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Mariana V.F. Echegaray, Rodrigo P. Mello, Guilherme M. Magnavita, Gustavo C. Leal, Fernanda S. Correia-Melo, Ana Paula Jesus-Nunes, Flávia Vieira, Igor D. Bandeira, Ana Teresa Caliman-Fontes, Manuela Telles, Lívia N. F. Guerreiro-Costa, Roberta Ferrari Marback, Breno Souza-Marques, Daniel H. Lins-Silva, Cassio Santos-Lima, Taiane de Azevedo Cardoso, Flávio Kapczinski, Acioly L.T. Lacerda, Lucas C. Quarantini

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Does the intensity of dissociation predict antidepressant effects 24 hours after infusion of racemic ketamine and esketamine in treatment-resistant depression? A secondary analysis from a randomized controlled trial.

Mariana V.F. Echegaray[1*], Rodrigo P. Mello[1,2*], Guilherme M. Magnavita[1], Gustavo C. Leal[1,2], Fernanda S. Correia-Melo[1,2], Ana Paula Jesus-Nunes[1,2], Flávia Vieira[1,2], Igor D. Bandeira[1,2], Ana Teresa Caliman-Fontes[1], Manuela Telles[1,2], Lívia N. F. Guerreiro-Costa[1,2], Roberta Ferrari Marback[1,2], Breno Souza-Marques[1,2], Daniel H. Lins-Silva[1], Cassio Santos-Lima[1,4], Taiane de Azevedo Cardoso[5], Flávio Kapczinski[5], Acioly L.T. Lacerda[6,7], Lucas C. Quarantini[1,2,3]

*These authors contributed equally to this work.

Affiliations:

1. Laboratório de Neuropsicofarmacologia, Serviço de Psiquiatria do Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia, Salvador, Brazil.
2. Programa de Pós-graduação em Medicina e Saúde, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, Brazil.
3. Departamento de Neurociências e Saúde Mental, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, Brazil.
4. Programa de Pós-graduação em Psicologia, Instituto de Psicologia, Universidade Federal da Bahia, Salvador, Brazil.
5. Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, Canada.
6. Laboratório Interdisciplinar de Neurociências Clínicas, Universidade Federal de São Paulo, São Paulo, Brazil.
7. Instituto Sinapse de Neurociências Clínicas, Campinas, Brazil.

Corresponding author: Lucas C. Quarantini
Mailing address: Hospital Universitário Professor Edgard Santos, Serviço de Psiquiatria, 3° andar, 40110-060, Salvador, BA, Brazil
Email: lcq@ufba.br
Telephone: 55 71 32838075

Abstract

Background: Ketamine and esketamine have both shown significant antidepressant effects in treatment-resistant depression (TRD), and conflicting evidence suggests that induced dissociation by these drugs can be a clinical predictor of esketamine/ketamine's efficacy.

Methods: This study is a secondary analysis from a bi-center, randomized, controlled trial. Participants were randomly assigned 1:1 to receive an IV infusion of esketamine (.25 mg/kg) or racemic ketamine (.50 mg/kg) over 40 minutes. Dissociative symptoms were assessed using the Clinician-Administered Dissociative State Scale (CADSS) 40 minutes following the beginning of the infusion. The variation in depression scores was measured with the Montgomery-Asberg Depression Rating Scale (MADRS), which was administered before the intervention as a baseline measure and 24 hrs, 72 hrs, and 7 days following infusion.

Results: Sixty-one patients were included in the analysis. Examining CADSS scores of 15 or below, for every 1-point increment in the CADSS score, there was a mean change of -0.5 (SD = 0.25; p-value 0.04) of predicted MADRS score from baseline to 24 hrs. The results for 72 hrs and 7 days following infusion were not significant. Limitations: This study was not designed to assess the relationship between ketamine or esketamine-induced dissociation and antidepressant effects as the main outcome, therefore confounding variables for this relationship were not controlled.

Conclusions: We suggest a positive relationship between dissociation intensity, measured by CADSS, and antidepressant effect 24 hours after ketamine and esketamine infusion for a CADSS score of up to 15 points.

INTRODUCTION

Major depressive disorder (MDD) is a recurrent and disabling psychiatric condition, and it is the single biggest contributor to non-fatal health loss worldwide (1). The main goal for the treatment of MDD is to achieve remission, which translates to patients returning to their previous level of functioning (2). Approximately one-third of patients with MDD fail to achieve remission through the available treatment, which is associated with a poor prognosis in clinical and functional terms (3–6).

Over the last decades, new strategies to manage treatment-resistant depression (TRD) have been proposed. N-methyl-D-aspartate (NMDA) antagonists, such as ketamine and its enantiomers, S (+)-ketamine (esketamine) and R (-)-ketamine (arketamine) have demonstrated a robust antidepressant effect and acceptable tolerability in the short term (7–12). Recently, The Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline included a single infusion of racemic ketamine as level 1 evidence to treat TRD (13), and the Food and Drug Administration (FDA) also approved intranasal esketamine for TRD (14).

Identifying predictors of response to ketamine or esketamine's efficacy can facilitate patient selection for more intensive regimes, therefore decreasing expenditure on futile care and side effects (15). A series of predictors are being tested, but results have not yet

proved conclusive (16). Although potentially less precise, clinical predictors may represent a cheaper and simpler strategy to maximize the effects of ketamine and esketamine (17).

The validity of dissociation as a clinical predictor of antidepressant efficacy has been extensively studied and the results are contrasting (6,17–20). A recent systematic review addressed this matter and concluded that further clarification is needed since 2 out of 5 studies found a significant correlation between induced dissociation measured by Clinician-Administered Dissociative State Scale (CADSS) (21). In addition, only one publication examined the relationship between esketamine induced dissociation and antidepressant effects (22).

The aim of this study was to assess the relationship between racemic ketamine or esketamine induced dissociation and antidepressant effects 24 hours, 72 hours and 7 days following infusion in TRD subjects. We hypothesized that a higher intensity of dissociative side effects would predict improvement in depressive symptoms. We performed a post-hoc analysis of the first head-to-head study between ketamine and esketamine (9).

METHODS

Study design and location

This study is a secondary analysis from a randomized, active-controlled, double-blinded trial with two parallel groups conducted at the Federal University of Bahia (UFBA) and the Federal University of São Paulo (UNIFESP), located in Brazil (9).

Ethics approval and consent to participate

The study was approved by the local Institutional Review Board (Professor Edgard Santos University Hospital Number: 46657415.0.0000.0049 and São Paulo Hospital Number: 46657415.0.3001.5505) and follows the ethical principles of the Declaration of Helsinki, 2013. The study protocol was registered in the Japan Primary Registries Network (JPRN): UMIN000032355. Additional information is available in the previously published protocol (23).

Participants

We included participants over 18 years of age with an MDD diagnosis based on the DSM-IV criteria and confirmed by experienced psychiatrists and psychologists using the Brazilian version of the Mini International Neuropsychiatric Interview 5.0.0 (MINI- Plus) (24). All included patients were diagnosed with TRD, which is defined as a therapeutic failure after at least one adequate antidepressant treatment lasting for a minimum of 12 weeks, considering that there is no consensual definition of TRD and some studies classify this as its first stage (25).

Exclusion criteria were: (a) concomitant treatment with electroconvulsive therapy; (b) diagnosis of a psychotic disorder; (c) mental retardation/intellectual disability or dementia; (d) unstable heart disease; (e) current illicit drug use, and (f) concomitant use of benzodiazepines. In addition to using a less restrictive definition of TRD, we did not exclude other psychiatric or clinical comorbidities nor augmentation treatments for TRD, in order to obtain a naturalistic sample.

Patients maintained their previous treatment regimen (types of medications and doses remaining unchanged) for at least 15 days before randomization and were unable to change dosages or start to use new drugs during the study follow-up week (except for

non-benzodiazepine sleep inducers). All participants voluntarily agreed and signed the written Informed Consent Form.

Intervention

Participants received a single dose of one of the two drugs in the study: ketamine racemic mixture (0.5 mg/kg) or esketamine (0.25 mg/kg). Drugs were infused intravenously for over 40 minutes.

Randomization

Participants were randomized into esketamine and ketamine groups, on a 1:1 ratio, via electronic randomization software (http://www.randomizer.org), and carried out by a single independent investigator for both locations. The only professionals who knew which drug had been infused were the investigator responsible for the allocation and two nurses responsible for drug preparation (one for each center). These professionals did not participate in any clinical evaluation.

Outcomes and assessment

Dissociative symptoms were assessed using the 23 items-CADSS (26) at the 40th minute of drug infusion. CADSS has been the most widely used scale to assess dissociative symptoms induced by ketamine or esketamine (27–29). Depression severity was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) (30) score, which was administered before the intervention as a baseline measure and 24 hrs, 72 hrs, and 7 days following infusion.

Statistical analyses

Statistical analyses were conducted using IBM SPSS V. 25 for Windows and R statistical package (31). The normality of the samples was determined by Q–Q plot and histogram analysis. Descriptive statistics are presented as frequencies, means, and medians based on variable distribution. We used Student's t-tests for univariate comparisons of group means, Mann-Whitney U-test for univariate comparisons of group medians, and Pearson's chi-squared test or Fisher's exact test for univariate comparisons of proportions.

We calculated the absolute variation in the MADRS scores between baseline and the three post-infusion measurement points, at 24 hrs, 72 hrs, and 7 days. We then used a Locally Weighted Scatterplot Smoothing (LOESS) curve between each variation and the CADSS scores, allowing us to visually assess a non-linear relationship between antidepressant response and dissociation. These curves seemed to indicate a non-linear relationship resembling two straight lines with a break at 15 points of the CADSS. We then fitted a longitudinal fixed-effects model with time, treatment group, and CADSS scores as predictors. Fixed models are akin to mixed models, and they work by modeling the response variable – in our cases the MADRS score – as function of time and any number of specified covariates. Their main advantage is the paucity of assumptions when the outcome is measured at fixed time intervals, as we did. By using an unstructured covariance matrix, we can control for observation interdependence and calculate p-values while making little assumptions regarding the behavior of covariance over time. To better model the CADSS x MADRS non-linear relationship, we compared 4 different types of modeling strategies: a linear model, an exponential model, a quadratic model, and different piecewise linear splines with a single knot in different CADSS values. The piecewise spline was selected with a knot at 15 points on the CADSS scale based on model fit, AIC, Likelihood ratio tests, and p-values for the coefficients. All longitudinal models in the final report were applied using restricted maximum likelihood (REML).

We conducted all analyses with interaction terms allowing the ketamine and esketamine groups to be treated as separate from one another, to allow for effect modification on the CADSS x MADRS relationship by type of ketamine. Since these terms did not reveal different profiles for the types of ketamine, in relation to either p-value, model fit, or AIC, we decided to drop the interactions and treat both ketamine groups as similar. These findings are in line with results from the non-inferiority study, which showed no significant differences between both forms of ketamine, in terms of efficacy and safety outcomes.

RESULTS

The complete clinical outcomes of the trial have been published previously (9). Sixty-three patients were included in the original study, but CADSS scores were incomplete for 2 of these patients, so this secondary analysis only includes 61 of them. Of these patients,

32 received esketamine infusion and 29 received ketamine. There was no statistically significant difference between the two groups for the observed variables. Table 1 shows the participants' characteristics at baseline. Almost all of the participants in the esketamine group (90.6%) and the totality of participants in the ketamine group were found resistant to at least two previous antidepressant treatments.

Table 1. Baseline sociodemographic and clinical characteristics of the participants.

	Esketamine group N (%) 32 (52.4)	**Ketamine group N (%) 29 (47.5)**	**p value**
Female gender	18 (56.3)	20 (69)	0.30*
Ethnicity			0.47*
− White	11 (34.3)	13 (44.8)	
− Black	5 (15.6)	6 (20.7)	
− Mixed ethnicity	16 (50)	10 (34.4)	
Income			0.16*
− Below 1 MW	10 (31.2)	5 (17.2)	
− 1 to 3 MW	6 (18.7)	13 (44.8)	
− 3 to 6 MW	4 (12.5)	2 (6.9)	
− 6 to 10 MW	7 (21.8)	6 (20.7)	
− Above 10 MW	5 (15.6)	3 (10.3)	
≥ 2 therapeutic failures	29 (90.6)	29 (100)	0.14†
PTSD	0 (0)	3 (10.3)	0.10†
GAD	21 (65.6)	19 (67.9)	0.85*
PD	10 (55.6)	8 (44.4)	0.82*
	Mean (SD)	**Mean (SD)**	**p value**
Age	44.5 (13.7)	48.6 (15.1)	0.27‡
	Median (IQR)	**Median (IQR)**	**p value**
MADRS at baseline	31.5 (14)	32 (8)	0.96§

MW (Minimum Wage); MADRS (Montgomery-Åsberg Depression Rating Scale); PTSD (Post-Traumatic Stress Disorder); GAD (Generalized Anxiety Disorder); PD (Panic Disorder); SD (standard deviation); IQR (interquartile range); * Pearson's chi-squared test; † Fisher's exact test; ‡ Student's t-test; § Mann-Whitney U-test.

The median CADSS score was 9 (IQR 16; range 0-62) for the esketamine group and 15 (IQR 26; range 0-54) for the ketamine group, with no statistical difference between the

groups (p-value 0.4). For every 1-point increment in the CADSS score, in CADSS scores of 15 or below, there was a mean change of -0.5 (SD = 0.25; p-value 0.04) of predicted MADRS score from baseline to 24 hrs. For CADSS scores greater than 15, there was a mean change of 0.01 (95% CI: -0.11 to 0.3; p-value 0.3) of predicted MADRS score from baseline to 24 hrs. for every 1-point increase in CADSS. This relationship is illustrated in Figure 1a. The results for 72 hrs. (Figure 1b) and 7 days (Figure 1c) following infusion were nonsignificant (p-value 0.07 and 0.1, respectively). Considering CADSS scores of 15 or below, for every 1-point increment in the CADSS score, there was a mean change of -0.5 (SD = 0.28; p-value 0.07) in the predicted MADRS score from baseline to 72 hrs. and a mean change of -0.5 (SD = 0.31; p-value: 0.10) in the predicted MADRS score from baseline to 7 days.

Figure 1. Relation between Induced Dissociative Symptoms and Predicted Depressive Symptom Severity After Ketamine or Esketamine Infusion.

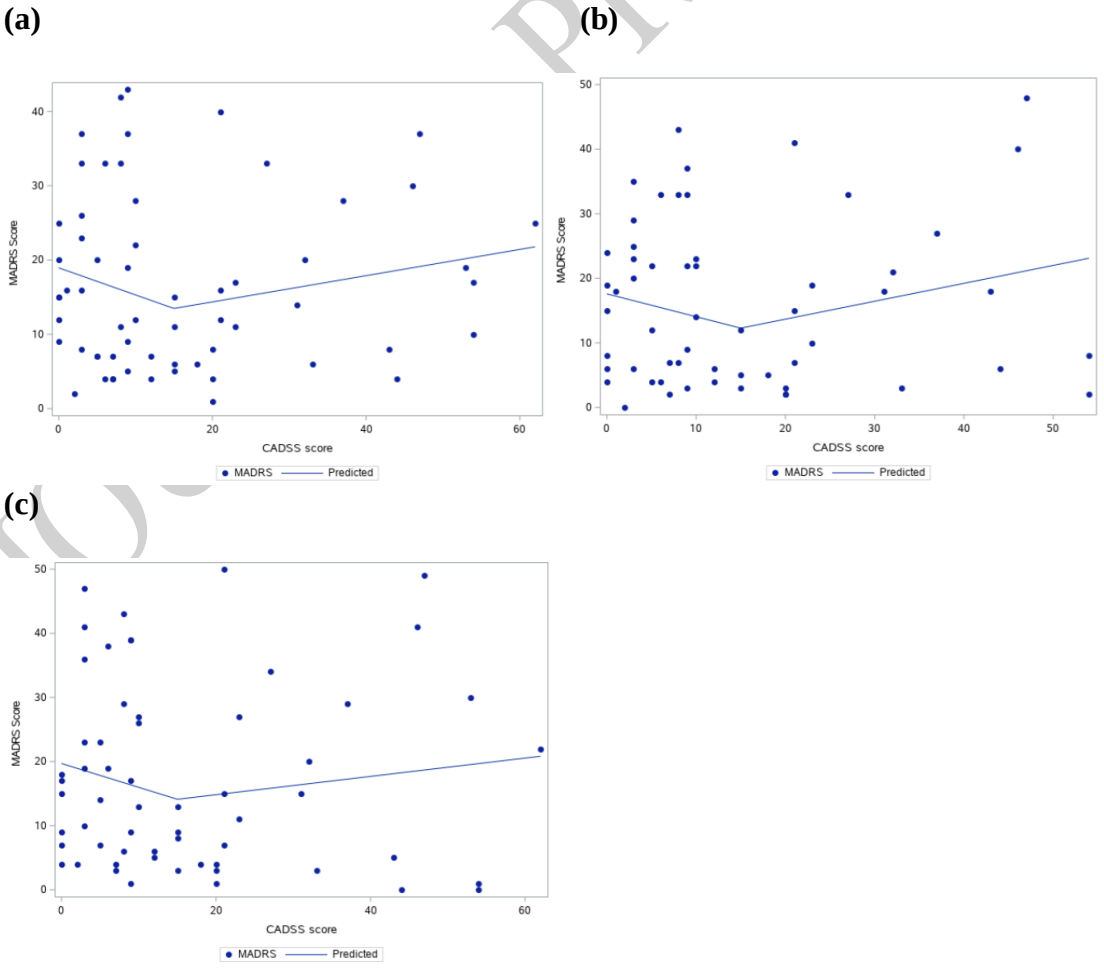

Fig. 1 Induced dissociative symptoms were measured by the Clinician-Administered Dissociative States Scale (CADSS) at the 40th minute of ketamine or esketamine infusion. Depressive symptom severity measured by Montgomery-Åsberg Depression Rating Scale (MADRS) scores. Predicted Depressive Symptom Severity was measured by a longitudinal fixed-effects model with CADSS scores and time [24hrs **(a)**, 72hrs **(b)** or 7 days **(c)**], treatment group and CADSS scores as predictors. Since these terms did not reveal different profiles for the types of ketamine, concerning p-values, model fit, or AIC, we decided to drop the interactions and treat both as ketamine. We selected the piecewise spline with a knot at 15 points on the CADSS scale as a model, based on model fit, AIC, Likelihood ratio tests, and p-values for the coefficients.

DISCUSSION

The findings of the present study suggest an association between the dissociation level induced by racemic ketamine and esketamine and antidepressant effects 24 hours after infusion. This relationship was similar between the ketamine and esketamine groups. Although induced dissociation may be a clinical marker of the antidepressant effect of ketamine and esketamine, this evidence has been restricted to CADSS scores up to 15. To our knowledge, this is the first study to demonstrate a specific cutoff point for this relationship between dissociation and the response to different enantiomeric forms of ketamine.

Luckenbaugh et al. (2014) carried out a study with 108 patients diagnosed with TRD or bipolar disorder, to evaluate possible predictors of antidepressant efficacy after ketamine use (0.5mg/kg by intravenous infusion over 40 min) (19). It showed a significant association between increased CADSS scores at 40 min and antidepressant efficacy measured by Hamilton Depression Rating Scale (HDRS) score at 230 min and 7 days, but not 24 hrs. Niciu et al. (2018) extended these findings by examining specific CADSS subscales (depersonalization, derealization, and amnesia) of 126 patients suffering from a major depressive episode (both unipolar and bipolar disorders), who also received a single (0.5mg/kg i.v.) ketamine infusion (32). The results demonstrated that depersonalization was positively related to antidepressant effects. It should be noted, however, that both studies have limitations in respect to the highly heterogeneous

population. Most recently, Phillips et al. (2020) assessed dissociation after infusion of 0.5 mg/kg of ketamine in 22 participants with TRD (20). They found a significant association between antidepressant response and variation on CADSS scores at 24hs post-infusion. The FDA approval for intranasal esketamine also concluded that dissociation is associated with increased relapse time. The analysis, however, could not differentiate whether this association was due to the placebo effect or due to direct antidepressant response (33).

The relationship between ketamine-induced dissociation and antidepressant response is not clear, as shown by studies with contrasting results. Valentine et al. (2011) found no association between an increase in CADSS scores and antidepressant effects after one intravenous ketamine infusion (0.5mg/kg) in 10 subjects with major depressive disorder (34). Lapidus et al. (2014) showed no association between dissociation intensity after administration of intranasal ketamine and antidepressant effects in 18 participants with depression who had failed at least one prior antidepressant trial (35). A recent study conducted with 99 participants with TRD also failed to show an association between CADSS scores and improvement in HDRS scores on Day 1 and Day 3 (18). Subjects were assigned to 5 arms, either to receive a single dose of ketamine 0.1mg/kg i.v., a single dose of ketamine 0.2mg/kg i.v., a single dose of ketamine 0.5mg/kg i.v., a single dose of ketamine 1mg/kg i.v. or a single dose of midazolam 0.045mg/kg i.v.(active placebo). Only the participants who received 0.5mg/kg (n = 22) and 1.0mg/kg of ketamine (n = 20) had a significant increase in CADSS scores, which could have affected the posterior analysis. A systematic review, including 17 studies of patients with depression, also did not find an association between CADDS and antidepressant response (36).

Two more recent studies have analyzed this relationship in multiple-dose treatments. Wlodarczyk et al. (2021) found no association in a study with 8 doses of intravenous ketamine (0.5mg/kg) in 49 inpatients with TRD or bipolar disorder (37). Chen et al. (2022) published the first results concerning esketamine induced dissociation (22). They analyzed data from three phase III trials of multiple doses of intranasal esketamine and did not find a correlation between dissociation and antidepressant effects. These previously mentioned conflicting results, regarding the relationship between dissociation and antidepressant action, were similar in the fact that they adopted a linear statistical

analysis. As it is unlikely that the psychometric variables show a linear relationship throughout the assessment, as required by Pearson's correlation, or even monotonic, as assumed by Spearman's correlation, this nonlinear exploratory analysis may be useful in future studies in the area.

There are possible explanations for our result. There is evidence that dissociative symptoms correlate with blood ketamine levels (38,39). The correlation between blood ketamine/esketamine levels and therapeutic efficacy, however, may be comprised on a therapeutic window for ketamine/esketamine that has not been defined yet (40). Singh et al. (2016) showed that lower doses of esketamine (0.2mg/kg versus 0.4mg/kg IV) have equivalent efficacy but better tolerability (11). The therapeutic window for other drugs has been established, but initial adjustments were necessary. It is now well known that higher doses of first-generation antipsychotics only induce more extrapyramidal effects. They do not increase efficacy in controlling psychotic symptoms (41). Nortriptyline also has a specific window for its antidepressant response; there is a curved relationship between its blood level and efficacy, meaning that a level that is too low or too high could compromise response (42). We hypothesize that a similar phenomenon may happen with ketamine/esketamine.

Another aspect to consider is the influence of the psychoactive state as an inherent part of the antidepressant effect, as is often credited to the therapeutic effects of serotonergic psychedelics such as psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and Ayahuasca (43). The CADSS, which aims to assess dissociation as an adverse effect, can be experienced by some individuals in a qualitatively negative way, especially at higher levels, which could also influence our findings. One study showed that ketamine non-responders had significantly higher scores than responders in the "anxious ego-disintegration" 5-Dimensional Altered State of Consciousness Rating Scale (5D-ASC) subscale, but another study, however, did not find a significant correlation between 5D-ASC dimensions and MADRS percentage change (44,45). Ketamine/esketamine can also induce other acute psychoactive effects, which are not well captured by CADSS, such as mystical experiences (46), characterized by feelings of oneness, experiences of joy, sacredness or holiness, and acknowledging that the experience provides a new understanding of the reality (47). A study that used ketamine

to treat cocaine addiction showed that mystical experiences, measured by the Hood Mysticism Scale, mediated therapeutic efficacy (48). In this study, dissociative symptoms assessed by CADSS were associated but did not mediate therapeutic efficacy.

A challenge to this relationship between dissociation and the antidepressant effect of ketamine is the possible role of R(-) - ketamine (arketamine). Animal studies (49,50) and only one study in humans (51) suggested that the use of arketamine would produce an antidepressant effect, without the occurrence of psychotomimetic effects. Indeed, many ketamine or esketamine responders do not experience drug provoked dissociation (22). A possible explanation is that dissociative experiences or other acute psychoactive effects induced by ketamine/esketamine may have an additional antidepressant effect, as occurs with serotonergic psychedelics. Furthermore, dissociation. Furthermore, it can be important as a cheap and safe clinical predictor of treatment efficacy, even if it is not important as a mediator of efficacy.

Limitations

These findings should be interpreted with caution, as our study had several limitations. Firstly, the results presented in this study were from a secondary objective. The study was not designed to assess the relationship between ketamine or esketamine induced dissociation and their antidepressant effects as the main outcome. Secondly, there may be confounding variables for this relationship that were not controlled for in this study, such as pharmacokinetic measures and personality disorders. To conduct the study in a naturalistic way, the diagnosis of a personality disorder was not an exclusion criterion in the protocol. As this variable was not evaluated, it was not possible to control for it. Most studies did not exclude comorbid BPD, and no studies controlled pharmacokinetic measures for this relationship.

Conclusion

Our study suggests a positive relationship between dissociation intensity, measured by CADSS, and antidepressant effect 24 hours after ketamine and esketamine infusion for a CADSS score of up to 15 points. By identifying the cutoff point to the relationship between dissociation and response, this study may enable future investigators to pursue a

therapeutic window for ketamine/esketamine. We suggest that further studies adjust this relationship for potential confounding variables.

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