

Ketamine treatment safety in treatment-resistant depression with somatic comorbidities: focus on dissociation and psychotic symptomatology.

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Abstract

Background and objectives: There is evidence for ketamine use in treatment-resistant depression (TRD). Several safety concerns arise regarding adverse drug reactions and specific subpopulations. The aim of this paper is to investigate the safety of intravenous ketamine treatment concerning dissociative and psychotic measures in TRD inpatients with Major Depressive Disorder (MDD) and Bipolar depression (BP) with somatic comorbidities.

Methods: The study population of forty-nine inpatients comprises of MDD and BP subjects treated with ketamine registered in the naturalistic observational protocol of the tertiary reference unit for mood disorders (NCT04226963). This dataset represents an intermittent analysis of an observational study performed for interim modelling of observational learning. The study may be underpowered due to the small sample size. The observations apply to the inhomogeneous TRD population in a single-site with no blinding and are limited to the acute administration.

Results: The epilepsy was significantly associated with changes in BPRS over time ($p=0.008$). Psychotic symptomatology with BPRS scores for comorbid somatic conditions excluding epilepsy turned out to be insignificant ($p = 0.198$) regardless of the diagnosis. However, for a subgroup of patients with epilepsy substantial fluctuation was seen across all administrations in the time course of the study.

Conclusions: In ketamine use, careful consideration of comorbidities and concomitant medication is needed. In ketamine administration, close-clinical supervision is necessary at every visit. Psychotic symptoms must be taken into consideration in planning treatment with TRD patients with epilepsy. Somatic comorbidity may impact dissociative symptomatology.

Trial Registration: Study registered: 04DEC2019, clinicaltrials.com no. NCT04226963
<https://clinicaltrials.gov/ct2/show/NCT04226963>

Background

Recent developments in rapid-acting antidepressants use in treatment-resistant depression (TRD) provide robust evidence for ketamine use in Major Depressive Disorder (MDD) and Bipolar Disorder type I (BP) providing an option for rapid remission of symptoms with several concerns on safety and tolerability of the drug {1}.

One of the major issues is the risk of adverse events associated with dissociative symptomatology {2}. There is some evidence for dissociative symptoms as the predictor of response in treatment-resistant depression (TRD) (both TRD-MDD and TRD-BP), however, it is limited to very few papers {3}, but even more studies including our own shows that there is no relationship between dissociative symptomatology and depression outcome. Overall, little is known on the course of the dissociative symptomatology in regards to ketamine use in affective disorders {4}. Dissociative states involve symptoms of gaps in memory, out of body experiences and depersonalization, derealization, and identity disturbance {5}. This

phenomenon is associated with ketamine administration. Dissociative symptoms cause a wide spectrum of phenomena, however per methodological guidance Clinician-Administered Dissociative States Scale (CADSS) and Brief Psychiatric Rating Scale (BPRS) positive symptoms subscale (BRPS+) are used to represent the overall intensity of the dissociative and potential treatment-emergent psychotic symptomatology {2-4, 6-10}.

Little data is available on ketamine use in TRD patients with somatic comorbidities {11}. In line with the measures of depression symptomatology, psychometric safety measures are used to assess dissociation and psychotic phenomena.

This study aims to assess safety of intravenous ketamine in course of eight administrations in inpatients with TRD presenting somatic comorbidities. There are many features of the disease that affect ease and difficulty in controlling depression and impact control strategies. A characteristic associated with by far the highest risk of poor outcome compared to others (patient, treatment, or disease) is the absence of complete remission and the presence of residual symptoms after appropriate treatment. This emphasizes the importance of trying to alleviate the symptoms of depression, if possible {12}.

Methods

The sample selection methods for this study have been described in detail elsewhere {13, 14}. Briefly, the study population comprises of subjects enrolled in a naturalistic safety and efficacy registry protocol for ketamine infusions in TRD. Inpatients diagnosed with a depressive episode in the course of major depression, recurrent depression, or bipolar affective disorder were involved. Patients were interviewed by a clinician psychiatrist to establish the diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria determined using a Mini International Neuropsychiatric Interview (MINI). All participants met the criteria for TRD, defined as an inadequate response to 2 or more antidepressants of different categories (assessed by Massachusetts General Hospital Antidepressant Treatment Response Questionnaire - ATRQ) in course of treatment of that particular episode. Bipolar TRD was defined as a clinically unsatisfactory response following at least two trials of dissimilar medicinal treatments in adequate doses and durations, within a specific phase of bipolar illness {15}. The study followed the rule single-patient and single-rater (the same patient was examined by the same clinician in all of the scales). During the screening patients were rated by the clinician using Montgomery–Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Columbia–Suicide Severity Rating Scale (C-SSRS), The Clinician-Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS) scales. Safety monitoring was performed by the attending psychiatrist before, during, and post-infusion every 15 minutes up to an hour and a half post-infusion. It included periodic assessment of vital signs (heart rate, body temperature, respiratory rate, blood pressure, oxygen saturation) and mental status examination, including assessment of BPRS and CADSS for the presence of respectively psychotic and dissociative symptoms. In order to demonstrate CADSS and BPRS fluctuations across treatment, CADSS and BPRS scores taken 30 minutes post drug administration were analysed.

Only medically stable, able to communicate and provide consent, adult inpatients aged 18-90 were enrolled to study. Some patients were significantly affected by somatic illness, however, all of the patients continued current medication during ketamine treatment without any changes to the substance and/or dosage. The detailed description of antiepileptic medication in patients with epilepsy is presented in Additional File 1. The exclusion criteria included a history of uncontrolled medical conditions, a previous adverse reaction to ketamine, active substance use, pregnancy, or breastfeeding. Somatic comorbidities were defined by the patient's self-reported medical history with corroborated full-passed medical records. Somatic comorbidities relevant to this study group population were: arterial hypertension, diabetes mellitus, hyperlipidaemia, post-stroke patients, and patients with epilepsy (Table 1).

This dataset represents the intermittent analysis of an observational study performed for the interim modelling of observational learning. The analyses are set per predefined and equally spaced annual increments for a study duration of 24 months with a population of 120 TRD subjects estimated for inclusion. The study was carried out in accordance with the latest version of the Declaration of Helsinki. For each participant, written consent was obtained after the procedures had been fully explained. The study recruitment procedures were approved by the Ethic Research Committee of the Institution. The study population comprises MDD and BP subjects treated with ketamine registered in the naturalistic observational protocol of the tertiary reference unit for mood disorders (NCT04226963).

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 ≤ 10 points {16}. The final three groups (responders, remitters, and nonremitters) were determined by MADRS score one week after the last ketamine infusion.

Table 1. Demographic and clinical variables.

		<i>N</i>	Responder	Remitter	Non-Responder	<i>p</i>	<i>V</i>
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
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
	BP	4 (8.2)	1 (11.1)	2 (25.0)	1 (3.1)	0.052	0.66
	MDD	12 (24.5)	5 (55.6)	1 (12.5)	6 (18.8)	0.177	0.33
	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
	SSRIs	23 (46.9)	5 (55.6)	2 (25.0)	16 (50.0)	0.413	0.20
	SNRIs	11 (22.4)	2 (22.2)	2 (25.0)	7 (21.9)	1.000	0.03
	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)		
	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)		
Mood stabilizers						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)		

N, sample size; *p*, probability value; V, Cramer's V; MDD, major depressive disorder; BP, bipolar disorder; TCA, other tricyclic antidepressant; SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective serotonin-noradrenaline reuptake inhibitors; ADTs, antidepressants.

Study design: Ketamine infusions

All patients continued baseline antidepressants, as well as treatment of chronic somatic diseases during ketamine infusions. This study used an observational design with the administration of eight ketamine intravenous infusions over 4 weeks in TRD subjects. Ketamine was dosed at 0.5 mg/kg based on the patient's actual body weight and infused intravenously over 40 min. Any significant adverse effect (e.g. nausea) was also monitored, either by safety measurements including vital signs or per safety observation by clinical investigators. The ECG was carried out before every second infusion and one week after the last ketamine infusion. One week after the last infusion laboratory tests, ECG, all mentioned scales were performed.

Statistical analysis

The analyses were conducted using statistical software the 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 analyzes were carried out with Fisher's exact test. To determine the differences between measurements, mixed models analysis was used. Analysis of quantitative variables was carried out by the Kruskal-Wallis test.

The medium-term rate of change of the analyzed variables was calculated using chain indexes - the harmonic average of all chain indexes was calculated. Based on the medium-term rate of change, the rate of change was calculated for a given variable and the relationships between the dynamics of change between variables were determined. $\alpha=0.05$ 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

Sociodemographic characteristics are displayed in Table 1. Out of 49 patients included in our study, 21 of them had somatic comorbidities. All of the patients were medically stable, including those significantly

affected by somatic illness continued current medication during ketamine treatment. A given type of somatic disease was set for the analyses performed as an inter-object factor. The detailed results of the analyses are presented in Table 2 and Table 3.

A post hoc, longitudinal analysis showed that the post-dose CADSS and BPRS total score declined over time.

Table 2.

CADSS scores and somatic comorbidities

comorbidities	<i>F</i>	<i>df</i>	<i>p</i>	η^2_p
comorbidity	1.09	13.556	0.368	0.07
arterial hypertension	0.73	4.408	0.583	0.02
diabetes	0.64	4.439	0.650	0.01
hyperlipidemia	2.35	4.583	0.047	0.05
post-stroke	0.90	4.360	0.471	0.02
epilepsy	1.66	4.426	0.155	0.04
other	0.60	4.517	0.685	0.01

Table 3.

BPRS scores and somatic comorbidities

comorbidities	<i>F</i>	<i>df</i>	<i>p</i>	η^2_p
Comorbidity	0,99	9,937	0,460	0,09
arterial hypertension	0,83	3,439	0,495	0,02
diabetes	1,27	3,434	0,288	0,04
hyperlipidemia	0,33	3,464	0,834	0,01
post-stroke	0,87	3,392	0,471	0,03
epilepsy	7,37	3,96	<0,001	0,18
other	0,61	3,439	0,629	0,02

Epilepsy was the only diagnosis significantly associated with changes in BPRS over time. The main effect for BPRS turned out to be significant, $F(3.959) = 8.53$; $p < 0.001$; $\eta^2_p = 0.20$, similar to the interaction. After considering the Bonferroni correction, simple effects for BPRS for people without epilepsy turned out to be insignificant, $F(7.28) = 1.53$; $p = 0.198$; $\eta^2_p = 0.28$, while significant for people with epilepsy, $F(7.28) = 3.54$; $p = 0.008$; $\eta^2_p = 0.47$. In patients with epilepsy, significant effects occurred for measurements after the infusion of 1, 6, and 8, with higher results obtained for patients with epilepsy.

The main effect for CADSS over time turned out to be significant for the diagnosis of hyperlipidemia, $F(4.583) = 5.04$; $p < 0.001$; $\eta^2p = 0.10$, similar to interaction. After the Bonferroni correction, simple effects for CADSS for people without hyperlipidemia turned out to be insignificant, $F(7.40) = 1.89$; $p = 0.097$; $\eta^2p = 0.25$ as in case of hyperlipidemia diagnosis, $F(7.40) = 1.92$; $p = 0.092$; $\eta^2p = 0.25$.

Discussion

The research demonstrates that CNS side effects related to ketamine intravenous infusions occur relatively frequently, especially with some comorbidities with ketamine as add-on treatment. However, they do not require drug discontinuation and overall intravenous ketamine appears to be well-tolerated as an add-on to current psychotropic medication in TRD.

In patients with epilepsy, significant effects occurred for measurements after the infusion of 1, 6, and 8, with higher results obtained for patients with epilepsy. In each case, both BPRS and CADSS values dropped to zero within 1 hour from the infusion.

Although modern antidepressants (Selective Serotonin Reuptake Inhibitors, Serotonin Noradrenaline Reuptake Inhibitors, noradrenergic and specific serotonergic antidepressants) are thought to be safe to use in epilepsy, 'there is very limited evidence demonstrating a significant effect of antidepressants on depressive symptoms in epilepsy {17, 18} and no data about TRD-MDD treatment in this population. Ketamine has both pro and anti-convulsive properties, however, apart from some sparse data published not long after the FDA registration of Ketalar, there are no controlled human studies of the effect of ketamine in epilepsy in anesthetic or subanesthetic dose {19}. Moreover, recently ketamine has been successfully used in the treatment of *status epilepticus*, and it has been suggested it has some neuroprotective properties {20}. As a result, we currently don't know what effect could we expect regarding its efficacy in controlling seizures and depression. No data exist on long-term repeated use of ketamine in patients with epilepsy.

The occurrence of various psychiatric disorders in people with epilepsy is high, with psychoses affecting 2–9% of patients {21}. In another cross-sectional study by Klaudee et al. (2019) {22} on Thai population, from a total of 170 patients with epilepsy 43 (25.3%) fulfilled diagnostic criteria for one or more psychiatric disorders where psychotic disorders were 8.2%. Other study found that apart from comorbid mood and anxiety disorders, patients with comorbid epilepsy with the interictal dysphoric disorder were also more likely to suffer from psychotic disorder {23}.

The symptomatology of mood disorders in epilepsy is often atypical, pleomorphic, and fails to fulfill DSM diagnostic criteria, thus the treatment of mood disorders in epilepsy often requires a non-standard, individual approach {23}. Clinical characteristics of TRD-BP being itself multidimensional and multifaceted so it may be hypothesized that higher scores in psychotic features in course of TRD-BP are not associated with psychotropic intervention but rather with clinical characteristics of both diseases (BP and epilepsy together).

There is a need for novel approaches for both TRD-MDD and TRD-BP in people with somatic comorbidities, as they are under-investigated, as most studies focus on healthy participants {24, 25}, i.e. depression is the most frequent comorbid psychiatric disorder in epilepsy {26}. Ketamine is known for its psychomimetic-adverse event potential {2, 27}. However, there is a safety concern regarding treatment with ketamine with comorbidities, while also little is known as for NMDA antagonists for refractory seizures, outcomes were poorly documented in the majority of the studies {28}. Overall, our study is in line with esketamine trials {24, 25, 29, 30}, as it shows to produce no harm with esketamine treatment and all of the patients experienced any persistent dissociative or psychotic symptoms during the follow-up visit. Interestingly, we have found in the literature that irreversible changes reported in rat brain, called 'Olney's lesions', developed after ketamine infusion. However, the human brain metabolism is different from rat brain metabolism, therefore such changes may not appear in human brain tissue {31}. There is also evidence that short-term exposure of GABAergic neurons to high doses of ketamine led to a significant loss of differentiated cells in one study, and noncell-death-inducing concentrations of ketamine (10 µg/ml) may still establish long-term transformation of dendritic arbor in differentiated neurons. The study by Vutskits et al. {32, 33} also demonstrated persistent (>24 h) administration of ketamine at concentrations as low as 0.01 µg/ml can interfere with the maintenance of dendritic arbor architecture. These results raise the possibility that persistent exposure to subanesthetic doses of ketamine, could still damage neuronal maintenance and development, without affecting cell survival. Further studies are needed to explore that matter, not only due to psychomimetic symptomatology present more frequently in people with epilepsy, but also for the possible long-range side-effect of possible ketamine treatment.

The presented study provides significant information that in ketamine use, careful consideration of comorbidities and concomitant medication is needed, while ketamine administration close-clinical supervision is necessary at every visit. Somatic comorbidity may impact dissociative symptomatology, and psychotic symptoms, in particular, must be taken into consideration in planning treatment with TRD patients with epilepsy.

Limitation

The methodological strength of our study was to strengthen the point that the tolerability and general safety of the administration of the drug and that result being in support with some previous ketamine studies mentioned above.

However, the study may be underpowered with regard to the small sample size. The research was performed as a single-site study, there was no treatment blinding, during this observational protocol study. The observations apply to treatment-resistant patients and include both, unipolar and bipolar depressed patients. Some concerns remain in terms of establishing an effective protocol to maintain the clinical antidepressant effect of ketamine seen with acute administration while managing long-term safety. The CADSS has limitations as a tool to measure the acute effects of ketamine infusions {34}. Also, was that no CADSS assessment was obtained only once post-dose (30 minutes post-dose) without a few measurements time points, so we could not establish the precise time course of either the peak

dissociative symptoms or of their resolution (thus, relying on the esketamine/ketamine literature, it may be expected that these side effects would have resolved by the 2-hour time point, but the data acquired here do not allow that interval. The findings provide support for further consideration of ketamine-related CNS symptomatology into the relevance of these stated in the treatment outcome. With no long-term psychotomimetic side-effects reported it is important to replicate the finding in a larger sample in the long-term safety study design to demonstrate no sequelae.

Conclusion

The study results demonstrate good safety and tolerability profile of CNS adverse drug reactions with short-term treatment with intravenous ketamine as an add-on intervention to current standard-of-care psychotropic medication in TRD-MDD and TRD-BP inpatients with somatic comorbidities. Although somatic comorbidity may impact dissociative symptomatology, psychotic symptoms must be taken into consideration in planning treatment with TRD patients with epilepsy.

We advise careful consideration of comorbidities and concomitant medication is needed, as well as in ketamine administration close-clinical supervision is necessary at every visit.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Independent Ethics Committee of the Medical University of Gdansk NKBBN/172/2017; 172-674/2019, NCT04226963. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication

N/A

Availability of data and material

All datasets generated for this study are included in the article/supplementary material.

Competing interests

Dr. Adam Włodarczyk has received research support from Actavis, Eli Lilly, Minerva Neurosciences, Sunovion Pharmaceuticals, KCR, Janssen, Otsuka, Apodemus, Cortexyme, Acadia.

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Authors' contributions

Włodarczyk A – manage literature search and analysis, wrote the first draft of the manuscript

Cubała WJ – designed the study and wrote the protocol, manage literature searches and analyses.

Gałuszko-Węgielnik M – designed the study, wrote the protocol.

Wiglusz MS – manage literature searches and analyses

All authors contributed to and have approved the final manuscript.

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