine protocol (30 (83.3%) vs 15 (51.7%) in patients remitted and not remitted respectively, p=0.006); with a number of administration greater than 19 (23 (63.9%) vs 10 (34.5%) in patients remitted and not remitted respectively, p=0.018); and was less frequent when dissociative symptoms occurred during esketamine administration (5 (13.9%) vs 12 (41.4%) in patients remitted and not remitted respectively, p=0.015). The results are shown in table 1. Figure 2B highlights clinical improvement measured through the CGI-I scale over the follow-up according to the occurrence of dissociative symptoms subsequently to esketamine intake.

In the multivariate analysis taking into account possible confounding factors, the occurrence of remission over the follow-up was associated with the absence of dissociative symptoms during esketamine administration, and with completing the standard esketamine protocol (OR=0.229

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95%CI [0.054-0.966], p=0.045; and OR=4.538 95%CI [1.213-16.974], p=0.025 in model 1, respectively). The results are shown in table 2. In model 2, receiving more than 19 esketamine administrations was associated with remission over the follow-up (OR=6.513 95%CI [1.693-25.060], p=0.006).

Factors associated with the number of esketamine administrations.

During the treatment course, 20 patients (30.8%) discontinued esketamine before completing the standard protocol (induction and maintenance phases), while 33 patients (50.8%) received more than the median of 19 treatments. In the univariate analysis, drowsiness following esketamine administration was the only factor significantly associated with receiving more than 19 treatments (drowsiness occurred in 21.9% of patients (n=7) who received more than 19 administrations compared to 0% in those who received fewer than 19, p=0.005). The results are detailed in Table 3.

In the multivariate analysis taking into account possible confounding factors, this association did not remain significant. Results are not shown.

DISCUSSION

In this naturalistic retrospective study, most of the patients with TRD receiving esketamine showed remission over the course of the treatment. Remission rates were positively associated with the number of esketamine administrations and with the absence of dissociative symptoms recorded over the follow-up. Receiving more than 19 administrations increased overall chances of remission. Finally, no clinical factors predicted the total quantity of esketamine received.

Factors associated with esketamine efficacy

Although the placebo controlled Transform 1 clinical trial and the Transform 3 study in older adults failed to show significant effect of esketamine nasal spray as an add-on treatment of TRD

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[21], Popova et al. (2019) reported efficacy of flexible doses of esketamine against placebo measured through the MADRS score at 4 weeks [22]. Doses varied between 56 and 84 mg. Esketamine effect was predominant in clinical subgroups including females, patients aged between 45 and 64 years, or prior treatment failures ≥ 3 [22]. Similarly, esketamine was more effective in patients with ≥3 prior antidepressant failures in the Transform 1 trial [21]. Ochs-Ross et al. (2020) reported a significant difference in patients aged between 65 and 74, while not in those aged 75 and over [23].

In our study, the overall remission rate was related with the number of esketamine administrations. While expending the length of esketamine treatment may be associated with higher rates of patients showing remission, longer follow-up may increase chances to observe natural remission of depressive symptoms. Further comparative studies should be conducted to confirm the specific effect of extending esketamine administration upon achieving remission in patients who failed to improve during induction and maintenance phases. Moreover, from the 36 patients who achieved remission over the follow-up, 9 (25%) filled remission criteria at the final evaluation. Hence, maintaining remission remains challenging in individuals with TRD, although other studies showed higher rates of remission maintenance at study endpoints [24; 25]. Other therapeutic strategies involving non-invasive brain stimultation protocols were suggested to help prevent depression relapse [26]. Hence, their efficacy in maintaining remission may be tested whether in combination, or as comparator to esketamine in TRD [27]. In addition, we reported that remission rate was inversely associated with the frequency of dissociative symptoms. A prior systematic review suggested an absence of association between dissociation and antidepressant outcomes in the patients treated with esketamine [28]. Subsequent post-hoc analyses found no relationship between dissociation scores measured with the Clinician Administered Dissociative States Scale (CADSS) and the effect of esketamine in patients with TRD [29; 30]. In a recent study, the intensity of dissociative symptoms explained

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the antidepressant effect only within the 24 hours subsequent to the administration [31], while this effect occurred within a specific range of CADSS level [31]. Those diverging results may relate to different methodologies regarding dissociation assessment, as in our study the occurrence of dissociative symptoms were recorded according to ICD-10 criteria. Furthermore, the intensity of the dissociative symptoms was not quantified, which prevented us to investigate its relationship with the antidepressant response.

Also, we found no significant relationship between the remission rate and sociodemographic factors including age and gender, although individuals aged over 50 and females tended to be more represented in patients showing remission. The lack of association may be due to limited statistical power.

Factors associated with completing standard protocol

In our study, 69% of the patients finalized the standard esketamine protocol. Discontinuation rates appear higher than in prior controlled randomized trials [10]. As esketamine intake was proposed as part of routine care, it is likely that the administration protocol may have been applied with increased flexibility. No factors predicted the overall quantities of esketamine administered.

Interestingly, treatment adverse effects were not related with discontinuation rates over the follow-up, which confirms the general favorable tolerability profile reported in prior studies [32]. The most frequent adverse event reported in our real-world study was the occurrence of dissociative symptoms (27%). This is in accordance with rates of dissociative symptoms reported by Popova [16], that reached 26% in the active treatment group [22].

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Limitations and strengths of the study

This study reflects the real-world use of esketamine as an adjunctive treatment for TRD in psychiatric clinics, hence it is limited by several factors. First, although we assessed the remission of depression through Morrens' criteria involving the measure of CGI-S score [19], our results should be confirmed with other scales such as the MADRS which has been widely validated in depression treatment trials [18]. Second, our study lacked control group. Further comparative studies may help confirm the specific effect of esketamine treatment length upon the remission rates, against the natural evolution of the disease. Nevertheless, as our study was conducted in individuals bearing TRD, depression is unlikely to show spontaneous remission at short or mid-term in our sample. Also, the size of the sample with complete data remains limited as some variables (such as CGI) were not systematically collected by clinicians at all time points. In fact, the post hoc power analysis on the sample size of 65 patients showed a statistical power of 67.7% related to CGI scores. Moreover, interobserver differences may have skewed the results within each psychiatric centres or between hospitals. However, we found no centre effects when performing multivariate analysis. Finally, this study is retrospective with an open label design, and data were retrieved from clinical records. This prevented us from further comparison with other standardized protocols. This also limited the possibility to control results for a wider range of potential confounding factors as they were not all systematically recorded in patient files. While the patients included in the analysis responded to TRD criteria as defined by the European Medicine Agency (that is failure to achieve response to at least two prior antidepressant trials of different classes despite adequate dose, duration and adherence), the exhaustive list of prior administered treatments was not collected in the current study. Hence, we were not able to investigate the impact of the number of prior treatment failure on the patients' outcomes. Nevertheless, prior real-world studies failed to evidence any effect of

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the number of antidepressant trials lifetime [12], nor effects of the number of concomitant antidepressant medication [33].

Conversely, our study has several strengths. This is a naturalistic study reflecting real daily clinical practice. Hence, the results are more generalizable since the patient sample was less strictly selected, especially regarding the existence of psychiatric comorbidities. Furthermore, the use of CGI-S as outcome reflects clinical practice due to its large utilization by clinicians. In addition, remission criteria based on CGI-S have been previously validated [19].

Conclusions

This real-world naturalistic study suggests that adjunctive treatment with intranasal esketamine may be beneficial for most patients with TRD. Our results suggest that the length of esketamine treatment may predict remission rates in TRD. Especially, extending the numbers of esketamine administration may increase the chances to obtain remission. This results should be confirmed in further comparative studies assessing the natural evolution of depression. Furthermore, we found that the adverse effects measured did not significantly impact the treatment course. Hence, the use of esketamine appears well tolerated in routine clinical care with overall favorable outcomes. Those outcomes may be easily assessed through evaluation tools widely used in psychiatric practice. Further naturalistic studies are needed to evaluate esketamine utilization in long term.

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DATA AVAILABILITY: Data will be made available upon request.

CRediT taxonomy for contributors:

Dr Conejero and Pr Baca-Garcia had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization: Ismael Conejero, Raquel Alvarez García, Alejandro Porras-Segovia, Ana María De Granda Beltrán, Sergio Benavente López, Ezequiel Di Stasio, Jorge Lopez-Castroman, Philippe Courtet, Enrique Baca-Garcia.

Data curation: Lucía Albarracín-García, Raquel Alvarez García, Alejandro Porras-Segovia, Ana María De Granda Beltrán, Sergio Benavente López, Ezequiel Di Stasio

Funing acquisition: Enrique Baca-Garcia

Investigation: Raquel Alvarez García, Alejandro Porras-Segovia, Ana María De Granda Beltrán, Sergio Benavente López, Ezequiel Di Stasio

Formal Analysis: Ismael Conejero, Alejandro Porras-Segovia

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Methodology: Ismael Conejero, Alejandro Porras-Segovia, Jorge Lopez-Castroman, Philippe Courtet, Enrique Baca-Garcia,

Supervision: Enrique Baca-Garcia

Writing-Original Draft: Ismael Conejero, Alejandro Porras-Segovia.

Writing- review & editing: Alejandro Porras-Segovia, Jorge Lopez-Castroman, Philippe Courtet, Ismael Conejero, Enrique Baca-Garcia.

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Figure captions:

Figure 1: Flow Chart

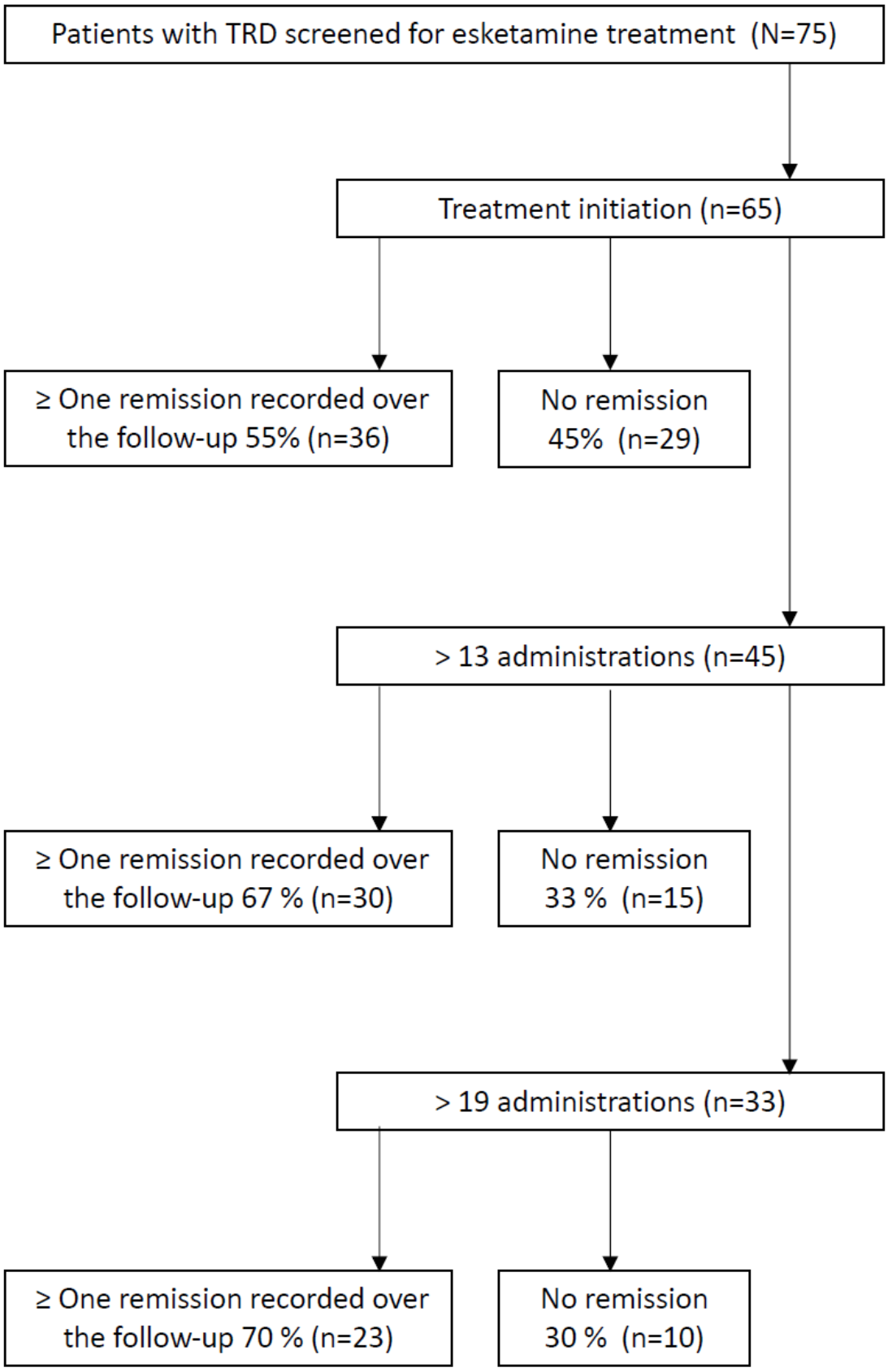

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Figure 2: A) Clinical improvement measured through the CGI-I scale over the follow-up. B) Clinical improvement measured through the CGI-I scale over the follow-up according to the occurrence of dissociative symptoms subsequently to esketamine intake.

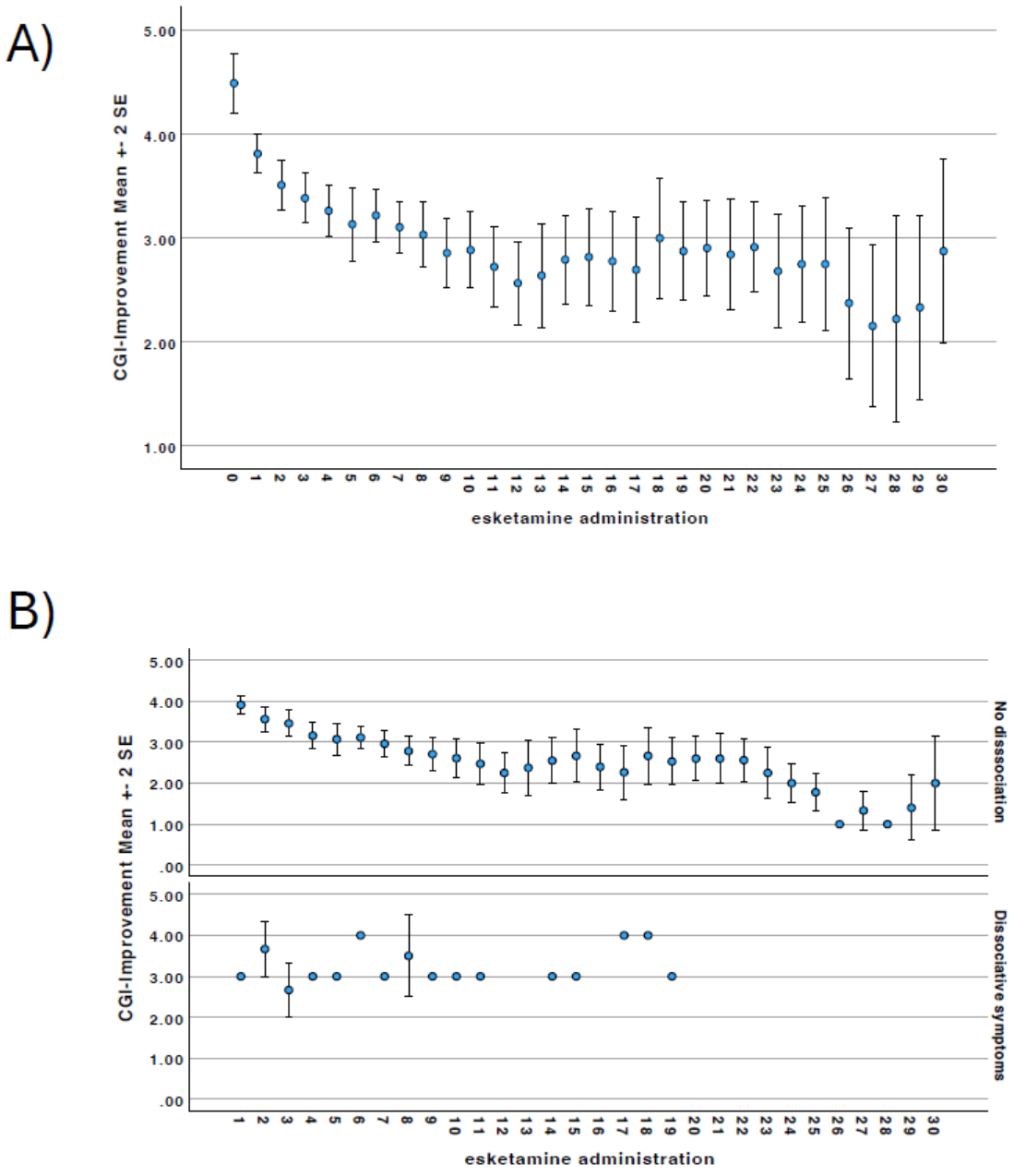

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Table 1. Occurrence of remission recorded with CGI-S over the follow-up according to the clinical characteristics at baseline and to the number of treatment administration.[a]

Clinical characteristics[b]	**Whole sample (n= 65)**	**≥ One remission (n= 36)**	**No remission (n= 29)**	**Significance (p-value)**
Age	53.09 [10.15]	53.83 [10.17]	51.93 [11.18]	0.476
<50	21 (32.3%)	10 (27.8%)	11 (37.9%)	0.384
>50	44 (67.7%)	26 (72.2%)	18 (62.1%)	
Gender (female)				
Female	34 (52.3%)	21 (58.3%)	13 (44.8%)	0.279
Male	31 (47.7%)	15 (41.7%)	16 (55.2%)	
Number of administrations	20.42 [14.60]	25.11 [16.46]	14.97 [9.65]	0.005
Number of esketamine administrations (median number in whole sample = 19)				
< 19	32 (49.2%)	13 (36.1%)	19 (65.5%)	0.018
> 19	33 (50.8%)	23 (63.9%)	10 (34.5%)	
Number of esketamine administration (standard protocol =13)				
< 13	20 (30.8%)	6 (16.7%)	14 (48.3%)	0.006
> 13	45 (69.2%)	30 (83.3%)	15 (51.7%)	
Mean Esketamine dosage	66.04 [15.39]	65.03 [16.68]	67.28 [13.81]	0.562
Dissociative episode during treatment (missing=1)	17 (26.6%)	5 (13.9%)	12 (41.4%)	0.015
Psychiatric comorbidities				
Bipolar disorder	3 (4.6%)	1 (2.8%)	2 (6.9%)	0.431
Recurrent depression (F33)	39 (60%)	21 (58.3%)	18 (62.1%)	0.760
Substance use disorder (F10.)	8 (12.3%)	5 (13.9%)	3 (10.3%)	0.665
Personality disorder (F60.)	24 (36.9%)	14 (38.9%)	10 (34.5%)	0.714
Anxiety disorders (F40.)	38 (58.5%)	23 (63.9%)	15 (51.7%)	0.323
Suicidal ideation	21 (32.3%)	12 (33.3%)	9 (31%)	0.844
Treatment adverse effects				
Headache	6 (9.4%)	3 (8.6%)	3 (10.3%)	0.809
Hypertensive episodes	14 (21.9%)	7 (20%)	7 (24.1%)	0.690
Anxiety	9 (14.1%)	6 (17.1%)	3 (10.3%)	0.436
Drowsiness	7 (10.9%)	5 (14.3%)	2 (6.9%)	0.346

[a] Remission is defined according to Morrens Criteria: CGI-S < 4 or CGI-S decrease ≥ 2 from baseline
[b] Data are means [Standard Deviation], or number (%).

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Table 2. Occurrence of remission over the follow-up according to the clinical characteristics and to the number of esketamine administration. [a]

	≥ One remission					
	Model 1			Model 2		
Clinical characteristics	**Estimated odds ratio (exp(b))**[b]	**95% CI for Exp(b)**	**Significance (p-value)**	**Estimated odds ratio (exp(b))**[b]	**95% CI for Exp(b)**	**Significance (p-value)**
Age > 50 (years)	1.167	0.305-4.470	0.821	1.475	0.369 – 5.887	0.582
Gender (male)	0.378	0.084-1.697	0.204	0.394	0.088 – 1.763	0.223
Dissociative episode during treatment	0.229	0.054-0.966	0.045	0.131	0.027 – 0.621	0.011
Center [c]						
HRJC	0.421	0.042-4.252	0.464	0.686	0.078 – 6.036	0.734
HIE	0.305	0.052-1.769	0.185	0.198	0.030 – 1.303	0.092
HGV	2.865	0.471-17.430	0.253	3.380	0.512 – 22.304	0.206
Number of Esketamine administration > 13	4.538	1.213-16.974	0.025	-	-	-
Number of Esketamine administration > 19 (median)	-	-	-	6.513	1.693- 25.060	0.006

[a] Data are means [Standard Deviation], or number (%).
[b.] The association between the clinical characteristics and treatment patterns, and the overall improvement of depression was tested in a logistic regression model. We included Age, gender and center in both models 1 & 2.
[c] HRJC: Rey Juan Carlos University Hospital; HIE: Infanta Elena Hospital; HGV: General University Hospital of Villalba.

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Table 3. Quantities of esketamine intake according to the clinical characteristics at baseline and to the adverse effects of treatment. [a]

Clinical characteristics	Whole sample (n= 65)	≥ 13 Esketamine administrations (Standard protocol, n= 45)	Significance (p-value)	≥ 19 Esketamine administrations (n= 33)	Significance (p-value)
Age	53.09 [10.15]	53.27 [10.99]	0.750	52.64 [10.04]	0.790
<50	21 (32.3%)	13 (28.9%)	0.377	11 (33.3%)	0.857
>50	44 (67.7%)	32 (71.1%)		22 (66.7%)	
Gender (female)					
Female	34 (52.3%)	22 (48.9%)	0.408	16 (48.5%)	0.531
Male	31 (47.7%)	23 (51.1%)		17 (51.5%)	
Psychiatric comorbidities					
Bipolar disorder	3 (4.6%)	2 (4.4%)	0.922	1 (3%)	0.536
Recurrent depression (F33)	39 (60%)	26 (57.8%)	0.583	22 (66.7%)	0.265
Substance use disorder (F10.)	8 (12.3%)	6 (13.3%)	0.706	6 (18.2%)	0.143
Personality disorder (F60.)	24 (36.9%)	18 (40%)	0.441	15 (45.5%)	0.148
Anxiety disorders (F40.)	38 (58.5%)	26 (57.8%)	0.867	21 (63.6%)	0.390
Suicidal ideation	21 (32.3%)	16 (35.6%)	0.401	8 (24.2%)	0.158
Treatment adverse effects (missing=1)					
Dissociative episode during treatment	17 (26.6%)	10 (22.7%)	0.303	9 (28.1%)	0.777
Cephalalgia	6 (9.4%)	6 (13.6%)	0.083	5 (15.6%)	0.086
HTA	14 (21.9%)	11 (25%)	0.370	8 (25%)	0.545
Anxiety	9 (14.1%)	7 (15.9%)	0.528	7 (21.9%)	0.072
Drowsiness	7 (10.9%)	7 (15.9%)	0.059	7 (21.9%)	0.005

[a]Data are means [Standard Deviation], or number (%).

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