





Intravenous Ketamine Infusions in Treatment-Resistant Bipolar Depression: An Open-Label Naturalistic Observational Study

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Purpose: Bipolar disorder is a chronic and recurrent condition often associated with treatment resistance and suicidality. There is an unmet need for effective treatment in this group of patients. Ketamine has been demonstrated to have antidepressant and antisuicidal properties in unipolar depression. Most of the available studies concern unipolar depression. Here, we present the efficacy and safety of IV ketamine as an add-on treatment in patients with bipolar I and bipolar II depression.

Patients and Methods: Thirteen patients with treatment-resistant bipolar depression (TRBD) received eight IV infusions of 0.5 mg/kg ketamine twice a week over four weeks. This is an open-label naturalistic observational study. Ketamine is an add-on treatment. Depressive symptoms were measured with the Montgomery–Asberg Depression Rating Scale (MADRS), and manic symptoms were measured with the Young Mania Rating Scale (YMRS). Psychomimetic symptoms were assessed with the Clinician-Administered Dissociative States Scale (CADSS) and the Brief Psychiatric Rating Scale (BPRS).

Results: The rates of response and remission after the seventh infusion of ketamine were 61.5% and 46.2%, respectively. A significant antisuicidal effect was observed in responders at the 7th infusion. Suicidality was measured with item 10 on the MADRS scale. The average time to respond was between 21.1 and 23.2 days to remission. There was an increase in the CADSS scores during the treatment compared to baseline and follow-up, but no differences between responders and non-responders were observed. No affective switch was observed according to the YMRS scale scores. Ketamine treatment was associated with a transient increase in arterial blood pressure. No serious adverse events, however, were observed.

Conclusion: This report presents the preliminary results of IV ketamine effectiveness and safety in treatment-resistant bipolar depression. The findings suggest that it is a feasible, safe and well-tolerated treatment option in this group of patients. There is a definite need for more studies in this field.

Keywords: bipolar depression, intravenous ketamine, safety, tolerability, treatment-resistant bipolar disorder

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Introduction

Bipolar disorder (BD) is a debilitating and recurrent psychiatric condition affecting more than 1% of the population. The risk of suicide in this group of patients is high.^{1,2} Bipolar depression is often treatment resistant.^{3–5} To our knowledge, there are currently 140 trials of ketamine conducted in psychiatric disorders. Most of them include MDD patients, only 0.7% include specifically bipolar patients, and



5.7% include both.⁶ Ketamine in BD is clearly understudied, although its rapid antidepressant and antisuicidal effect in MDD suggests that it could be useful in bipolar patients.^{7–11} A few studies have investigated the effect of a single infusion of ketamine as an add-on treatment in BD, with the response rate at around 50%.^{9–15} Studies involving the multiple administration of ketamine in bipolar patients, however, are scarce.^{16–19} Treatment resistance in bipolar disorder is common, although the exact prevalence is hard to assess.²⁰ Data on pharmacotherapeutic strategies in this group of patients are still insufficient. There are also little data on the efficacy, safety and tolerability of ketamine in the TRBD population.^{9,10}

This report presents the effect of repeated IV ketamine infusions on mood and suicidality in TRBD I and II patients with monitoring of manic, dissociative and psychomimetic symptoms along with somatic safety measures. The study was conducted in a real-world setting and included patients who were treated with multiple psychotropic medications.

Materials and Methods

Patients

The study population includes subjects enrolled in a naturalistic observational registry protocol for IV ketamine treatment in TRD (NCT04226963). The methodology is described in detail elsewhere.²¹ The present study comprises a population of thirteen patients with depressive episodes without psychotic features in the course of bipolar disorder. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). All participants exhibited treatment resistance for the current episode, defined as a clinically unsatisfactory response to two approved and adequate interventions for bipolar depression.²²

The study was carried out in accordance with the latest version of the Declaration of Helsinki.²³ For each participant, written informed consent was obtained after the procedures had been fully explained. The study protocol was approved by the Ethic Research Committee of the Medical University of Gdańsk (NKBBN/172/2017; 172–674/2019).

Study Design

Eight IV ketamine infusions were administered over 4 weeks as an add-on treatment. The ketamine dose was 0.5 mg/kg infused over 40 min. Safety monitoring

included the assessment of vital signs, BPRS and CADSS at baseline and 1 hour after the infusion.

The primary outcomes were the response and remission rates. Response was defined as a 50% or higher reduction in MADRS from the baseline. The criterion of remission was 10 or less points in MADRS.²⁴ The groups (remitters, responders, non-remitters) were determined at the 7th infusion. Secondary outcomes were suicidal thoughts measured by item 10 in MADRS, time to response and remission, manic symptoms measured by YMRS, psychotic symptoms and dissociative symptoms measured by CADSS and BPRS.

Statistical Analyses

The data were analyzed with the IBM SPSS Statistics package ver 25. The normality of the continuous variables was examined by the Shapiro–Wilk test. The demographic and clinical characteristics of responder and non-responder groups (defined using the MADRS score after seventh infusion) were compared using Fisher's exact test for categorical variables and an independent sample *t*-test or the Mann–Whitney *U*-test for continuous variables (an appropriate effect size for each test was provided). Kaplan–Meier survival analysis was applied to analyze the average time to response and remission. Comparisons of the MADRS total score (as this variable met the criteria for applying the parametric test) were analyzed using the ANOVA mixed model with Tukey's post hoc test. MADRS item no. 10, YMRS, BPRS and CADSS were analyzed first using Friedman's ANOVA (with Dunn's post hoc test) to assess the score change during the subsequent infusions in two groups. Next, the differences between the responders and non-responders at each assessment time point were examined using Mann–Whitney *U*-tests with correction for multiple comparisons. All the statistical tests were two-tailed and were considered to be significant at $p < 0.05$.

Results

Demographics and Concomitant Treatment

There were no significant differences in any demographic or clinical characteristics between the responder and non-responder groups. Data are presented in [Table 1](#).

Ketamine is an add-on treatment. The concomitant psychotropic medications for every included patient are presented in [Table 2](#).

Table 1 Demographic and Clinical Characteristics in the Responder and the Non-Responder Group

Variables	Total Sample (N=13)	Responders(n=8)	Non-Responders (n=5)	Difference; Effect Size
Age	49.5 (15.1)	51.3 (11.5)	46.6 (20.9)	$t=0.52$; $d=0.30$
BMI	29.0 (6.3)	28.6 (7.0)	29.6 (5.6)	$t=-0.26$; $d=0.15$
Depression duration (weeks)	24.0 (16–36)	18.5 (14–31)	26.0 (24–96)	$Z=-0.74$; $\eta^2=0.04$
Number of episodes				
Depressive	7.6 (4.0)	9.0 (4.3)	5.4 (2.3)	$t=-1.70$; $d=0.97$
Manic	2.0 (2.0)	2.5 (2.3)	1.2 (0.8)	$t=-1.18$; $d=0.68$
Hypomanic	1.0 (0.8)	1.3 (0.7)	0.8 (0.8)	$t=-1.04$; $d=0.59$
Mixed	0 (0–0)	0 (0–0)	0 (0–0)	$Z=0.07$; $\eta^2<0.01$
Baseline results (before infusion)				
MADRS	30.1 (9.0)	30.1 (10.3)	30.0 (7.7)	$t=0.02$; $d=0.01$
MADRS item no. 10	2.0 (1–4)	3.0 (0.5–5)	1.0 (1–2)	$Z=0.82$; $\eta^2=0.05$
YMRS	3.0 (1–4)	3.5 (2–6)	2.0 (0–3)	$Z=1.33$; $\eta^2=0.14$
BPRS	0 (0–0)	0 (0–1.5)	0 (0–0)	$Z=0.00$; $\eta^2<0.01$
CADSS	0 (0–0)	0 (0–0)	0 (0–0)	$Z=0.63$; $\eta^2=0.03$
Sex				
Females	10 (76.9%)	5 (62.5%)	5 (100%)	Fisher=ns; $\phi=0.43$
Males	3 (23.1%)	3 (37.5%)	0 (0%)	
Secondary	7 (7.7%)	5 (62.5%)	2 (40.0%)	Fisher=1.84; $V=0.38$
Vocational	1 (53.8%)	1 (12.5%)	0 (0%)	
Higher	5 (38.5%)	2 (25.0%)	3 (60.0%)	
Employment status				
Employed	2 (15.4%)	2 (25.0%)	0 (0%)	Fisher=1.53; $V=0.37$
Unemployed	8 (61.5%)	4 (50.0%)	4 (80.0%)	
Pension	3 (23.1%)	2 (25.0%)	1 (20.0%)	
Bipolar subtype				
I	10 (76.9%)	6 (75.0%)	4 (80.0%)	Fisher=ns; $\phi=0.06$
II	3 (23.1%)	2 (25.0%)	1 (20.0%)	
Comorbidities				
Epilepsy	4 (30.8%)	3 (37.5%)	1 (20.0%)	Fisher=ns; $\phi=0.18$
Hypertension	5 (38.5%)	4 (50.0%)	1 (20.0%)	Fisher=ns; $\phi=0.30$
Diabetes	2(15.4%)	2 (25.0%)	0 (0%)	Fisher=ns; $\phi=0.34$
Hypercholesterolemia	2(15.4%)	2 (25.0%)	0 (0%)	Fisher=ns; $\phi=0.34$
Other	5 (38.5%)	4 (50.0%)	1 (20.0%)	Fisher=ns; $\phi=0.30$
Co-existing treatment				
Mood stabilizers	10 (76.9%)	7 (87.5%)	3 (60.0%)	Fisher=ns; $\phi=0.32$
2 nd generation antipsychotics	9 (69.2%)	6 (75.0%)	3 (60.0%)	Fisher=ns; $\phi=0.16$
Antidepressants	9 (69.2%)	5 (62.5%)	4 (80.0%)	Fisher=ns; $\phi=-0.18$

Notes: For the t -test, the mean and standard deviations are given; in the case of the U -test, the median and 25%-75% quartiles are given; for Fisher's Exact Test, the number of patients and percentage are given. t – t statistics (Student's t -test for independent samples), d – Cohen's d (effect size for t -test), Z – Z statistics (Mann–Whitney U -test for independent samples), η^2 – eta-square (effect size for U -test), Fisher – Fisher's Exact Test, ns – not significant, ϕ – phi or V – Cramer's V (effect size for contingency tables).
Abbreviations: BMI, Body Mass Index; MADRS, Montgomery–Asberg Depression Rating Scale Young; YMRS, Mania Rating Scale; CADSS, Clinician-Administered Dissociative States Scale; BPRS, Brief Psychiatric Rating Scale.

Table 2 Coexisting Psychotropic Treatment

Patient No.	Mood Stabilizers			Antipsychotics		Antidepressants	Benzodiazepines
1	Valproic acid 2000mg/d			Quetiapine 500mg/d	Venlafaxine 150mg/d		
2	Valproic acid 2000mg/d			Quetiapine 400mg/d	Duloxetine 120mg/d		
3	Lithium 750mg/d				Venlafaxine 225mg/d	Mirtazapine 45mg/d	
4	Lithium 1000mg/d			Aripiprazole 15mg/d			
5	Lithium 1000mg	Lamotrigine 200mg/d	Valproic acid 1300/d				Lorazepam 2.5 mg
6	Lamotrygine 100mg/d	Pregabalin 300mg/d		Olanzapine 5mg/d	Bupropione 300mg/d	Mirtazapine 30mg/d	Lorazepam 2 mg/d
7				Quetiapine 600mg	Citalopram 30mg		Lorazepam 3mg
8	Valproic acid 1200mg/d	Lamotrigine 200mg/d					
9	Valproic acid 3000mg/d						
10	Valproic acid 2000mg/d	Lamotrigine 200mg/d		Risperidone 5mg/d	Fluoxetine 30mg/d		
11	Valproic acid 1500/d	Lamotrigine 200mg/d			Venlafaxine 300mg/d		
12	Lithium carbonicum 1250mg/d	Lamotrigine 100mg/d		Quetiapine 50mg/d			
13	Lithium 1000mg/d			Olanzapine 20mg/d	Fluoxetine 40mg/d		Lorazepam 1mg

Antidepressant and Antisuicidal Effects

The baseline average MADRS score was 30. The average number of previous depressive episodes was 7.6, and the average duration of the current episode was 24 weeks. The results of the mixed ANOVA with the within-subjects factor and the between-subjects factor showed a significant interaction effect – $F(4.44) = 3.78$, $p = 0.010$, $\eta^2p = 0.26$.

We found that in the responder group, the MADRS score after the fifth infusion ($M = 15.5$) and the seventh infusion ($M = 8.3$) was significantly lower compared to the baseline ($M = 30.1$);

Tukey's post hoc test $p = 0.001$ and $p < 0.001$, respectively) which was not observed among non-responders.

Although, in the group of responders, there was an increase in MADRS scores between the 21st day (after 7 infusion) and the final measurement (28th day of follow-up), it was not statistically significant. Moreover, the final score was still significantly lower ($M = 15.9$) than at the baseline (Tukey's post hoc test $p = 0.002$). In the group of non-responders, the scores were still decreasing ($M = 20.8$) at the end of the study, but the decrease was not significant, neither compared to the results after the seventh infusion ($M = 25.8$) nor compared to the baseline results ($M = 30.0$) (Figure 1, Table 3).

Significant differences (Tukey's post hoc test) between the two groups in MADRS scores were found only after the seventh infusion – $M = 8.3$ (for responders) vs $M = 25.8$ (for non-responders), $p = 0.023$ (Figure 1, Table 3).

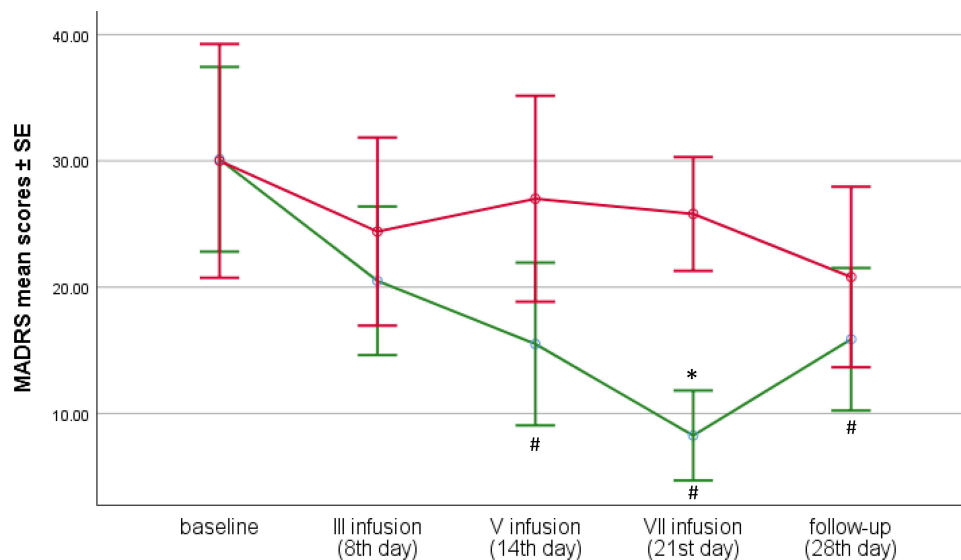


Figure 1 MADRS change after seven ketamine infusions in responders and non-responders. # indicates significant difference at a given time point when compared to baseline * indicates significant difference at a given time point between the responder and non-responder groups (p<0.05).

Partially similar conclusions were obtained when analyzing the results of the MADRS item no. 10. Due to the nature of the variable, non-parametric tests were used for the analysis. Friedman’s ANOVA performed in the subgroups showed that there is a significant change of the severity of suicidal thoughts during subsequent infusions - $\chi^2(4) = 13.87, p = 0.008, W = 0.27$ among the responders, but not in the non-responders group - $\chi^2(4) = 5.35, p = 0.256, W = 0.10$. In this first group of patients, the distribution of scores obtained in MADRS item no. 10 after the seventh infusion was different

and indicated a lower intensity of suicidal thoughts (Me = 0.00) than at the beginning of the study (Me = 3.00) – Dunn’s test $p = 0.006$. The other results, however, did not differ from each other. There were also no differences between the groups. The results are presented in Table 4.

Time to Response and Remission

Figure 2 presents Kaplan–Meier curves for time to response [average time: 21.1 (95% CI: 17.5 to 24.6); median time: 21.0 (95% CI: 15.0 to 27.0) days] and

Table 3 Mean Scores of MADRS at the Beginning and at the End of the Study, as Well as During Subsequent Infusions in the Total Sample and Separately Among Responders and Non-Responders (with Tukey’s Post-Hoc Tests)

Time Point	Total Sample (N=13)	Responders (n=8)	Non-Responders (n=5)	Between Group Difference – p-value; Effect Size
Baseline MADRS	30.1 (9.0)	30.1 (10.3)	30.0 (7.7)	1.000; $d=0.01$
3 rd infusion (8 th day) MADRS	22.0 (7.5)	20.5 (7.7)	24.4 (7.3)	0.998; $d=0.52$
5 th infusion (14 th day) MADRS	19.9 (9.8)	15.5 (8.3)	27.0 (8.3)	0.355; $d=1.39$
7th infusion (21st day) MADRS	15.0 (9.9)	8.3 (4.2)	25.8 (5.2)	0.023; $d=3.72$
Follow-up (28 th day) MADRS	17.8 (7.4)	15.9 (6.7)	20.8 (8.1)	0.989; $d=0.66$

Notes: The results are presented as means and standard deviations; d – Cohen’s d ; values in bold indicate statistically significant results.

Table 4 Median Scores of MADRS Item No. 10 at the Beginning and at the End of the Study, as Well as During Subsequent Infusions in the Total Sample and Separately Among Responders and Non-Responders (with U-Tests)

Time Point	Total Sample (N=13)	Responders (n=8)	Non-Responders (n=5)	Between Group Difference – p-value; Effect Size
Baseline MADRS item no. 10	2.0 (1–4)	3.0 (0.5–5)	1.0 (1–2)	0.412; $\eta^2=0.05$
3 rd infusion (8 th day) MADRS item no. 10	1.0 (0–3)	0.5 (0–2)	1.0 (0–3)	0.815; $\eta^2<0.01$
5 th infusion (14 th day) MADRS item no. 10	1.0 (0–2)	1.0 (0–2)	1.0 (1–3)	0.544; $\eta^2=0.03$
7 th infusion (21 st day) MADRS item no. 10	0 (0–1)	0 (0–0.5)	0 (0–2)	0.528; $\eta^2=0.03$
Follow-up (28 th day) MADRS item no. 10	1.0 (0–2)	1.0 (0–2)	2.0 (0–2)	0.820; $\eta^2<0.01$

remission [average time: 23.2 (95% CI: 19.9 to 26.6)]; neither the median time nor 95% CI for median time was reached. The rates of response and remission (after the seventh infusion) were 61.5% and 46.2%, respectively.

Cardiovascular Safety

Cardiovascular safety measures revealed a mild and temporary increase in the systolic and diastolic blood pressure, which returned to baseline values mostly within 1 hour after the beginning of the infusion. No significant changes

were observed in body temperature, the breath count and blood saturation. We did not observe any serious adverse events associated with ketamine treatment and the most common side effects were dizziness, nausea, headache and insomnia. Dissociation was most commonly observed after the first and the second infusion and the intensity of symptoms decreased during subsequent infusions. BPRS scores mildly increased during the infusions and returned to normal after treatment. We observed a decrease in YMRS scores after the 5th infusion mainly due to

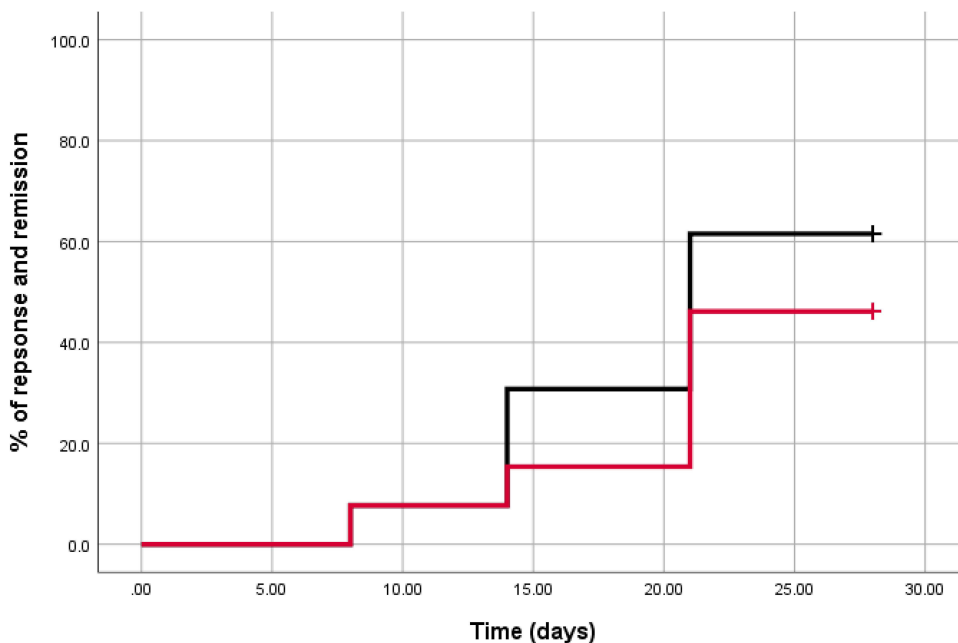


Figure 2 Kaplan–Meier curves for time to response and remission among bipolar patients. Black line indicates response, red line indicates remission.

a decrease in irritability and sleep disturbances in the responders group. No patient exhibited psychosis, new onset of suicidality or an affective switch.

Discussion

The results of this study indicate safety, efficacy and a good tolerability profile of ketamine in bipolar I and bipolar II depression. This study replicates recent findings on the antidepressive and antisuicidal effect of repeated IV ketamine infusions in TRBD. The rates of response and remission (after the seventh infusion) were 61.5% and 46.2%, respectively. Compared to Zheng¹⁸ (73, 63%), the effect of ketamine in this study was not as good, but the population in our study was older (49.5 vs 35.8) and the average number of depressive episodes was 7.6.¹⁸ Most patients in Zheng's study had no history of psychiatric hospitalization although the number of previous episodes is not reported. According to studies, the history of previous hospitalizations is negatively associated with the response to ketamine.^{25,26} The number of prior episodes is also positively associated with lower response rates.^{26,27} There are also studies suggesting lower response rates in older patients, although the number of studies in this population is very scarce.²⁸

Similarly to other studies, we observed an increase in response and remission rates with subsequent infusions.^{18,29} Nevertheless, the average time to response and remission were longer (21 and 23 days) compared to Zheng (9 and 12 days).¹⁸ It is possible that older patients with a severe course of bipolar disorder need more time to improve after ketamine treatment and possibly need more infusions. Ketamine improves neuroplasticity, synaptogenesis and BDNF levels.^{30,31} Studies have shown that low levels of BDNF are associated with an increased severity of bipolar episodes,^{32,33} and although the exact mechanism of the BDNF effect in bipolar disorder still needs to be elucidated, it is possible that these changes need more time to emerge in patients with a more severe course of the disease.

As in Zheng et al¹⁸ study, we also observed an increase in the MADRS score at follow-up (1 week after treatment). Although not statistically significant, this observation is in line with other reports.^{34,35} In line with other studies, we observed an antisuicidal effect reflected by a decrease in the score of item 10 in MADRS. This effect is described in a meta-analysis of single-infusion studies of MDD.³⁶ Recent studies on repeated doses of IV ketamine in MDD and BP also

confirmed its antisuicidal effect.^{17,18} A recent open-label clinical trial that administered six intravenous doses of 0.5mg/kg ketamine three times a week in patients with unipolar and bipolar depression reported a significant reduction in suicidal ideation – 24 h after the first infusion in 57% of patients and in 65% after the sixth infusion.³⁷ Some authors suggest that this effect is independent of the total depression symptom severity,^{38,39} but we did not observe this in our study.

Bipolar depression is a condition often requiring the use of a combinations of drugs. This should also be considered when analysing the ketamine response. Some evidence suggests that medications inducing cytochrome 450 CYP (2D6 and 3A4) may reduce the effect of ketamine and the inhibitors may increase the exposure to ketamine. Considering that most antipsychotics and antidepressants inhibit CYP 2D6, it can have a significant effect although this is unclear due to a lack of evidence. Genetic variations of CYP 2D6 may also influence the pharmacokinetics of ketamine.⁴⁰ There are some data on the lower antidepressant effect of ketamine in combination with benzodiazepines.^{41,42} One study has shown that lamotrigine, which inhibits glutamatergic signalling, may reduce the side effects of ketamine, but it is not known if it also reduces the antidepressant effect.⁴³

Particularly interesting in the context of bipolar disorder is the combination of ketamine and lithium. Both drugs share the mechanism of glycogen synthase kinase-3 (GSK-3) inhibition, which leads to the disinhibition of BDNF synthesis, long-term neuroplasticity and possibly mood stabilization.⁴⁴ Ketamine and lithium activate the mechanistic target of rapamycin (mTOR) and BDNF-tyrosine kinase receptor B (TrkB). As suggested by one animal study, lithium can maintain the restoration of spine density induced by a single injection of ketamine, and as a consequence, increase the antidepressant-like effects of ketamine in mice.⁴⁵ In summary, there is an unquestionable need for more studies in this field, and the mentioned interactions are mostly speculative. Another significant matter concerns the possibility of developing adverse events in the course of ketamine/esketamine/arketamine treatment with coexisting medications like mood stabilizers, antipsychotics, benzodiazepines and somatic medications, which were reported in a post-marketing pharmacovigilance records analysis of intranasal esketamine.⁴⁶ This can also be true for other enantiomers and the fact that we did not observe any significant side

effects may be due to the small number of patients studied.

In correspondence with other studies, we did not observe any serious adverse events. Cardiovascular and psychomimetic side effects were mild, attenuated by subsequent infusions and did not cause treatment discontinuation.^{18,47–49} We also did not observe treatment for emergent psychiatric conditions like psychosis or mania. This observation confirms that ketamine treatment is safe in bipolar disorder patients with comorbidities.

Although the risk of an affective switch in available studies seems low, manic symptoms should be monitored in bipolar patients treated with ketamine, especially those treated with antidepressants.⁵⁰ In this study, no affective switch was observed, although more studies on larger groups of bipolar patients are needed to confirm this observation.

Limitations

The main limitation is the small sample size. The open-label design limits the interpretation of ketamine's effect. The observations apply to treatment-resistant patients with bipolar depression. It must be emphasized that the results apply to short-term treatment, and although the observation replicates published studies, further long-term trials are needed in order to demonstrate the efficacy of the intervention. The relatively short duration of the study may affect the response rates and tolerability measures. Ketamine serum concentrations were not evaluated. The efficacy, safety and tolerability profile cannot be generalized to real-world settings until RCTs with large sample sizes of bipolar patients are conducted. No standardized adverse reaction form was used.

Conclusion

Intravenous ketamine appears to be effective, safe and well tolerated in the short-term treatment of resistant patients with bipolar depression. Older patients with a severe course of the disease possibly need more time to respond. This is a preliminary study, and there is a need to conduct large, randomized, controlled trials of ketamine in bipolar disorder.

Acknowledgments

This paper was granted by the Medical University of Gdańsk, Poland (Grant No. ST-02-0039/07/221).

Disclosure

Dr Alina Wilkowska reports grants from Medical University of Gdańsk, during the conduct of the study and has received research support from Angelini, Biogen, Eli Lilly and Company, Janssen-Cilag, Lundbeck, Polpharma, Sanofi and Valeant. Dr Adam Włodarczyk has received research support from Actavis, Eli Lilly, Minerva Neurosciences, Sunovion Pharmaceuticals, KCR, Janssen, Otsuka, Apodemus, Cortexyme, and Acadia. Dr Maria Gałuszko-Węgielnik has received research support from Janssen, Servier, Alkermes, KCR, Lilly, Biogen, and Celon. Dr Mariusz S Wiglusz has received research support from Acadia, Apodemus, Alkermes, Auspex Pharmaceuticals, Cephalon, Ferrier, Forest Laboratories, Gedeon Richter, GWPharmaceuticals, Janssen, Lundbeck, Orion, Otsuka, Servier, Speakers Bureau: Lundbeck, Servier. Prof. Wiesław J Cubała has received research support from Acadia, Actavis, Alkermes, Allergan, Angelini, Auspex, Biogen, Bristol-Myers Squibb, Cephalon, Cortexyme, Eli Lilly, Ferrier, Forest Laboratories, Gedeon Richter, GW Pharmaceuticals, Janssen, KCR, Lundbeck, Minerva, NeuroCo, NIH, 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. The authors report no other conflicts of interest in this work.

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