SHORT COMMUNICATION

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Copper and Impulsivity in Ketamine Treatment for Treatment-Resistant Mood Disorders

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ABSTRACT

Treatment-resistant mood disorders, including both major depressive disorder (MDD) and bipolar disorder (BD), are challenging to treat, as limited interventions exist. Ketamine exhibits an antidepressive effect in treatment-resistant depression. Abnormal copper levels might be associated with symptoms of depression. Impulsivity is related to measures of depression, both in MDD and in BD. The aim of this paper is to explore the associations between blood copper levels and impulsivity in patients who are treatment-resistant, in the course of treatment-resistant mood disorders. The paper does not support evidence for the link between copper concentrations and impulsivity outcomes in the course of short-term ketamine treatment.

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INTRODUCTION

Depression is a debilitating disorder impacting the general population. Although effective treatment strategies are known, their efficacy in treatment-resistant mood disorders is limited. As approximately one-third of depressed patients fail to achieve remission with the standard of care (SOC) approach, new antidepressive agents have been developed.[1-3] Ketamine exhibits an antidepressive effect in treatment-resistant mood disorders, with the main mechanism of action being attributed to N-methyl-D-aspartate receptor (NMDAR) antagonism.[4] An animal study revealed that prior exposure to ketamine deep-anesthesia affects inhibitory control, as ketamine-exposed animals maintained a subnormal impulsive rate in the initial periods of the delay.[5]

Copper deficiency appears to be associated with increased anxiety in depression, as well as in problems with attention. This copper-related symptomatology is closely associated with imbalanced monoaminergic function and alterations in γ-amino butyric acid (GABA)-mediated neurotransmission.[6] Copper is essential for brain development, cellular respiration, and neurotransmitter synthesis, with copper deficiency being observed in cognitive impairment and motor function.[7-9] However, excessive copper is also associated with cognitive impairment and impulsivity as well as neuropsychiatric presentation.[10] The neurobehavioral deficits in copper metabolism issues are accompanied by the inappropriate metabolism of monoamines[11] and impaired GABAergic function through blockade of GABA receptor binding.[12] Moreover, patients with Wilson's disease have very high levels of copper in the liver and brain, but serum copper is deficient.[13]

Abnormal serum copper level might be associated with symptoms of depression,[14] as it is involved in various aspects of the biochemical mechanisms of both depressive symptomatology and the antidepressant mechanisms of action, including ketamine.[15,16] Animal study results indicate that copper loading in divalent metal transporter-1 (DMT1) deficit can induce oxidative stress and impair GABA metabolism, promoting impulsivity-like behavior.[17] The results of a small study on male children with attention deficit hyperactivity disorder (ADHD) suggest that plasma copper and ceruloplasmin levels may have an effect on event-related potentials in ADHD, indicating the impact on information processing. It has also been suggested that copper levels may have a negative effect on neural sound coding, and that ceruloplasmin levels may have a positive effect on cognitive control, conflict monitoring, and stimulus discrimination in children with ADHD.[18]

Impulsivity, as measured by the Barratt Impulsiveness Scale (BIS-11), is related to measures of depression, both in major depressive disorder (MDD) and in bipolar disorder (BD). It is related differentially to measures of depression and mania, as non-planning impulsivity correlates with depression scores and may be regarded as a marker of functional remission.[19] Impulsivity in depressed patients

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Table 1. Demographic and Clinical Characteristics of the Study Population

	N	Responder	Remitter	Non-responder	*P*	*V*
Male, (%)	21 (42.9)	6 (66.7)	2 (25.0)	13 (40.6)	.229	0.26
Female, (%)	28 (57.1)	3 (33.3)	6 (75.0)	19 (59.4)		
Age, in years, (%)	50.02 (13.83)	53.11 (7.06)	42.88 (15.78)	50.94 (14.51)	.336	0.00
Ketamine treatment for:						
MDD (%)	35 (71.4)	8 (88.9)	5 (62.5)	22 (68.8)	.475	0.19
BP (%)	14 (28.6)	2 (11.1)	5 (37.5)	7 (31.2)	.485	0.18

could be a result of co-existing manic pole symptoms and anxious distress.[20] Impulsivity could also be a component of the depressive state itself. The BIS-11 scores correlated most strongly with hopelessness and anhedonia, rather than subjective depression.[19] Impulsivity in nonbipolar subjects with major depressive episodes is characterized as increased attentional, behavioral, and non-planning impulsivity.[21] On the other hand, impulsivity could be described as a trait, affecting maladaptive coping strategies and impairing decision-making skills, connected with affective disorders, impulse control, and substance use disorder.[22]

The aim of this paper is to explore the associations of blood serum copper levels and impulsivity scored by BIS-11 in patients with treatment-resistant mood disorders.

METHODS

The abbreviated demographic and clinical characteristics of the study population are shown in Table 1. The study population included subjects enrolled in a naturalistic observational registry protocol for ketamine intravenous infusions in treatment-resistant mood disorders (NCT04226963), that have been previously described in detail elsewhere.[23,24] Briefly, inpatients diagnosed with depressive episodes in the course of MDD or BD were included. The diagnosis was established by a clinical psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria with the Mini International Neuropsychiatric Interview (MINI). All participants exhibited treatment resistance for the current depressive episode. In the screening period, the BIS-11 scores were collected. The rule of single-patient and single-rater was followed during the study. Only medically stable subjects were enrolled in the study. Ketamine was administered along with SOC psychotropic medication.

The BIS-11 is the gold standard that has shaped current impulse control theories and played a key role in the study of impulsivity and its biological, psychological, and behavioral correlates.[25]

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study protocol was approved by the Independent Ethics Committee of the Medical Univerity of Gdańsk (NKBBN/172/2017; 172-674/2019). All the study participants gave written informed consent to participate.

MAIN POINTS

- Ketamine exhibits an antidepressive effect in treatment-resistant depression.Abnormal copper levels might be associated with symptoms of depression.
- Impulsivity is related to measures of depression, both in major depressive disorder (MDD) and in bipolar disorder (BD).
- The aim of this paper is to explore the associations between blood copper levels and impulsivity in patients who are treatment-resistant, in the course of treatment-resistant mood disorders.
- The paper does not support evidence for a link between copper concentrations and impulsivity outcomes in the course of short-term ketamine treatment.

STUDY DESIGN

The study followed an observational design. All patients continued baseline psychotropic SOC, as well as necessary treatment of chronic somatic diseases during ketamine infusions. The therapeutic intervention was based on the administration of 8 ketamine intravenous infusions over 4 weeks. Ketamine was dosed at 0.5 mg/kg based on the patient's actual body weight, and infused intravenously over 40 minutes.

Safety was monitored by the attending psychiatrist before, during, and post-infusion, at every 15-minute interval for up to an hour-and-a-half post-infusion, including a periodic assessment of vital signs (heart rate, body temperature, respiratory rate, blood pressure, and oxygen saturation). The BIS-11 scores were reported before the first, third, fifth, and seventh infusion, and 1 week after the last infusion.

The electrocardiogram (ECG), copper and magnesium level assessments were carried out weekly, before every second infusion, and 1 week after the last ketamine infusion. Serum copper concentrations were determined by the direct colorimetric measurement method using a commercially available 2-reagent 6K93-30 MULTIGENT Copper kit (SENTINEL CH. SpA, Italy), with a detection limit of 3 μg/dL (0.47 μmol/L). The blood was sampled for heparin and immediately centrifuged at 4000 rpm, with the serum transferred and sent for assay.

Table 2. Spearman Correlations Between the Medium-Term Rate of Changes in Serum Copper Concentration and BIS-11 Scoring, Including Attention, Motor, and Non-Planning Subscales of BIS-11

	Cu	
	r_s	*P*
BIS-11	0.014	.936
Attention	−0.035	.838
Motor	−0.068	.695
Non-planning	−0.110	.522

Statistical Analysis

The Shapiro–Wilk test was used to assess normal distribution of continuous data. Normally distributed variables were compared using the Student's *t*-test, and all other continuous data were compared with nonparametric Mann–Whitney *U*-test. The Spearman rank correlation coefficient was used to assess correlations between the obtained variables. All tests were 2-tailed, with an alpha = 0.05. Statistical analyses were done with the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

In post hoc analysis, no correlation between copper levels and BIS-11 scores, including global score as well as the subscores, was found (Table 2).

DISCUSSION

This study results demonstrate no correlation between serum copper concentration and impulsivity, as measured by BIS-11, in treatment-resistant individuals with mood disorders who were treated with intravenous ketamine as add-on treatment.

Although human data are limited, the observational studies did not indicate copper levels fluctuations in course of short-term, intravenous ketamine treatment.[23] The animal model points out the link between copper deficiency and impulsive-like behavior.[17] Ketamine exposure also affected inhibitory control in rats.[5]

Studies on copper levels in MDD subjects produce inhomogeneous results.[26-28] It can be noted that in Wilson's disease—an inherited metabolic disorder related to disturbances of copper metabolism—higher impulsiveness occurs as one of the first psychiatric manifestations.[29] To the best of our knowledge, there have been no studies focusing on the relationship between copper ions and impulsivity in depression.

Copper remains an important microelement in catecholamine metabolism, functioning of the NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), GABA, kainate and glycine receptors, synaptogenesis, neurogenesis, cognitive functions, antioxidant processes, and regulation of the immunological system.[30-33] Moreover, NMDA-independent action of ketamine has been identified in animal studies, as ketamine-induced pairing of $G_{\alpha s}$ and adenylyl cyclase. Through this mechanism, increased intracellular cyclic adenosine monophosphate (cAMP), which affected the phosphorylation of cAMP response element-binding protein (CREB), which in turn increased brain-derived neurotrophic factor (BDNF) expression, was observed.[34]

This study hypothesized that, based on the exploratory finding between copper levels with impulsivity in the course of ketamine treatment in treatment-resistant mood disorders, copper ions might affect the global impulsiveness and its subscores, with the expectation of negative correlation between copper levels and the psychometric score.[26] However, no such observation was found in post hoc analysis. It may be hypothesized, that on the contrary to monoaminergic antidepressants, ketamine's mode of action may not address impulsiveness as a measure of remission of treatment-resistant mood disorders where divalent ion dysregulation takes place, resulting in immune, monoaminergic, and endocrine imbalance.

Limitation

Several potential limitations of the study should be noted. Randomization to an inactive placebo comparator, separation by diagnosis, measurements of ketamine and its metabolites in the blood, measurement of copper levels in central spinal fluid (CSF), and measurement for ceruloplasmin serum levels were all absent in this study. Finally, multiple confounding factors (e.g., nutritional status, the limit of detection, etc.) could have influenced our results.

CONCLUSION

The present study does not support the hypothesis of a significant correlation between copper concentration and impulsiveness scoring in ketamine intravenous add-on treatment in patients with treatment-resistant mood disorders.

Ethics Committee Approval: Ethical committee aproval was received from the Independent Ethics Committee of the institution (NKBBN/172/2017; 172-674/2019).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

Authors' Contribution: Design – J.S., W.J.C., M.G.W.; Literature Review – A.S., N.G.; Writing – J.S.; Language Correction – M.G.W.

Conflict of Interest: Jakub Słupski has received research support from Actavis, Eli Lilly, Minerva, Sunovion, Celon. Wieslaw Jerzy Cubała has received research support from Actavis, Alkermes, Allergan, Angelini, Auspex, Biogen, Bristol-Myers Squibb, Celon, 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 Celon, GW Pharmaceuticals, Janssen, KCR, Quintiles, and Roche.

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