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Effectiveness of ketamine in depressed patients resistant to ECT or rTMS therapy

Paweł Gosek[1], Magdalena Chojnacka[1], Przemysław Bieńkowski[2], Łukasz Święcicki[1]

Department of Affective Disorders, II Psychiatric Clinic IPiN, Warsaw
Head of the Department: prof. dr hab. n. med. T. Parnowski
[2] Department of Nervous System Pharmacology and Physiology IPiN, Warsaw
Head of the Department: prof. dr hab. n. med. P. Bieńkowski

Summary

Objectives. In the last decade several authors described a robust and clinically relevant alleviation of depressive symptoms after infusions of the uncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist - ketamine. In the majority of published reports ketamine was administrated to patients with depression resistant to pharmacotherapy, but not to ECT. We present a series of 5 subjects suffering from multimodal treatment-resistant depression (including ECT or rTMS and various medications) treated with intravenous infusions of ketamine in a subanesthetic dose of 0.5 mg/kg in the naturalistic setting. To the best of our knowledge it is the first report on ketamine infusion in patient resistant to antidepressants and rTMS

Methods. Two subjects have been diagnosed with MDD, one with BD, two with severe depressive episode. The efficacy and possible adverse events were monitored using psychometric scales. Basic life parameters and ECG were observed.

Results. Ketamine's infusions showed transient antidepressant efficacy. Improvement rate in our group was significant lower than in previously reported. Ketamine was generally well tolerated. We noted transient BP variations and appearance of mild and transient dissociative symptoms. Low early response rate may be correlated with resistance to previous multimodal treatment, high rate of somatization and anxiety comorbidity or heterogeneity of our group.

Conclusions. Our findings do not support the use of ketamine infusions as the monotherapy in the subgroup of patients with multimodal treatment resistant depression.

Key words: depression, treatment, ketamine

Introduction

Treatment-resistant depression (TRD) affects up to 20% of depressed patients and is suggested to be the main factor of the social and economic burden of depression worldwide, rather then severity of major depression [1-3]. The operational criteria of TRD in the research studies varies, from failure to respond to one standard antidepressant trials, through failure of multiple antidepressant classes and augmentation strategies to failure to ECT. Currently, there are no universally accepted definition of TRD [4].

In line with the glutamatergic hypothesis of depression (reviewed in Psychiatria Polska by Permoda-Osip and Rybakowski, 2011; Gosek et al, 2012 and Pilc et al, 2013 in Biological Psychiatry) [5-8] several authors have proposed ketamine as a therapeutic option for treament-resistant depression [9-11]. Although mechanisms of anttidepressive action of glutaminergic modulators remains not investigated enough [25, 26], in most studies, ketamine showed a rapid and relatively short-lasting antidepressant effects in treatment-resistant depression [6, 12, 13, 15, 19] defined as a failure to respond to at least one standard antidepressant trial [12, 13], two antidepressant trials [14], „current or past" resistance to two antidepressant trials [6, 15]. In some studies, TRD criteria were unclear or not reported (reviewed by aan het Rot et al., 2012) [18]. To the best of our knowledge, efficacy of ketamine in depression resistant to antidepressants and ECT was analyzed in one study (Ibrahim et al., 2011) [6]. The authors have reported a minor and short-lasting antidepressant effect of a single ketamine infusion. Follow-up of ketamine effectiveness was restricted to 3.83 h postinfusion. Given the above, real-life clinical efficacy and safety of ketamine infusions in ECT-resistant depression remains unclear.

In the present report, we show five cases of patients resistant to multiple therapeutics and ECT (or to multiple therapeutics and rTMS) treated with one to three ketamine infusions. In contrast to the report of Ibrahim et al. [6] (2011), the patients were formally assessed up to 48 h post-infusion with the aid of MADRS, BDI and CADSS [20-22] and clinical observations were prolonged to 7 days post-infusion.

Method

The subjects (aged: 26–60, mean 45,4) were admitted to the Department of Affective Disorders because of an insufficient or lack of improvement in the current depressive episode lasting from 5 to 48 months (mean: 28,0). All of the subjects fulfill ICD-10 criteria for episode of depression and all suffered from TRD (defined as two or more failed antidepressant trials in the current episode, with adequate dosage and length, including one with tricyclic antidepressant and ECT or rTMS in one patient). Subjects were detailed informed about procedure, received and signed written informed consent. The study was performed as an therapeutic medical experiment (off-label use of ketamine) and bioethics committee of the Institute of Psychiatry and Neurology was informed about the procedure.

Ketamine infusions (0.5 mg/kg, i.v. over 40 minutes) were performed in the presence of an anesthesiologist with continuous ECG and basic life parameters monitoring as described by Berman et al. (2000) [16]. Number of infusions was based on clinical judgment of tolerance and effectiveness with respect to patients preferences, and the therapeutic manner of the trial. Symptoms of depression were monitored using Beck Depression Inventory (Beck, 1974) and Montgomery Assberg Depression Rating Scale (Montgomery, Asberg, 1979) 2 hours before the infusion, after 120 minutes, after 24 and 48 hours. Reduction of 50% or more on MADRS 120 minutes postifusion was consider as a rapid response and reduction of 50% or more on MADRS 24 hours postinfusion was considered as the early response on ketamine treatment. Side effects were monitored and Clinician-Administered Dissociative States Scale (CADSS, Bremner 1998) 2 hours before infusion, during and up to 20 minutes after infusion. In Table 1 – *next page*, effectiveness and tolerance of ketamine infusions is summarized.

Table 1. **Effectiveness and safety of ketamine infusions.**

Infusion No	MADRS 2h before infusion	MADRS 120 minutes postinfusion	MADRS after 24h	MADRS after 48h	BDI 2h before infusion	BDI after 24h	CADSS 2h before infusion	CADSS during infusion	CADSS 20 minutes after infusion
Case 1									
1	38	27	39	37	23	43	3	12	3
Case 2									
1	28	25	27	27	29	25	7	11	17
2	26	18	22	26	24	22	2	22	7
3	30	21	25	26	29	26	0	16	1
Case 3									
1	24	18	18	20	17	13	3	12	7
Case 4									
1	20	20	20	20	19	17	1	0	2
Case 5									
1	26	15	23	25	26	20	1	8	1
2	25	24	26	26	22	22	1	2	1

MADRS – Montgomery Assberg Depression Rating Scale, BDI –- Beck Depression Inventory, CADSS – Clinician-Administered Dissociative States Scale.

Case 1

A 51-year-old female patient, CR, admitted to our clinic with symptoms of treatment-resistant episode of depression (MDE) lasting for over 48 months. The patient among others complained on sadness, feelings of guilt, worthlessness, loss of interests and memory disturbance. On admission CR was in a deeply decreased mood and demonstrated a distinct psychomotor retardation. A coexisting breast cancer. Before the admission she was treated among others with fluoxetine, fluvoxamine + reboxetine, venlafaxine, mirtazapine + trimipramine + quetiapine. ECT treatment caused a mild but transient improvement. After the application of ketamine rapid but mild symptomal improvement observed, what was absent following day and patient herself reported worsening of the symptoms. During the procedure mild dissociative symptoms was observed (see Table 1 for details) and mild formal thought disorders were noted by a treating psychiatrists. During following 7-days follow up period clinical relevant improvement was not observed. Due to a lack of long-lasting response treatment was discontinued. Subsequently CR was qualified to a repeated ECT treatment.

Case 2

A 26-year-old male MK, diagnosed with major depressive disorder (MDD) and personality cluster C disorder, was referred to our department with symptoms of apathy, decreased mood, loss of interests, anxiousness, suicidal ideations and deep psychomotor

retardation. Patient had been in psychiatric treatment for over 8 years. Current episode has been lasting for over 2 years and several treatment options (including antidepressants: paroxetine, sertraline, venlafaxine, mirtazapine, agomelatine; mood stabilizers: valproate; neuroleptics: olanzapine and aripiprazole; psychotherapy, and full course of repetitive Transcranial Magnetic Stimulation twice a week for 4 weeks) haven't provided any persistent improvement. Due to a coexistent atypical malformation in the periventricular area of the brain ECT treatment was contraindicated. Clinically significant short-lasting improvement (120 minutes postinfusions) was observed after all three infusions (Table 1), but not after 24h, as well as during following week after last procedure. During the first ketamine infusion MK reported mild dissociative symptoms in the form of derealisation. We observed discrete formal thought disorders in the form of an incoherent and distractible speech and temporary loss of goal. During the following infusions MK reported similar mild dissociative symptoms, but thought disturbance was not observed. During first three infusions the patient's condition didn't improve as expected, and the treatment was discontinued. Subsequently MK received bupropion with fluoxetine and depressive symptoms partial improved.

Case 3

EK, a 54-year-old female patient diagnosed with MDD, was admitted with symptoms of depression with significant features of somatization. Current episode started two years before admission, EK was treated in an outpatient setting with escitalopram, vanlafaxine, mianserin, clomipramine in turn, together with lithium, carbamazepine and amisulpride without any significant improvement. She was hospitalized twice since recurrence, and during the second admission ECT treatment was performed, without any significant improvement. After single ketamine infusion we observed mild improvement, but criteria for rapid or early response had not been fulfill. During the ketamine infusion we observed mild dissociative symptoms and mild paresthesia, restricted to 2 hours postinfusion. The patient refused to continue infusions. Repeated ECT and clomipramine treatment resulted in a stable remission.

Case 4

BD, a 36-year-old female diagnosed with MDE, in the psychiatric treatment for 20 months because of depressive symptoms with a severe pain in the chest, limbs and lumbar area. The patient was carefully diagnosed by several departments to exclude any severe somatic condition and referred to our department with the diagnosis of depression and stubborn psychogenic pain syndrome. Before the admission DB was treated with antidepressants (including: duloxetine, trazodon, mianserine, venlafaxine, amitryptyline), antipsychotics (including: quetiapine, perfenazine, aripiprazole, olanzapine) and analgesics in monotherapy and combined treatment - without relief to the pain. In our department BD received an ECT. She reported diminished anxiousness and a minimal improvement of the mood, sleep pattern and appetite, but pain didn't relieve. Ketamine infusion was proposed. The procedure was well tolerated, but there was no response after 120 minutes, 24 and 48 hours postinfusion. CGI score didn't

change in following week. Treatment was discontinued. The patient discharged to outpatient clinic with bupropion and quetiapine.

Case 5

MO, a 60-year-old female patient, in the psychiatric treatment for over 35 years, diagnosed with a bipolar depression, currently admitted with the symptoms of depression in the form of depressed mood, apathy, anxiousness, sleep and attention disturbance. The current episode started six months before the admission and the patient was treated with lamotrygine + lithium + olanzapine, lamotrygine + lithium + imipramine, lamotrygine + lithium + clomipramine, ECT with insufficient improvement. After first infusion short-lasting significant improvement observed, with worsening to baseline MADRS score after 48h. After the second infusions of ketamine we didn't observe any clinically significant improvement. We noticed transient dissociative symptoms during first infusion. CGI score didn't change in following week. The patient started treatment with moclobemide and after 4 weeks was discharged in stable improvement.

Discussion

Treatment-resistant depression, especially if ECT is contraindicated or ineffective, is one of the most challenging psychiatric conditions in naturalistic setting. Intravenous ketamine treatment could be consider in this group of patients as an therapeutic experiment. Level of improvement after ketamine infusions in our group was significant lower than in previously published reports. In presented group ketamine infusions showed a mild symptomatic improvement shortly after the infusion in all except one patients, but criteria for rapid response (120 minutes postinfusion) or early response (after 24 hours) was not fulfilled. We consider several potential explanations of unsatisfactory results of ketamine treatment. Lack of response could be explained with the previous resistance on multimodal therapeutic approach. All of the patients in our subgroup received ineffective TCA treatment before ketamine. Four of our patients (No. 1, 3, 4, 5) received ineffective ECT prior to ketamine infusions. It's possible that lower response rate on ECT is correlated with weaker general symptomatic improvement after infusions of katamine, which was observed by Ibrahim et al. (2011), but just up to 230 minutes postinfusion. Contrary to Ibrahim et al. [6] in our group none of the patients achieved response. Other explanation of insufficient effectiveness of ketamine infusions could be heterogeneity of our subgroup. Recently published analysis reviled superior antidepressant efficacy of ketamine in MDD patients than in BD group (aan het Rot et al., 2012) [18]. In our group patients with MDD were in minority. Interesting, in case of patient diagnosed with BD (No. 5), nevertheless lack of the clinical response after two ketamine infusion, we observed robust response on conventional antidepressant posteriorly (moclobemide added to lithium and lamotrygine). Psychic and somatic anxiety symptoms are linked to increased likelihood of non-response to antidepressants (Papakostas et al., 2008) [23]. In our group two patients (No. 3 and No. 4) demonstrated a severe somatization, one - severe and persistent psychogenic pain syndrome (No. 4). They didn't benefit from ketamine infusions. In the process of somatization a mechanism other than glutaminergic and other than involved in mood regulation brain structures can be involved, as proposed by Lemche et al. (2013) [24].

In several reports infusions of ketamine were described as well-tolerated (reviewed by aan het Rot et al., 2012) [18] and symptoms of derealisation and vegetative alternation were mild and transient. During 5 of 8 infusions we observed an elevation of CADSS score over 10. One patient described dissociative symptoms as „extremely unpleasant" and resigned from treatment. Remainders described ketamine infusions mostly as „neutral" or „unpleasant". Of the reported dissociative symptoms the most common were: feeling of unreality, sense of body changing, sense of time disturbance and confusion. Discrete formal thoughts disturbance were observed sporadically. We didn't observe any significant BP or HR variations, nor any cardiac complications in ECG tests. In none of the cases the infusion had to be stopped due to adverse events.

Our findings do not support the use of ketamine infusions as the monotherapy in the subgroup of patients with multimodal treatment resistant depression. Small size of the sample is a clear limitation of this report. Factors associated with desirable response on ketemine infusions in TRD are still unclear. Subsequent randomized, placebo controlled trials are needed to evaluate ketamine's safety, antidepressant potential, tolerance and maintenance strategy, especially in the ECT resistant depression.

Эффективность применения кетамина у пациентов с депрессией резистентной к лечению электрошоками или pTMC

Содержание

Задание. В последних годах опубликовано много описаний, относящихся к возможности получения быстрой и клинически существенного улучшения психического состояния у пациентов с диагнозом депрессии после ввдения антагонистов Н-метило-Д-аспарагиновых рецепторов (НМДА – кетамина). Большинство исследований относится к введению пациентам с резистентной к лекарствам, что однако не обозначало устойчивости к лечению электрошоками. В настоящей работе представлено 5 случаев пациентов, резистентных к различным методам биологического лечения (в том к фармакологическому, электрошоковому и pTMC), у которых в натуральных условиях применен катамин в субанестетической дозе 05 мг/кг. Согласно с опытом Авторов представлен впервые метод лечения кетамином у пациента с депрессией, резистентной к фармакологическому лечению и pTMC.

Метод. В описанной группе у двоих больных распознание депрессии с рецидивами, у одного диагностирована двухполюсная аффективная болезнь, а у двух очередных тяжелый депрессивный эпизод. Эффективность и возможные побочные явления наблюдались при использовании психометрических шкал, сходными основными жизненными параметрами, а также запись ЭКГ во время инфузий кетамина.

Результаты. В описываемой группе больных отмечено частичное улучшение психического состояния, однако эффективность лечения была существенно меньшей, нежели описываемые результаты в известных сообщениях. Отмечена хорошая переносимость, временные колебания артериального давления, а также переходящее появление незначительных диссоциативных симптомов. Недостаточно положительные результаты лечения кетамином могут быть связаны с устойчивостью к предварительно применяемым методам биологического лечения, взаимное появление симптомов фобии и соматизации, или же гетерогенность описываемой группы больных.

Выводы. Представленные результаты исследований не указывают на применение кетамина при монотерапии у пациентов с депрессией, резистентной к биологическому лечению.

Ключевые слова: депрессия, лечение, кетамин.

Wirksamkeit der Anwendung von Ketamin bei Patienten mit EKT – oder rTMS – resistenten Depression

Zusammenfassung

Ziel. In den letzten Jahren wurden viele Beschreibungen veröffentlicht, die die Möglichkeit einer schnellen und klinisch signifikanter Besserung des psychischen Befindens bei Patienten mit

der diagnostizierten Depression nach der Gabe des NMDA – Rezeptor - Antagonisten (NMDA-N-Methyl-D-Aspartat) besprechen – Ketamin. Die meisten Studien betreffen die Gabe von Ketamin für die Patienten mit der Medikamenten-resistenten Depression, was aber nicht bedeutet, dass es eine EKT – resistente Depression ist. In der vorliegenden Studie besprechen wir 5 Fälle der Patienten mit einer Depression, die gegen unterschiedliche biologische Behandlungsmethoden (darunter pharmakologische Behandlung, EKT, rTMS) resistent ist. Bei diesen Personen wurde in naturalistischen Bedingungen Ketamin in der subanesthetischen Dosis 0,5 mg/kg eingesetzt. Gemäß dem Wissensstand der Autoren dieser Arbeit ist das der erste beschriebene Fall einer Behandlung mit Ketamin beim Patienten mit der rTMS- resistenten und Medikamenten-resistenten Depression.

Methode. In der beschriebenen Gruppe wurden bei zwei Patienten rezidive Depression, bei einem affektive zweipolige Krankheit, bei zwei anderen schwere depressive Episode diagnostiziert. Die Wirksamkeit und die möglichen Nebenwirkungen wurden mittels der psychometrischen Skalen beobachtet, auch ähnlich die basalen Lebensparameter, EKG bei der Ketamin – Infusion.

Ergebnisse. In der beschriebenen Gruppe wurde eine vorübergehende Besserung des psychischen Befindens bemerkt, jedoch war die Effektivität der Behandlung signifikant niedriger als man es aus den bisherigen Meldungen schlussfolgern könnte. Es schlug an, Blutdruck schwankte vorübergehend und vorübergehend traten milde dissoziative Symptome auf. Die nicht ganz zufriedenstellenden Ergebnisse der Ketamin - Kur können mit ihrer Resistenz gegen frühere Versuche der biologischen Behandlung, Komorbidität mit Angstsymptomen und Somatisierung oder Heterogenität der beschriebenen Gruppe verbunden sein.

Schlussfolgerungen. Die besprochenen Ergebnisse sprechen nicht für die Anwendung von Ketamin in der Monotherapie in der Gruppe der Patienten mit der Depression, die gegen biologische Behandlung resistent ist.

Schlüsselwörter: Depression, Behandlung, Ketamin

L'efficacité de kétamine chez les patients avec la dépression résistant à l'ECT (électroconvulsivothérapie) ou rTMS (repetitive Transcranial Magnetic Stimulation)

Résumé

Objectif. Au cours de dernières années on a décrit plusieurs cas d'amélioration de l'état mental des patients dépressifs après l'application de kétamine –NMDA (N-methyl-D-aspartate- glutamate).

La plupart d'eux concerne les cas des patients avec la dépression résistante à la pharmacothérapie mais non à l'ECT. Ce travail présente les cas de 5 patients, résistant aux diverses méthodes thérapeutiques (pharmacothérapie, ECT, rTMS), traités de kétamine – dose 0,5 mg/kg (subanestethic dose) dans les conditions naturalistiques. D'après les auteurs ce sont les premiers cas décrits des patients résistant à la pharmacothérapie et à rTMS, traités de kétamine.

Méthode. Dans ce groupe décrit de 5 patients deux ont le diagnostic de la dépression récidivante, un – de la maladie affective bipolaire, deux autres – de l'épisode dépressif majeur. L'efficacité et les effets défavorables sont analysés avec les échelles psychométriques, les paramètres principaux de vie et ECG sont observés aussi.

Résultats. Dans ce groupe examiné on note l'amélioration transitoire de l'état mental, pourtant kétamine est moins efficace que dans les cas décrits auparavant dans la littérature en question. Elle est bien tolérée, parfois elle cause les variations transitoires de la tension artérielle et aussi les symptômes dissociatifs transitoires. Cette efficacité thérapeutique un peu bornée de kétamine peut se lier avec la résistance aux thérapies précédentes et avec la comorbidité d'anxiété, de somatisation ou avec la hétérogénéité du groupe examiné.

Conclusions. Les résultats présentés n'encouragent pas à l'usage de kétamine dans la monothérapie de la dépression résistant.

Mots clés : dépression, traitement, kétamine

References

1. Souery D, Papakostas GI, Trivedi MH. *Treatment-resistant depression*. J. Clin. Psychiatry 2006; 67(supl. 6): 16–22.

2. Fosdick L, Silberman A, Beckman M, Spivak B, Amital D. *The economic impact of depression: resistance or severity?* Eur. Neuropsychopharmacol. 2010; 20(10): 671–675.
3. Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. *Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder*. Curr. Med. Res. Opin. 2010; 26(10): 2475–2484.
4. Fornaro M, Giosuè P. *Current nosology of treatment resistant depression: a controversy resistant to revision*. Clin. Pract. Epidemiol. Ment. Health 2010; 6: 20–24.
5. Zarate CA Jr, Du J, Quiroz J, Gray NA, Denicoff KD, Singh J i wsp. *Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system*. Ann. N. Y. Acad. Sci. 2003; 1003: 273–291.
6. Machado-Vieira R, Manji HK, Zarate CA. *The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders*. Neuroscientist 2009; 15: 525–539.
7. Permoda-Osip A, Rybakowski J. Koncepcja glutaminergiczna chorób afetywnych. Psychiatr. Pol. 2011; 45(6): 875–888.
8. Gosek P, Chojnacka M, Bieńkowski P, Święcicki Ł. Zastosowanie antagonisty receptorów NMDA (N-metylo-D-asparaginianu) – ketaminy w leczeniu depresji lekoopornej. Psychiatr. Pol. 2012; 46(2): 283–294.
9. Tardito D, Perez J, Tiraboschi E, Musazzi L, Racagni G, Popoli M. *Signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms in the action of antidepressant: A critical overview*. Pharmacol. Rev. 2006; 58: 115–134.
10. Pittenger C, Duman RS. *Stress, depression, and neuroplasticity. A convergence of mechanisms*. Neuropsychopharmacol. 2008; 33: 88–109.
11. Hashimoto K. *Emerging role of glutamate in the pathophysiology of major depressive disorder*. Brain Res. Rev. 2009; 61: 105–123.
12. Skolnick P, Popik P, Trullas R. *Glutamate-based antidepressants: 20 years on*. Trends Pharmacol. Sci. 2009; 30: 563–569.
13. Pilc A, Wierońska JM, Skolnick P. *Glutamate-based antidepressants: preclinical psychopharmacology*. Biol. Psychiatry 2013; 73: 1125–1132.
14. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S i wsp. *A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression*. Arch. Gen. Psychiatry 2010; 67(8): 793–802.
15. Zarate CA, Brutsche NE, Ibrahim L, Franco-Chaves J, DiazGranados N, Cravchik A i wsp. *Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial*. Biol. Psychiatry 2012; 71: 939 –946.
16. Ibrahim L, Diazgranados N, Luckenbaugh DA, Machado-Vieira R, Baumann J, Mallinger AG i wsp. *Rapid decrease in depressive symptoms with an N-methyl-D-aspartate antagonist in ECT-resistant major depression*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2011; 35: 1155–1159.
17. Rybakowski JK, Permoda-Osip A, Skibińska M, Adamski R, Bartkowska-Śniatkowska A. *Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved?* Hum. Psychopharmacol. 2013; 28(1): 87–90.
18. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA i wsp. *A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression*. Arch. Gen. Psychiatry 2006; 63(8): 856–864.
19. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS i wsp. *Antidepressant effects of ketamine in depressed patients*. Biol. Psychiatry 2000; 47: 351–354.
20. Valentine GW, Mason GF, Gomez R, Fasula M, Watzl J, Pittman B i wsp. *The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS*. Psychiatry Res. Neuroimaging 2011; 191: 122–127.

21. aan het Rot M, Zarate CA, Charney D, Mathew SJ. *Ketamine for depression: where do we go from here*. Biol. Psychiatry 2012; 72: 537–547.
22. Beck AT, Beamesderfer A. *Assessment of depression: the depression inventory*. Mod. Probl. Pharmacopsychiatry 1974; 7: 151–169.
23. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS i wsp. *Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS)*. J. Trauma. Stress 1998; 11: 125–136.
24. Montgomery SA, Asberg M. *A new depression scale designed to be sensitive to change*. Br. J. Psychiatry 1979; 134: 382–389.
25. Papakostas GI, Fava M. *Predictors, moderators and mediators (correlates) of treatment outcome in major depressive disorder*. Dialouges Clin. Neurosci. 2008; 10(4): 439–451.
26. Lemche E, Giampietro VP, Brammer MJ, Surguladze SA, Williams SC, Phillips ML. *Somatization severity associated with postero-medial complex structures*. Sci. Rep. 2013; 3: 103.

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