

# Central nervous system-related safety and tolerability of add-on ketamine to antidepressant medication in treatment-resistant depression: focus on the unique safety profile of bipolar depression

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## Abstract

**Background:** There is evidence supporting the use of ketamine in treatment-resistant depression (TRD). However, there are some safety and tolerability concerns associated with ketamine. This study aimed to investigate ketamine's safety and tolerability to the central nervous system and to assess the relationship between dissociative symptomatology and psychometric outcomes during and after intravenous ketamine treatment concurrent with treatment by varying psychotropic medications in treatment-refractory inpatients with major depressive disorder (MDD) and bipolar disorder (BP).

**Methods:** A total of 49 patients with MDD and BP were included in this study. The subjects were administered ketamine and were assessed for changes using an observational protocol.

**Results:** No antidepressants were associated with psychomimetic symptomatology except for citalopram ( $p=0.019$ ). Patients treated with citalopram showed a higher intensity of psychomimetic symptomatology. The use of classic mood-stabilizers was significantly associated with an increase in psychomimetic symptomatology according to the Brief Psychiatric Rating Scale (BPRS; lamotrigine  $p=0.009$ , valproate  $p=0.048$ , lithium  $p=0.012$ ). No sequelae were observed.

**Conclusions:** Despite the limitations that this study may be underpowered due to the small sample size, the sample consisted of a heterogeneous TRD population in a single site, and there no blinding of who underwent only acute ketamine administration, our observations indicate ketamine use requires close safety and tolerability monitoring with regards to psychomimetic and dissociative symptoms in TRD-BP and careful management for MDD patients.

**ClinicalTrials.gov identifier:** NCT04226963

**Keywords:** dissociation, ketamine, psychosis, safety, tolerability, treatment-resistant depression

Received: 1 July 2020; revised manuscript accepted: 27 March 2021.

## Introduction

There is robust evidence that ketamine provides rapid symptomatic remission of treatment-resistant depression (TRD) in both major depressive disorder (MDD) and bipolar disorder type I (BP).

Still, several concerns exist regarding its safety and tolerability.<sup>1-6</sup> In particular, adverse events associated with dissociative symptomatology are a major concern.<sup>7</sup> Dissociative symptoms can cause a wide variety of phenomena and are associated with

*Ther Adv Psychopharmacol*

2021, Vol. 11: 1-11

DOI: 10.1177/  
20451253211011021

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treatment response in both TRD associated with MDD (TRD-MDD) and TRD associated with BP (TRD-BP).<sup>2</sup> However, one previous study reported no relationship between dissociative symptomatology and depression outcome.<sup>4</sup> The Clinician-Administered Dissociative States Scale (CADSS) as well as the Brief Psychiatric Rating Scale (BRPS) positive symptoms subscale (BPRS+) are used to represent the overall intensity of dissociative and potential treatment-emergent psychotic symptomatology.<sup>1-4,7</sup>

The aim of this study was to investigate the relationship between dissociative symptomatology and psychomimetic effects during and following intravenous ketamine treatment with psychotropic medication in TRD-MDD and TRD-BP inpatients.<sup>8</sup>

### Methods and population

The sample selection methods for this study have been described in detail elsewhere.<sup>9,10</sup> Briefly, the patient sample comprised subjects enrolled in a naturalistic observational safety and efficacy registry protocol for ketamine infusions in TRD. Inpatients diagnosed with TRD-MDD and TRD-BP were included. Patients were interviewed by a clinical psychiatrist to establish a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria using the Mini International Neuropsychiatric Interview (MINI). All MDD patients exhibited treatment resistance for the current episode, defined as an inadequate response to two or more antidepressants [assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)]. TRD-BP was defined as a clinically unsatisfactory response to two approved and adequate interventions for bipolar depression.<sup>11</sup> Changes in concurrent psychotropics were allowed only after the follow-up period if the patients were inadequate responders to ketamine treatment. The current study followed a single-patient, single-rater rule. During the screening, patients were rated by a clinician using the Montgomery-Åsberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Columbia-Suicide Severity Rating Scale (C-SSRS), the CADSS, and the BPRS. The CADSS was chosen for analysis as it is the instrument most widely used in previous mood disorder studies to assess the acute psychoactive effects of ketamine.<sup>7</sup> The CADSS includes a 19-item scale used to evaluate the patient's answers (subjective items) and an 8-item scale used by a trained

physician to assess the patient's responses during ketamine intake (objective items). The subjective items include three components: depersonalization, derealization, and amnesia.<sup>12</sup> The BPRS is an 18-item rating scale used to assess a range of psychotic and affective symptoms based on both observation of the subject and the subject's own self-report. A variant of the BPRS is the four-item BPRS+, which considers the positive symptoms of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization. The BPRS and the BPRS+ are used to assess treatment-emergent psychotic symptoms. In both tests, each symptom is rated on a scale from 0 to 6, where 1 is "not present" and 6 is "extremely severe" (the score of 0 represents a not assessed item).<sup>13</sup>

All patients enrolled in this study were medically stable and able to communicate and provide consent. Only adult inpatients aged 18–65 years were eligible to participate. None of the patients had suffered from psychotic symptoms during the course of their disease. Patients who were significantly affected by somatic illness were allowed to continue their current medication during ketamine treatment. The exclusion criteria included a history of uncontrolled medical conditions, a previous adverse reaction to ketamine, active substance use including alcohol and cannabis (verified by MINI and also urine toxicology on screening and follow up), and pregnancy or breastfeeding. None of the patients took benzodiazepines during the course of the study, although the protocol allowed small doses for emerging psychomimetic, dissociative states (e.g., 1 mg lorazepam). None of the patients received any mood stabilizers, including lithium, as an augmentation strategy.

Due to the substantial variability of psychotropic medications within the MDD and the BP groups, the patients were categorized according to medication. Still, all MDD subjects received antidepressants in monotherapy or augmented with a second antidepressant. All BP subjects received mood stabilizers in monotherapy or in combination with an evidence-based strategy to treat bipolar depression.

The study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland (approval code NKBBN/172-674/2019). The study was prospectively registered

at ClinicalTrials.gov with the identifier NCT04226963 on 04th December 2019 (<https://clinicaltrials.gov/ct2/show/NCT04226963>). All subjects provided written informed consent to participate in this study.

### Study design: ketamine infusions

This study followed an observational design, with all patients continuing baseline psychotropic standards of care as well as treatment of chronic somatic diseases during ketamine infusions. Study participants were administered eight ketamine infusions every  $3 \pm 2$  days over 4 weeks. Ketamine was administered at a dosage of 0.5 mg/kg of body weight infused intravenously over 40 min.

Safety monitoring was performed every 15 min before, during, and after infusion until 90 min after the infusion. This monitoring included the assessment of vital signs (heart rate, body temperature, respiratory rate, blood pressure, oxygen saturation) as well as the administration of mental status examinations, including assessments by the BPRS and the CADSS, to determine the presence of psychotic and/or dissociative symptoms. Any other significant adverse effects (e.g., nausea) were also monitored and recorded. Psychometric assessments by the MADRS and the YMRS were administered before the first, third, fifth, and seventh infusions as well as 1 week after the last infusion. An electrocardiogram was carried out before every second infusion and 1 week after the last ketamine infusion.

A subject was defined as a responder at a given time point if the percent improvement from the baseline total MADRS score was at least 50%. The patient was defined as a remitter at a given time point if the total MADRS score was  $\leq 10$  points.<sup>14</sup> The final three groups (responders, remitters, and nonremitters) were determined by MADRS score 1 week after the last ketamine infusion.

### Statistical analysis

All analyses were conducted using IBM SPSS Statistics 25.0. To determine the differences between responders, remitters, and non-responders for sociodemographic variables and the occurrence of diseases and treatment, frequency analyses were carried out with Fisher's exact test. Due to the small sample size, non-parametric tests were used, and inequalities among groups

were analyzed for both discrete and continuous variables.

The Mann–Whitney  $U$  test was used to compare groups in terms of ordinal or quantitative variables. For analyses involving more than two groups, the Kruskal–Wallis  $H$  test was used. To determine the differences between measurements, a mixed-model analysis was used. The medium-term rate of change for each analyzed variable was calculated using chain indexes, and the harmonic average of all chain indexes was calculated. Based on the medium-term rate of change, the rate of change was calculated for each variable and for the relationships between variables. An  $\alpha$  of 0.05 was adopted as the level of significance for this analysis;  $p$  values presented in the current report reflect those obtained from a *post hoc* Bonferroni analysis.

### Results

The clinical and demographic characteristics of the study group are presented in Table 1. The mean scores and standard deviations (SD) of psychometric scales during baseline were: MADRS = 28.59 (SD = 7.28); YMRS = 1.98 (SD = 2.74); CSSRS = 4.41 (SD = 5.064). Several analyses were performed using the type of drug administered as an intergroup factor. Other than risperidone ( $F = 3.13$ ;  $df = 4.487$ ;  $p = 0.012$ ), no psychotropic medications were associated with dissociative symptomatology. The patient who was receiving risperidone showed higher intensities of dissociation. Citalopram was the only antidepressant found to be associated with psychomimetic symptomatology ( $F = 3.31$ ;  $df = 3.363$ ;  $p = 0.019$ ), with patients receiving citalopram showing higher intensities of psychomimetic symptoms. The use of classic mood stabilizers was significantly associated with an increase in psychomimetic symptomatology according to the BPRS (lamotrigine  $F = 3.65$ ;  $df = 3.683$ ;  $p = 0.009$ , valproate  $F = 2.55$ ;  $df = 3.60$ ;  $p = 0.048$ , lithium  $F = 3.50$ ;  $df = 3.66$ ;  $p = 0.012$ ) (Figures 1–4).

For the patient receiving risperidone ( $n = 1$ ), a significant increase in CADSS occurred between the fifth and seventh infusions ( $p = 0.002$ ) and between the sixth and seventh infusions ( $p < 0.001$ ). A *post hoc* analysis with a Bonferroni alpha correction was performed. The CADSS score for the measurement after the seventh infusion was significantly higher

**Table 1.** Clinical and demographic characteristics of the study group.

	<b>N</b>	<b>Responder</b>	<b>Remitter</b>	<b>Non-responder</b>	<b>p</b>	<b>V</b>
Male sex (%)	21 (42.9)	6 (66.7)	2 (25.0)	13 (40.6)	0.229	0.26
Female sex (%)	28 (57.1)	3 (33.3)	6 (75.0)	19 (59.4)		
Mean age, in years	50.02	53.11	42.88	50.94	0.336	0.00
BMI	27.92 (5.67)	28.00 (4.64)	26.50 (4.72)	28.25 (6.21)	0.613	0.02
Ketamine treatment for:						
MDD	35 (71.4)	8 (88.9)	5 (62.5)	22 (68.8)	0.475	0.19
BP	14 (28.6)	2 (11.1)	5 (37.5)	7 (31.2)	0.485	0.18
Comorbidity					0.104	0.31
1	21 (42.9)	6 (66.7)	2 (25.0)	13 (40.6)		
2	10 (20.4)	2 (22.2)	1 (12.5)	7 (21.9)		
3	4 (8.2)	1 (11.1)	2 (25.0)	1 (3.1)		
Arterial hypertension	16 (32.7)	6 (66.7)	3 (37.5)	7 (21.9)	0.037	0.37
Diabetes mellitus	3 (6.1)	1 (11.1)	2 (25.0)	0 (0)	0.021	0.39
Hyperlipidaemia	9 (18.4)	3 (33.3)	1 (12.5)	5 (15.6)	0.545	0.19
Post-stroke	3 (6.1)	1 (11.1)	0 (0)	2 (6.3)	0.731	0.14
Post-myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	–	–
Epilepsy	6 (12.2)	0 (0)	3 (37.5)	3 (9.4)	0.060	0.36
Other	16 (32.7)	2 (22.2)	1 (12.5)	13 (40.6)	0.330	0.24
Coexisting treatment						
TCA	8 (16.3)	1 (11.1)	1 (13.5)	6 (18.8)	1.000	0.09
Clomipramine	4 (8.2)	0 (0)	1 (12.5)	3 (9.4)	0.789	0.15
Amitriptyline	4 (8.2)	1 (11.1)	0 (0)	3 (9.4)	1.000	0.13
SSRI total	23 (46.9)	5 (55.6)	2 (25.0)	16 (50.0)	0.413	0.20
Fluvoxamine	1 (2.0)	0 (0)	0 (0)	1 (3.1)	1.000	0.11
Paroxetine	5 (10.2)	1 (11.1)	0 (0)	4 (12.5)	0.813	0.15
Fluoxetine	8 (16.3)	2 (22.2)	0 (0)	6 (18.8)	0.534	0.20
Sertraline	3 (6.1)	1 (11.1)	0 (0)	2 (6.3)	0.731	0.14
Citalopram	4 (8.2)	0 (0)	2 (25.0)	2 (6.3)	0.179	0.29
Escitalopram	2 (4.1)	1 (11.1)	0 (0)	1 (3.1)	0.578	0.18
SNRI total	11 (22.4)	2 (22.2)	2 (25.0)	7 (21.9)	1.000	0.03

(Continued)

**Table 1.** (Continued)

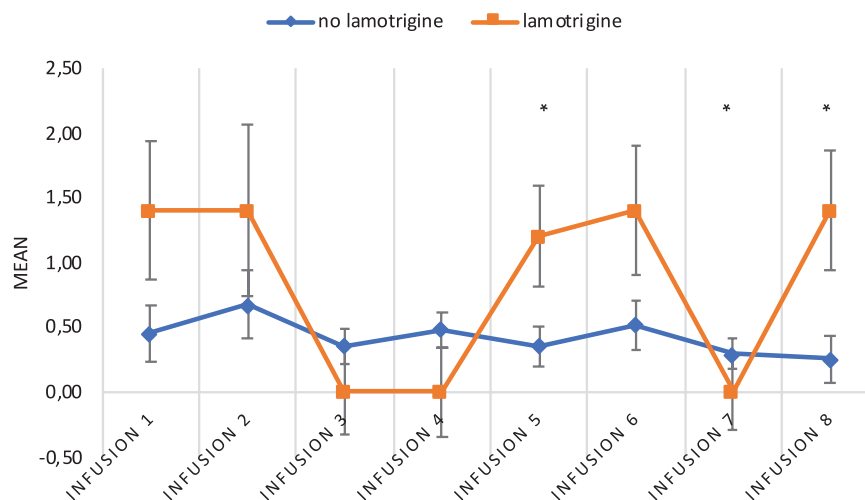
	<i>N</i>	Responder	Remitter	Non-responder	<i>p</i>	<i>V</i>
Venlafaxine	8 (16.3)	1 (11.1)	1 (12.5)	6 (18.8)	1.000	0.10
Duloxetine	3 (6.1)	1 (11.1)	1 (12.5)	1 (3.1)	0.273	0.17
Other ADTs:					0.749	0.14
1	15 (30.6)	4 (44.4)	2 (25.0)	9 (28.1)		
2	3 (6.1)	0 (0)	1 (12.5)	2 (6.3)		
Mirtazapine	9 (18.4)	2 (22.2)	1 (12.5)	6 (18.8)	1.000	0.08
Mianserin	3 (6.1)	1 (11.1)	0 (0)	2 (6.3)	0.731	0.14
Trazodone	4 (8.2)	1 (11.1)	1 (12.5)	2 (6.3)	0.432	0.10
Bupropion	3 (6.1)	0 (0)	1 (12.5)	2 (6.3)	0.488	0.15
Vortioxetine	2 (4.1)	0 (0)	1 (12.5)	1 (3.1)	0.333	0.20
Antipsychotics					0.806	0.15
1	12 (24.5)	2 (22.2)	1 (12.5)	9 (28.1)		
2	5 (10.2)	0 (0)	1 (12.5)	4 (12.5)		
Aripiprazole	6 (12.2)	0 (0)	1 (12.5)	5 (15.6)	0.685	0.18
Quetiapine	10 (20.4)	1 (11.1)	1 (12.5)	8 (25.0)	0.668	0.16
Olanzapine	5 (10.2)	1 (11.1)	1 (12.5)	3 (9.4)	1.000	0.04
Risperidone	1 (2.0)	0 (0)	0 (0)	1 (3.1)	1.000	0.11
Mood stabilizers <sup>15</sup>					0.348	0.29
1	15 (30.6)	2 (22.2)	4 (50.0)	9 (28.1)		
2	6 (12.2)	1 (11.1)	0 (0)	5 (15.6)		
3	1 (2.0)	0 (0)	1 (12.5)	0 (0)		
Lithium	5 (10.2)	0 (0)	1 (12.5)	4 (12.5)	0.643	0.16
Valproate	9 (18.4)	2 (22.2)	3 (37.5)	4 (12.5)	0.160	0.24
Lamotrigine	7 (14.3)	1 (11.1)	1 (12.5)	5 (15.6)	1.000	0.05

Standard deviation is provided in the brackets for age, BMI, ketamine treatment for, comorbidities, and coexisting treatment. ADTs, antidepressants; BMI, body mass index; BP, bipolar disorder; MDD, major depressive disorder; *N*, sample size; *p*, probability value; SNRI, selective serotonin-noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor; TCA, other tricyclic antidepressants; *V*, Cramer's *V*.

than those following the fifth and sixth infusions. Among the patients not taking risperidone ( $n = 48$ ), the CADSS score was significantly lower following the eighth infusion when compared with the second infusion ( $p = 0.007$ ). A simple effects analysis of the CADSS results showed that an effect occurred both among subject receiving risperidone  $F(7.40) = 3.84$ ;

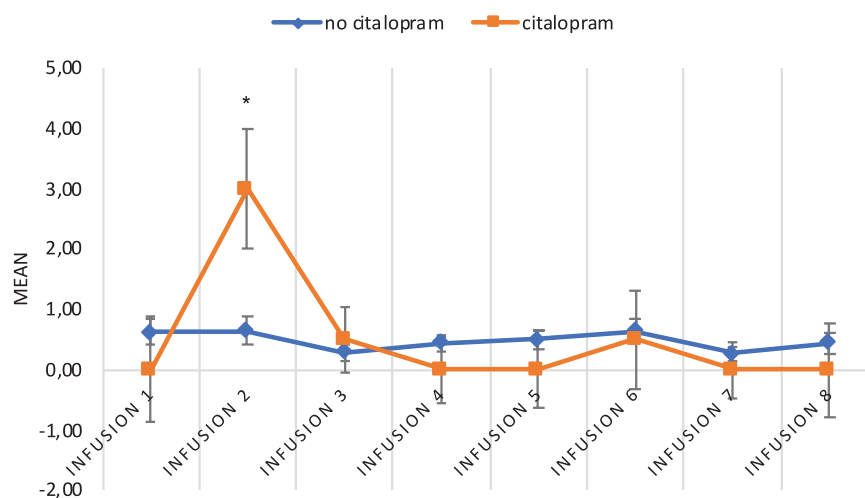
$p = 0.003$ ;  $\eta^2p = 0.40$ , and among those not receiving risperidone  $F(7.40) = 2.47$ ;  $p = 0.033$ ;  $\eta^2p = 0.30$ .

Significantly higher scores in BPRS were observed after the second infusion between patients who were taking citalopram ( $n = 4$ ) (Figure 2) and those who were not [ $n = 45$ ,  $F(1.34) = 5.41$ ;



**Figure 1.** Means and standard errors for the BPRS scores were measured after subsequent ketamine infusions in groups with and without lamotrigine coexisting treatment.

\*Significantly higher BPRS scores were observed between patients who were being treated with lamotrigine ( $n=7$ ) and those who were not ( $n=42$ ), with regards to BPRS score after the eighth infusion. A detailed analysis of the results showed that the BPRS score was higher after the fifth infusion compared with that after the seventh infusion. The differences between the remaining measurements were not significant ( $p > 0.05$ ). BPRS, Brief Psychiatric Rating Scale.



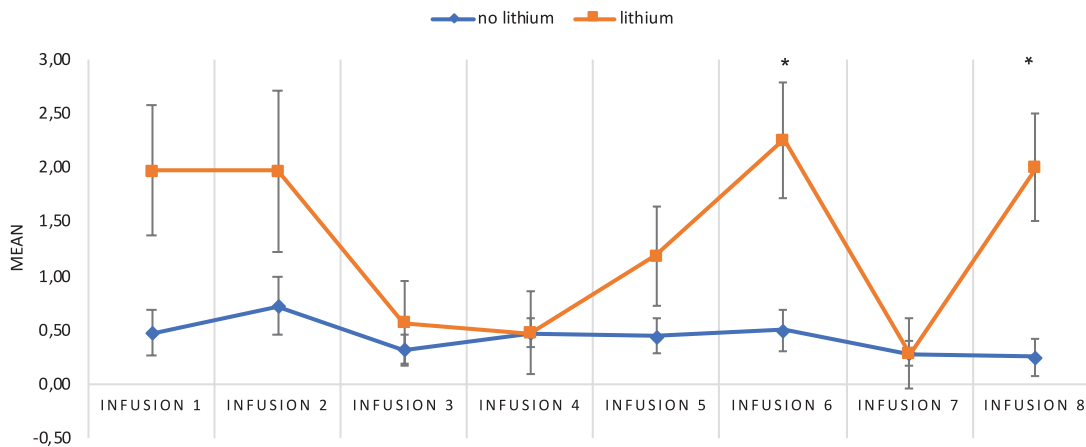
**Figure 2.** Means and standard errors for the BPRS scores were measured after subsequent ketamine infusions in groups with and without citalopram coexisting treatment.

\*Significantly higher scores in BPRS were observed, after the second infusion between patients who were taking citalopram ( $n=4$ ) and those who were not ( $n=45$ ). BPRS, Brief Psychiatric Rating Scale.

$p=0.026$ ;  $\eta^2p=0.14$ ]. For the remaining measurements, the differences between the groups were statistically non-significant ( $p > 0.05$ ). A simple effects analysis for BPRS showed that the effect for subjects not taking citalopram was non-significant,  $F(7.28) = 1.57$ ;  $p=0.187$ ;  $\eta^2p=0.28$ , while the effect for those taking citalopram was significant  $F(7.28) = 3.19$ ;  $p=0.013$ ;  $\eta^2p=0.44$ . There were significant differences between the BPRS values

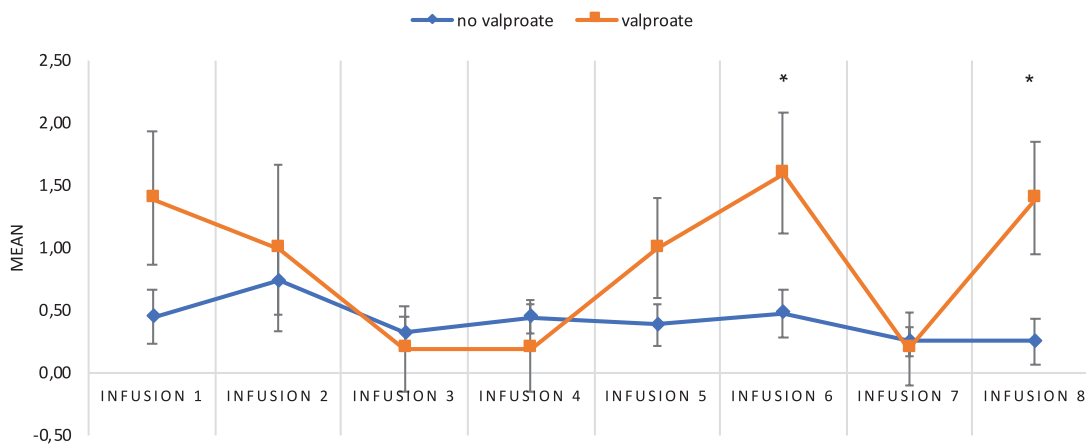
for the first and second infusions ( $p=0.002$ ), the second and fifth infusions ( $p=0.020$ ), and the second and eighth infusions ( $p=0.019$ ).

There were significantly higher BPRS scores between patients being treated with lithium ( $n=5$ ) (Figure 3) and those who were not, after the sixth infusion,  $F(1.34) = 4.88$ ;  $p=0.034$ ;  $\eta^2p=0.13$ , and after the last (eighth) infusion  $F$



**Figure 3.** Means and standard errors for the BPRS scores were measured after subsequent ketamine infusions in groups with and without coexisting lithium treatment.

\*Significantly higher BPRS scores were observed between patients being treated with lithium ( $n=5$ ) and those who were not ( $n=44$ ), after the sixth infusion, and after the eighth infusion. BPRS, Brief Psychiatric Rating Scale.



**Figure 4.** Means and standard errors for the BPRS scores were measured after subsequent ketamine infusions in groups with and without valproate coexisting treatment.

\*Significantly higher BPRS scores were observed between patients being treated with valproate ( $n=9$ ) and those who were not ( $n=40$ ) following the sixth infusion, and after the eighth infusion. BPRS, Brief Psychiatric Rating Scale.

(1.34) = 8.31;  $p=0.007$ ;  $\eta^2p=0.20$ . At both measurement points, patients taking lithium showed higher BPRS scores than the patients not taking lithium ( $n=44$ ). A simple effects analysis for BPRS showed no significant differences within the group receiving lithium  $F(7.28)=1.67$ ;  $p=0.157$ ;  $\eta^2p=0.30$ , and within the group not receiving lithium  $F(7.28)=1.74$ ;  $p=0.141$ ;  $\eta^2p=0.30$ .

There were significantly higher BPRS scores between patients being treated with valproate ( $n=9$ ) (Figure 4) and those who were not ( $n=40$ ), following the sixth infusion,  $F(1.34)=4.68$ ;

$p=0.038$ ;  $\eta^2p=0.12$ , and after the eighth infusion,  $F(1.34)=5.43$ ;  $p=0.026$ ;  $\eta^2p=0.14$ . For both measurement points, subjects taking valproate showed higher BPRS scores than those not taking valproate. A simple effects analysis for BPRS showed no significant differences within the group receiving valproate,  $F(7.28)=1.36$ ;  $p=0.259$ ;  $\eta^2p=0.26$ , and within the group not receiving valproate  $F(7.28)=1.41$ ;  $p=0.240$ ;  $\eta^2p=0.26$ .

There were significantly higher BPRS scores between patients who were being treated with lamotrigine ( $n=7$ ) (Figure 1) and those who were



**Table 2.** CADSS scores comparison before and after the ketamine infusions.

	CADSS before		CADSS after (the infusion)		Z	p	r
	M (SD)	Me (IQR)	M (SD)	Me (IQR)			
Infusion 1	0.18 (0.49)	0 (0)	13.63 (9.14)	14 (13)	-5.97	<0.001	-0.85
Infusion 2	0.35 (1.48)	0 (0)	14.90 (11.92)	13 (15.5)	-5.97	<0.001	-0.85
Infusion 3	0.55 (2.41)	0 (0)	11.43 (13.14)	8 (12)	-5.42	<0.001	-0.77
Infusion 4	0.27 (1.30)	0 (0)	11.94 (11.58)	10 (12.5)	-5.72	<0.001	-0.82
Infusion 5	0.22 (0.77)	0 (0)	10.63 (8.04)	9 (10.5)	-5.65	<0.001	-0.81
Infusion 6	0.36 (1.58)	0 (0)	10.15 (8.80)	9.5 (13.5)	-4.70	<0.001	-0.82
Infusion 7	0.22 (1.16)	0 (0)	9.53 (10.27)	6 (15)	-5.31	<0.001	-0.76
Infusion 8	0.24 (1.16)	0 (0)	8.16 (9.04)	5 (10)	-5.38	<0.001	-0.77
Pre-post	0.45 (1.72)	0 (0)	0.90 (3.16)	0 (0)	-0.86	0.389	-0.12

CADSS, Clinician-Administered Dissociative States Scale; IQR, interquartile range; M, mean; Me, median; SD, standard deviation.

not ( $n=42$ ) with regards to BPRS score after the eighth infusion,  $F(1.34)=5.43$ ;  $p=0.026$ ;  $\eta^2p=0.14$ . Patients receiving lamotrigine had a higher BPRS score following the eighth infusion compared with patients who were not taking lamotrigine. A simple effects analysis for BPRS showed no significant differences for subjects not taking the drug,  $F(7.28)=1.68$ ;  $p=0.155$ ;  $\eta^2p=0.30$ , while the differences in the group receiving lamotrigine was significant;  $F(7.28)=2.83$ ;  $p=0.023$ ;  $\eta^2p=0.42$ . A detailed analysis of the results showed that the BPRS score was higher after the fifth infusion compared with that after the seventh infusion ( $p=0.003$ ). The differences between the remaining measurements were not significant ( $p>0.05$ ).

For all subjects, both the BPRS and the CADSS scores dropped to asymptomatic levels within 1 h of each infusion. No significant associations were observed within the bipolar/depressive groups regarding psychomimetic or dissociative symptoms according to MADRS scores (the BPRS and CADSS scores by treatment groups are presented as Supplemental Material in Figures S5 and S6).

To show the tolerability and severity of the dissociation, Table 2 presents a comparison between CADSS scores before and after infusions. The post ketamine effects were observed without sequelae.

## Discussion

The current literature suggests that central nervous system (CNS) side effects related to intravenous infusion of ketamine occur relatively frequently.<sup>1,16-22</sup> However, drug discontinuation is not required prior to ketamine infusion, and intravenous ketamine appears to usually be well-tolerated as an add-on to other psychotropic medications in TRD. Data from previous randomized clinical trials involving ketamine/esketamine in small-to-moderate samples of TRD patients indicate that the safety and tolerability of ketamine are generally good.<sup>1,17,18,23,24</sup> The current study suggests that the safety and tolerability of ketamine may be negatively affected when it is administered as an add-on to certain other psychopharmacological treatments.

Our results suggest that the dissociative- and psychomimetic-related side effects of ketamine might be associated with concomitant medication type in addition to diagnosis. In particular, our results suggest that risperidone is an outlier in ketamine treatment safety. Although our data cannot be generalized because only one patient was receiving concomitant treatment with risperidone, this patient's treatment response did differ significantly from the rest of the subjects. These results, on the other hand, do not support those reported by Schmechtig *et al.* in a study with a larger number of patients.<sup>25</sup>



In the current study, the patient receiving risperidone showed significant changes over time in dissociative symptomatology, as measured by the CADSS. No other psychotropic medications were associated with similar results. A detailed analysis of the simple effects of risperidone revealed that the patient receiving risperidone showed a significantly higher CADSS score compared with the other patients in our sample after both the seventh ( $p=0.003$ ) and eighth ( $p=0.010$ ) infusion. For the remaining measurement points, the differences between the groups were non-significant ( $p>0.05$ ). As for psychotic symptomatology, our analysis showed significant differences in BPRS over time occurring for four different concomitant antidepressant medications: citalopram, lithium, valproate, and lamotrigine. Various mechanisms within the CNS can potentially explain the emergence of psychomimetic and dissociative symptoms in response to ketamine administration. In particular, increases in psychotomimetic symptoms might be caused by an increase in dopamine neurotransmission, although this explanation is controversial.<sup>26–28</sup> As for dissociative symptomatology, there is strong evidence that dissociative symptoms arise as a result of enhanced glutamate release following ketamine infusion. Depolarization of cortical projection neurons arises from inhibition of GABAergic cortical interneurons, enhancement of long-term potentiation leading to increased glutamate signaling, and increased AMPA-to-NMDA postsynaptic receptor throughput.<sup>29,30</sup> Still, further research is needed to support the data obtained in our study.

Our results are in agreement with those of other TRD studies that have reported no association between intensity of dissociative and/or psychomimetic symptomatology and antidepressive treatment by ketamine.<sup>23,24</sup> However, other studies have reported results that support the existence of such an association.<sup>20,30</sup> To our knowledge, no study has published data on the relationship between concomitant medication type and ketamine-related adverse events in TRD. Our finding can support the development of drug combinations guidelines, especially for those groups of patients who are particularly vulnerable to CNS-related adverse effects from ketamine treatment.

The current study demonstrates an overall good safety profile with regards to dissociative and psychotic symptomatology following ketamine administration for patients receiving antipsychotics and antidepressants, as all of the negative

effects of ketamine treatment observed in the present study had abated by the end of the patient's visit, and no sequelae were observed in any patients. The patients receiving mood stabilizers appeared to be more prone to psychotic symptomatology during ketamine treatment. In particular, add-on treatment with ketamine for patients receiving concurrent citalopram should be treated with caution.

### *Strengths*

This study adds to the current body of knowledge regarding the tolerability and general safety of ketamine administration, and our results support those of several previous studies mentioned above. The current study used a diverse sample of patients that included patients with comorbidities and disparate concomitant medications. This sample is thus likely to represent the population of patients who would be the most likely to utilize ketamine treatment for TRD.

### *Limitations*

This study has several limitations. Firstly, our study may be underpowered due to the small sample size. Additionally, the research was performed at a single-site, and the observational design did not include either treatment blinding or a control group. The observations apply to treatment-resistant patients, including both unipolar and bipolar depressed patients. A further limitation of the current study is the short follow-up time. Future studies will be necessary to assess both the clinical antidepressant effects of ketamine following acute administration as well as the long-term safety associated with this treatment. Finally, CADSS scores were only assessed 30 min after each dose rather than at several time points. Thus, we were unable to establish a precise time course for either the peak of dissociative symptoms or for their resolution. Our results indicate that future studies should further investigate the role of ketamine-related CNS symptomatology in TRD. We found no papers on long-term psychotomimetic side-effects following ketamine infusion, but, in the future, it will be important to replicate this finding and confirm the lack of sequelae using a longer-term study design in a larger sample.

As the data is limited with regard to the study population presented, small groups, and single-cases, the results shall be interpreted with caution, as a preliminary report in the field.

## Conclusion

In patients with TRD, intravenous ketamine appears to produce clinically relevant and measurable CNS-related adverse events that seem to be related to concomitant psychotropic medication type. Citalopram was observed to be associated with an increase in psychomimetic symptomatology. We also observed that TRD-BP patients receiving mood stabilizers exhibited higher rates of psychotic symptomatology (as for valproic acid, lamotrigine, and lithium). Importantly, symptom improvement following ketamine infusion does not appear to be related to either dissociative or psychomimetic symptomatology. Overall, CNS-related adverse effects were not associated with persistent neurological or cognitive sequelae. While adverse events were relatively common during ketamine therapy, most were mild or moderate in intensity and did not necessitate discontinuation of ketamine. However, somatic comorbidities may also affect dissociative symptomatology, and thus psychotic symptoms must be taken into consideration when treating TRD patients. We found that CNS-related symptoms abated within 1 h of ketamine administration. Our results suggest that ketamine is a safe and generally well-tolerated treatment for TRD.

## Conflict of interest statement

W has received research support from Actavis, Eli Lilly, Minerva Neurosciences, Sunovion Pharmaceuticals, KCR, Janssen, Otsuka, Apodemus, Cortexyme, Acadia. WJC has received research support from Actavis, Alkermes, Allergan, Auspex, Biogen, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrier, Forest Laboratories, Gedeon Richter, GW Pharmaceuticals, Janssen, KCR, Lundbeck, Orion, Otsuka, Sanofi, and Servier; he has served on speakers bureaus for Adamed, Angelini, AstraZeneca, Bristol-Myers Squibb, Celon, GlaxoSmithKline, Janssen, Krka, Lekam, Lundbeck, Novartis, Orion, Pfizer, Polfa Tarchomin, Sanofi, Servier, and Zentiva; and he has served as a consultant for GW Pharmaceuticals, Janssen, KCR, Quintiles, and Roche. MG-W has received research support from Janssen, Servier, Alkermes, KCR, Lilly, Biogen, Celon; JS has received research support from Actavis, Eli Lilly, Minerva Neurosciences, Sunovion Pharmaceuticals, KCR, Janssen, Otsuka, Apodemus, Cortexyme, Acadia.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship,

and/or publication of this article: This work was supported by the Medical University of Gdańsk, Poland [grant number ST-02-0039/07/221]. The funders had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

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## Supplemental material

Supplemental material for this article is available online.

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