Ketamine treatment safety and tolerability 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 and tolerability concerns arise regarding adverse drug reactions and specific subpopulations. The aim of this paper is to investigate the relationship between dissociative and psychometric measures in course of intravenous ketamine treatment in TRD inpatients with Major Depressive Disorder and Bipolar depression.

Methods: The study population of 49 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). The study may be underpowered due to the small sample size. The observations apply to 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 the diagnosis.

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 {1–4}.

One of the major issues is the risk of adverse events associated with dissociative symptomatology {5}. 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 {2}, 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 of ketamine use in affective disorders {4}. Dissociative symptoms cause wide spectrum of phenomena, however per methodological guidance the Clinician Administered Dissociative States Scale (CADSS) and (Brief Psychiatric Rating Scale) BRPS + are used. That may represent the overall intensity of the dissociative symptomatology {1–5}.

Little data is available on ketamine use in TRD patients with somatic comorbidities {6}.

The aim of this paper is to investigate the safety and tolerability of Central Nervous System (CNS) in relationship between dissociative measures and psychometric outcomes in course of intravenous ketamine treatment with comorbidities in treatment refractory inpatients with MDD and BP.

Methods

The study population comprises of subjects enrolled in a naturalistic safety and efficacy registry protocol for ketamine infusions in TRD. Inpatients diagnosed with depressive episode in the course of major depression, recurrent depression or bipolar affective disorder were involved. Patients were interviewed by clinician psychiatrist to establish the diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria determined using a Mini International Neuropsychiatric Interview (MINI). All participants met criteria for TRD, defined as inadequate response to 2 or more antidepressants (assessed by Massachusetts General Hospital Antidepressant Treatment Response Questionnaire - ATRQ) in course of treatment of that particular episode. Bipolar TRD was defined as clinically unsatisfactory response following at least two trials of dissimilar medicinal treatments in adequate doses and durations, within a specific phase of bipolar illness {7}. Study followed the rule single-patient and single- rater. 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.

Only medically stable, able to communicate and provide consent, adult inpatients aged 18–90 were enrolled to study. Some patients significantly affected by somatic illness continued current medication during ketamine treatment. The exclusion criteria included a history of uncontrolled medical conditions, a previous adverse reaction to ketamine, active substance use, pregnancy or breastfeeding.

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 Reasearch Committee of the Institution. The study population comprises of MDD and BP subjects treated with ketamine registered in the naturalistic observational protocol of the tertiary reference unit for mood disorders (NCT04226963).

(Table 1. Demographic and clinical variables)

Table 1. Demographic and clinical variables.

		N	responder	remitter	non-responder	p	V
Male, sex	(%)	21 (42.9)	6 (66.7)	2 (25.0)	13 (40.6)	0.229	0.26
age, in years		50.02 (13.83)	53.11 (7.06)	42.88 (15.78)	50.94 (14.51)	0.336 ¹	0.00
ketamine treatment for:							
	MDD ¹	35 (71.4)	8 (88.9)	5 (62.5)	22 (68.8)	0.475	0.19
	BP ² subtype						
	BP I	12 (24.5)	1 (11.1)	3 (37.5)	8 (25.0)	0.485	0.18
	BP II	4 (8.2)	1 (11.1)	2 (25.0)	1 (3.1)	0.070	0.29
comorbidities						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
	hyperlipidemia	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 infarct	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 ³		8 (16.3)	1 (11.1)	1 (13.5)	6 (18.8)	1.000	0.09
SSRI ⁴		23 (46.9)	5 (55.6)	2 (25.0)	16 (50.0)	0.413	0.20
SNRI ⁵		11 (22.4)	2 (22.2)	2 (25.0)	7 (21.9)	1.000	0.03
Other ADTs ⁶ :						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)		
Antipsychotic medication						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 ⁶						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)		

¹ MDD – major depressive disorder

² BP – bipolar disorder

³ TCA – other than mentioned tricyclic antidepressants

⁴ SSRI – selective serotonin reuptake inhibitors

⁵ SNRI – selective serotonin-noradrenaline reuptake inhibitors

⁶ADTs – antidepressant medication

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

Study Design: Ketamine Infusions

All patients continued baseline antidepressants, as well as treatment of chronic somatic diseases during ketamine infusions. The study therapeutic intervention was based on the administration of 8 ketamine infusions over 4 weeks. Ketamine was dosed at 0.5 mg/kg based on the patient's actual body weight and infused intravenous over 40 min. Safety monitoring was performed by the attending psychiatrist before, during and post-infusion every 15 minutes up to 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. Any other significant adverse effect (e.g. nausea) was also monitored. The ECG was carried out before every second infusion and one week after last ketamine infusion. One week after 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 for 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 the purposes of this 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, 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 interobject factor. The detailed results of the analyses are presented in Table 2.

(Table 2. CADSS scores and somatic comorbidities)

Epilepsy was the only diagnosis significantly associated with changes in BPRS over time. The main effect for BPRS turned out to be significant, $F(3.959) = 8.53$; $p < 0.001$; $\eta^2p = 0.20$, similar to the interaction. After considering the Bonferroni correction, simple effects for BPRS for people without epilepsy turned out to be insignificant, $F(7.28) = 1.53$; $p = 0.198$; $\eta^2p = 0.28$, while significant for people with epilepsy, $F(7.28) = 3.54$; $p = 0.008$; $\eta^2p = 0.47$. 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 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 {8,9} 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 effect of ketamine in epilepsy in anesthetic or subanesthetic dose {10}. Moreover, recently ketamine has been successfully used in treatment of *status epilepticus*, and it has been suggested it has some neuroprotective properties {11}. 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 {12}. In another cross-sectional study by Klaudee et al. (2019) {13} on Thai population, from 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 interictal dysphoric disorder were also more likely to suffer from psychotic disorder {14}.

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 {14}. 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 is 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 {15,16}, i.e. depression is the most frequent comorbid psychiatric disorder in epilepsy {17}. Ketamine is known for its psychomimetic-adverse event potential {5,18}. However, there are safety concerns 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 {19}. Overall, our study is in line with esketamine trials {15,16,20,21}, as it shown to produce no harm with esketamine treatment and all of the patients experienced any persistent dissociative or psychotic symptoms during follow-up visit. Interestingly, we have found in 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 {22}. There is also an 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. {23,24} 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 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, it is possible that the study is underpowered with regards to the small sample size. The research was performed as 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 depression 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. 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, we expect 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 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 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 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 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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