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SHORT COMMUNICATION

Residual Depressive Symptoms in Treatment-Resistant Bipolar Depression Following Short-Term Ketamine Administration

Michał Pastuszak[1] · Wiesław Jerzy Cubała[1] · Aleksander Kwaśny[1]

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Abstract

Background Residual symptoms are frequently observed in a significant number of patients with depression, indicating an unmet need for effective management strategies to achieve functional recovery.

Objective This observational study aimed to evaluate the impact of ketamine infusions on depressive symptoms in patients with bipolar disorder who continued their baseline psychotropic and chronic somatic treatments.

Methods Datasets of the two consecutive real-world registries (NCT04226963 for 2019–2022; NCT05565352 from 2023 onward) for the tertiary reference center for psychiatry at the Medical University of Gdańsk (Poland) for the safety and tolerability of ketamine use in mood and anxiety disorders were retrospectively analyzed. Depressive symptoms were assessed using the Inventory of Depressive Symptomatology Self-Report 30 (IDS-SR30). Residual symptoms were identified in patients who achieved a treatment response, defined as a 50% or greater reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline to the seventh infusion.

Results Overall, 14 out of 22 patients met the criteria for response. The most commonly persistent depressive symptoms included sad mood (85.7%), view of my future (78.6%), difficulty falling asleep, and leaden paralysis/physical energy (both 71.4%), with the most severe being difficulty falling asleep (64.3%) and sad mood (42.9%).

Conclusions This observational post hoc analysis indicates that the most frequently observed residual depressive symptoms were low mood, altered view of future, sleep disturbances, and low energy levels. This study should be treated with caution as causality does not apply, however, it reports on a real-world population of subjects with treatment-resistant bipolar depression. Establishing standardized definitions for residual symptoms could enhance the quality and comparability of future research in this area.

Key Points

1. The most frequent residual symptoms were low mood, difficulty falling asleep, and low energy levels.
2. The most common symptoms of at least moderate intensity were low mood and difficulty falling asleep.
3. Establishing standardized definitions for residual symptoms could enhance the quality and comparability of future research in this area.

1 Introduction

Bipolar disorder (BD) is a chronic, lifelong condition characterized by a debilitating course. While a proportion of patients meet the formal criteria for remission, they continue to experience significant functional impairment [1, 2].

The effective management of depression presents a significant challenge, as even among those who achieve remission, a substantial proportion of patients continue to endure residual symptoms, such as persistent low mood, disrupted sleep, diminished interest, and cognitive difficulties [3]. The investigation into residual symptoms in BD is not as extensive as in major depressive disorder (MDD). Nonetheless, studies have indicated that residual symptoms impact the overall psychosocial functioning of euthymic individuals diagnosed with BD. Notably, cognitive impairment and depressive subsyndromal symptoms have garnered significant research

✉ Aleksander Kwaśny
akwasny@gumed.edu.pl

[1] Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, 80-214 Gdańsk, Poland

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attention [4]. Certain residual symptoms, including lingering mood symptoms, emotional dysregulation, sleep disturbances, sexual dysfunction, perceived stigma, and perceived cognitive impairment, substantially contribute to explaining the overall functional impairment in patients with BD in clinical remission. Residual depressive symptoms seem to affect both overall functioning and specific domains [5]. Specifically, residual depressive symptoms were strongly linked to deficiencies in interpersonal and occupational functioning [6, 7], while cognitive dysfunction was associated with impairments in cognitive and vocational performance [8].

Racemic ketamine is a prototypical rapid-acting antidepressant and its enantiomers have been utilized for nearly two decades in the treatment of both unipolar and bipolar depression, demonstrating a potent antidepressant effect [9, 10].

Current concepts for treatment outcome definition shifts to functional recovery rather than the previously used response or remission models. This approach aligns better with both acute and maintenance treatment effects, aiming for recovery to the premorbid state, which is of utmost importance to patients [11]. However, information regarding residual symptoms following ketamine treatment in patients with treatment-resistant bipolar depression (TRD-BD) is limited. Therefore, the objective of this retrospective analysis is to examine the frequency and characteristics of residual symptoms persisting after ketamine treatment in TRD-BD.

2 Methods

2.1 Participants

The methodology has been extensively detailed elsewhere [12]. In summary, this study comprised patients sourced from two compatible datasets from registries NCT04226963 (2019–2022) and NCT05565352 (from 2023 onward) conducted at the Medical University of Gdańsk (Poland). Both datasets adhered to similar observation protocols concerning safety, tolerability, and psychometric assessments. Inclusion criteria encompassed depressive episodes in BD according to DSM-5 criteria, defined as a clinically unsatisfactory response to two approved and adequate interventions for bipolar depression, following the definition by Poon et al. [13]. The study included a total of 22 participants, with 13 patients enrolled from the NCT04226963 and 9 patients sourced from the NCT05565352 registries, all of them experiencing BD without psychotic features. Both protocols received approval from the institutional review board NKBBN/172–674/2019 and NKBBN/172–447/2022 in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

2.2 Study Design

This study employed an observational design, allowing patients to continue their baseline psychotropic and chronic somatic disease (i.e., hypertension, hypercholesterolemia, diabetes among others) treatments during ketamine infusions. The therapeutic regimen consisted of eight intravenous ketamine infusions administered over a 4-week duration in conjunction with standard care practices. Ketamine dosage was adjusted to 0.5 mg/kg on the basis of the patient's actual body weight and delivered intravenously over a 40-min timeframe.

2.3 Psychometric Measures

Depressive symptoms were assessed using the Inventory of Depressive Symptomatology Self-Report 30 (IDS-SR 30), a self-report questionnaire extensively assessing diverse depressive symptoms. Participants rated each symptom's severity on a scale of 0–3, with higher scores denoting more severe symptoms [14].

Patients were deemed to have residual symptoms if they exhibited treatment response, defined as a reduction of 50% or more in the Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline up to the seventh infusion on the basis of physician's rating.

In this study, we used definition of residual symptoms as symptoms present at baseline and persisting at exit, despite global and considerable (> 50%) treatment response [15]. Following the application of this definition, 14 out of 22 patients fulfilled the response criteria.

Treatment-emergent symptoms (TES) lack a precise definition [16], therefore, we decided to use a definition of symptoms that were not present at baseline but were present at exit [15]. Such symptoms were not considered residual symptoms and were not included in analyses.

3 Results

3.1 Baseline Characteristics

Sample consisted of 14 patients, with BD type I ($n = 10$) and type II ($n = 4$). Detailed description of the sample characteristics is displayed in Table 1.

Table 1 Clinical and demographical characteristics of study population

Variables	Responder ($n = 14$)
Age	
Mean (SD)	47.79 (13.37)
Sex	
Female	11 (78.57%)
Male	3 (21.43%)
BD Type	
Bipolar disorder type I	10 (71.43%)
Bipolar disorder type II	4 (28.57%)
Current episode duration (median, weeks)	18
Number of past episodes (median)	9.5
Education	
Vocational	1 (7.14%)
Secondary	8 (57.14%)
Higher	5 (35.71%)
Employment status	
Unemployed	3 (21.43%)
Pensioner/Retired	7 (50%)
Employed	4 (28.57%)
Studying	0 (0%)
Concomitant meds	
TCA	2 (14.29%)
SSRI	4 (28.57%)
SNRI	4 (28.57%)
Other*	2 (14.29%)
Antipsychotics	9 (64.29%)
Mood stabilizers	13 (92.86%)
IDS-SR 30 total score	
Mean (SD)	40.12 (15.41)

IDS SR-30 Inventory of Depressive Symptomatology Self-Report 30 item, *BD* bipolar disorder, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitors, *SNRI*, serotonin and noradrenaline reuptake inhibitors, *TCA* tricyclic antidepressants

*Mirtazapine, mianserin, trazodone, bupropion, vortioxetine

3.2 Residual Symptoms

The most common residual depressive symptoms were "feeling sad" (85.7%), "view of my future" (78.6%), "falling asleep," and "leaden paralysis/physical energy" (both 71.4%). Other common residual symptoms that persisted in more than the half of patients (> 50%) were "sleep during the night," "feeling anxious or tense," "the quality of mood," "concentration/decision-making," "view of myself," "energy level," and "aches and pains." The prevalence of all residual symptoms is presented in Table 2.

Among residual depressive symptoms with at least moderate severity, "falling asleep" was the most often reported symptom (64.3%), followed by "feeling sad" (42.9%) and "sleep during the night," "the quality of mood," "view of my future," and "interest in sex" (all 35.7%). The division of residual symptoms between at least mild or moderate is presented in Table 3.

4 Discussion

This study reports the prevalence and characteristics of residual depressive symptoms in inpatients with TRD-BD who responded to short-term ketamine administration. The most frequent residual symptoms were low mood, difficulty falling asleep, and low energy levels. The most common symptoms of at least moderate intensity were difficulty falling asleep and low mood.

To the best of our knowledge, no studies researching residual symptoms in TRD-BD treated with ketamine were published. In a cross-sectional study of 844 patients with BD, 69% of patients had residual depressive symptoms and the most frequently observed symptom of anxiety was psychic anxiety (34%), followed by impaired insight (29%), difficulties at work and in other activities (28%), and difficulty falling asleep (22%) [17]. A retrospective analysis of electroconvulsive therapy (ECT) demonstrated that the highest rates of residual symptoms were observed in the domains of sleep disturbances and depressive mood, affecting both patients who responded to ECT and those who did not. However, a significant heterogeneity of the group with only 20% patients diagnosed with bipolar depression and results are not stratified per diagnosis [18]. In the benchmark MDD study STAR*D, responders to citalopram ($n = 428$) most commonly reported residual depressive symptoms of midnocturnal insomnia (81.6%), sad mood (70.8%), and decreased concentration and decision-making (70.6%) [14], while remitters ($n = 943$) most often reported symptoms such as weight gain (71.3%), mid-nocturnal insomnia (54.9%), increased appetite (50.6%), sleep-onset insomnia (29.5%), and sad mood (27.1%) [19]. On the contrary, it is crucial to differentiate between residual symptoms and TES. When comparing findings from the previous report on this cohort, which focused on TES, significant distinctions between these two types of symptoms are evident [20].

Longitudinal observations of patients with subsyndromal symptoms (which could equal residual symptoms using current terminology) indicate that these symptoms persist for twice as long as depressive episodes, with depressive symptoms occurring three times more frequently than manic symptoms over an 18-month follow-up period [21]. Another cohort of individuals with bipolar I and II disorders was prospectively followed for approximately 3 years to assess the duration spent in various stages of subsyndromal, minor, and major mood states. Patients were symptomatic for about

Table 2 Residual symptoms in responders

IDS-SR 30 item	Percentage with symptoms at baseline	Percentage with residual symptoms*
Falling asleep	100	71.4
Sleep during the night	92.9	57.1
Waking up too early	50	14.3
Sleeping too much	50	21.4
Feeling sad	100	85.7
Feeling irritable	50	35.7
Feeling anxious or tense	78.6	64.3
Response of your mood to good or desired events	71.4	35.7
Mood in relation to the time of day	35.7	28.6
The quality of your mood	85.7	57.1
Decreased appetite	50	21.4
Increased appetite	42.9	21.4
Decreased weight	35.7	21.4
Increased weight	35.7	14.3
Concentration/decision-making	78.6	57.1
View of myself	92.9	57.1
View of my future	100	78.6
Thoughts of death or suicide	57.1	28.6
General interest	78.6	42.9
Energy level	78.6	57.1
Capacity for pleasure or enjoyment (excluding sex)	85.7	50
Interest in sex	92.9	50
Feeling slowed down	71.4	35.7
Feeling restless	57.1	35.7
Aches and pains	85.7	64.3
Other bodily symptoms	64.3	50
Panic/phobic symptoms	57.1	28.6
Constipation/diarrhea	78.6	42.9
Interpersonal sensitivity	85.7	50
Leaden paralysis/physical energy	85.7	71.4

IDS-SR Inventory of Depressive Symptomatology Self Report

*Patients who did not have the symptom at baseline and only had the symptom at exit are not included

half of the observation period. Additionally, when symptomatic, patients experienced subsyndromal and minor affective symptoms, both manic and depressive, more frequently than discrete episodes of acute mania or major depression [22]. This underscores the necessity of tailoring treatment according to the disease stage, including periods outside of full-blown mania and depressive episodes.

The definition of residual symptoms in depression remains unclear, with diverse interpretations found in the scientific literature. Currently, residual symptoms are conceptualized as persistent depressive manifestations that continue even after formal remission, characterized by subthreshold symptom levels [19, 23]. This broad understanding includes symptoms that persist despite a significant clinical response to appropriate therapy [24]. However, definitions in the literature lack consistency. Some researchers define residual symptoms as those persisting after achieving treatment response or remission, indicating that while the primary depressive episode may have improved, certain symptoms linger at a less severe intensity. Others describe them as enduring symptoms of therapy-resistant depression, implying that despite ongoing treatment efforts, these symptoms do not abate [3, 15, 25].

In this study, residual symptoms were considered present if patients exhibited at least a 50% improvement from baseline [15]. This definition was adopted because it is commonly used in the literature and was practical given the sample size. Furthermore, we wanted to clearly distinguish residual symptoms from TES. The definition utilized, that symptoms were not present at baseline but were present at

Table 3 Severity of residual symptoms at the end of ketamine treatment as compared with all 22 included subjects

IDS-SR 30 item	Percentage with at least mild* symptom severity	Percentage with at least moderate** symptom severity
Falling asleep	71.4	64.3
Sleep during the night	57.1	35.7
Waking up too early	14.3	7.1
Sleeping too much	21.4	7.1
Feeling sad	85.7	42.9
Feeling irritable	35.7	7.1
Feeling anxious or tense	64.3	14.3
Response of your mood to good or desired events	35.7	28.6
Mood in relation to the time of day	28.6	14.3
The quality of your mood	57.1	35.7
Decreased appetite	21.4	0
Increased appetite	21.4	7.1
Decreased weight	21.4	14.3
Increased weight	14.3	0
Concentration/decision-making	57.1	14.3
View of myself	57.1	28.6
View of my future	78.6	35.7
Thoughts of death or suicide	28.6	14.3
General interest	42.9	21.4
Energy level	57.1	28.6
Capacity for pleasure or enjoyment (excluding sex)	50	21.4
Interest in sex	50	35.7
Feeling slowed down	35.7	14.3
Feeling restless	35.7	7.1
Aches and pains	64.3	14.3
Other bodily symptoms	50	21.4
Panic/phobic symptoms	28.6	14.3
Constipation/diarrhea	42.9	21.4
Interpersonal sensitivity	50	14.3
Leaden paralysis/physical energy	71.4	28.6

IDS-SR, Inventory of Depressive Symptomatology Self Report

*IDS-SR $\geq$ 1

**IDS-SR $\geq$ 2

exit, is not ideal; however, it is pragmatic taking into account the short-term observation. It is acknowledged that the frequency and intensity of depressive symptoms can fluctuate, and some symptoms might not be consistently classified within the appropriate group. Numerous definitions exist for TES [16]. The chosen definition can influence the reported frequency of residual symptoms, given the indistinct boundaries between these phenomena.

This inconsistency in definitions complicates the understanding and treatment of depression. It is warranted that clinical manifestation of residual depressive symptoms differs depending on the definition used. For instance, patients who meet the criteria for formal remission may differ significantly from those who respond to antidepressants but continue to experience multiple residual symptoms [15, 19]. Residual symptoms can impact overall quality of life and functional outcomes, making their accurate identification and management crucial [5]. The variability in definitions underscores the need for a standardized approach to characterizing residual symptoms, which would facilitate more effective treatment strategies and improve patient outcomes.

Establishing regulatory and professional definitions for residual symptoms would enhance the clarity and consistency of research methodologies, ensuring uniformity in data collection and interpretation. This standardization could lead to more accurate comparisons across studies, ultimately improving the reliability of findings and facilitating the

development of targeted treatments for patients experiencing residual symptoms [26].

The study has notable limitations. It is an open-label trial without a placebo control group or blinded raters, with a relatively small sample size and a gender imbalance favoring female participants, potentially limiting generalizability. It was not designed to assess residual symptoms, which were assessed solely through self-reported measures. Moreover, the sample exhibits diversity in oral antidepressant use, resulting in variable side effects that might be considered TES, but were already present at baseline and were subsequently considered as residual symptoms. Conducting larger randomized controlled trials, utilizing both clinician-rated and patient-reported measures, would enhance comprehension of the phenomenon. It appears justified that establishing regulatory and/or professional definitions for residual symptoms could enhance the quality of future research.

Nonetheless, this study has its strengths. Primarily, it investigates a unique population of individuals with TRD-BD treated with short-term ketamine, a subject that has not been previously documented. Additionally, the evaluation of responder status was conducted using rater-based outcome measures, which are currently regarded as the gold standard in clinical research.

5 Conclusions

A significant proportion of patients with TRD-BD treated with short-term ketamine suffered from residual depressive symptoms. The most commonly reported residual symptoms were low mood, difficulty falling asleep, and low energy levels. Additionally, the symptoms of at least moderate intensity that were most frequently observed were difficulty falling asleep and low mood. Functional recovery should be the ultimate goal in the treatment of BD.

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Declarations

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Authorship Statement Michał Pastuszak: conceptualization, data curation, formal analysis, methodology, project administration, and writing—original draft; Wiesław Jerzy Cubała: conceptualization, formal analysis, methodology, supervision, and writing—review and editing; Aleksander Kwaśny: conceptualization, data curation, formal analysis, methodology, project administration, and writing—review & editing. All authors read and approved the final version.

Data Availability The data can be provided by the authors upon reasonable request.

Ethics Approval This study was registered in ClinicalTrials.gov under the identifiers NCT04226963 and NCT05565352 and the protocols for the study was approved by Ethic Research Committee of the Medical University of Gdańsk (NKBBN/172–674/2019 and NKBBN/172–447/2022). The study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

Consent to Participate All participants provided written informed consent prior to the enrollment in the study.

Consent for Publication Not applicable.

Code Availability Not applicable.

Conflict of Interest Michał Pastuszak received research support from Beckley Psytech and MSD. Aleksander Kwaśny received research support from Beckley Psytech, GH Research, and MSD. Wiesław Jerzy Cubała has received grants from Acadia, Angelini, Celon, Cortexyme, GH Research, HMNC Brain Health, IntraCellular Therapies, Janssen, MSD, Novartis, and Otsuka. He has also received honoraria from Angelini, Celon, Janssen, Novartis, and Sanofi. He is a member of advisory boards in Angelini, Celon (terminated), Douglas Pharmaceuticals, Janssen, MSD, Novartis, and Sanofi.

References

1. World Health Organisation. The global burden of disease: 2004 update. Geneva: WHO press; 2008.
2. MacQueen GM, Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr Scand. 2001;103:163–70.
3. Iovieno N, van Nieuwenhuizen A, Clain A, Baer L, Nierenberg AA. Residual symptoms after remission of major depressive disorder with fluoxetine and risk of relapse. Depress Anxiety. 2011;28(2):137–44. https://doi.org/10.1002/da.20768.
4. Sanchez-Moreno J, Martinez-Aran A, Tabares-Seisdedos R, Torrent C, Vieta E, Ayuso-Mateos JL. Functioning and disability in bipolar disorder: an extensive review. Psychother Psychosom. 2009;78:285–97.
5. Samalin L, de Chazeron I, Vieta E, Bellivier F, Llorca PM. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. Bipolar Disord. 2016;18(2):164–73. https://doi.org/10.1111/bdi.12376.
6. Rosa AR, Bonnin CM, Mazzarini L, Amann B, Kapczinski FP, Vieta E. Clinical predictors of interpersonal functioning in patients with bipolar disorder. Rev Psiquiatr Salud Ment. 2009;2:83–8.

7. Simon GE, Ludman EJ, Unutzer J, Operskalski BH, Bauer MS. Severity of mood symptoms and work productivity in people treated for bipolar disorder. Bipolar Disord. 2008;10:718–25.
8. Mur M, Portella MJ, Martinez-Aran A, Pifarre J, Vieta E. Influence of clinical and neuropsychological variables on the psychosocial and occupational outcome of remitted bipolar patients. Psychopathology. 2009;42:148–56.
9. Kraus C, Rabl U, Vanicek T, Carlberg L, Popovic A, Spies M, Bartova L, Gryglewski G, Papageorgiou K, Lanzenberger R, Willeit M, Winkler D, Rybakowski JK, Kasper S. Administration of ketamine for unipolar and bipolar depression. Int J Psychiatry Clin Pract. 2017;21(1):2–12. https://doi.org/10.1080/13651501.2016.1254802.
10. Alnefeesi Y, Chen-Li D, Krane E, Jawad MY, Rodrigues NB, Ceban F, Di Vincenzo JD, Meshkat S, Ho RCM, Gill H, Teopiz KM, Cao B, Lee Y, McIntyre RS, Rosenblat JD. Real-world effectiveness of ketamine in treatment-resistant depression: a systematic review & meta-analysis. J Psychiatr Res. 2022;151:693–709. https://doi.org/10.1016/j.jpsychires.2022.04.037.
11. Fekadu A, Wooderson SC, Rane LJ, Markopoulou K, Poon L, Cleare AJ. Long-term impact of residual symptoms in treatment-resistant depression. Can J Psychiatry. 2011;56:549–57. https://doi.org/10.1177/070674371105600906.
12. Wilkowska A, Wiglusz MS, Arciszewska-Leszczuk A, Gałuszko-Węgielnik M, Cubała WJ. Anhedonia in bipolar depression treated with ketamine. Bipolar Disord. 2024. https://doi.org/10.1111/bdi.13409.
13. Poon SH, Sim K, Sum MY, Kuswanto CN, Baldessarini RJ. Evidence-based options for treatment-resistant adult bi- polar disorder patients. Bipolar Disord. 2012;14:573–84. https://doi.org/10.1111/j.1399-5618.2012.01042.x.
14. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M, STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163(1):28–40. https://doi.org/10.1176/appi.ajp.163.1.28.
15. McClintock SM, Husain MM, Wisniewski SR, Nierenberg AA, Stewart JW, Trivedi MH, Cook I, Morris D, Warden D, Rush AJ. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. J Clin Psychopharmacol. 2011;31(2):180–6. https://doi.org/10.1097/JCP.0b013e31820ebd2c.
16. Nilsson ME, Koke SC. Defining treatment-emergent adverse events with the medical dictionary for regulatory activities (MedDRA). Drug Inf J. 2001;35(4):1289–99. https://doi.org/10.1177/009286150103500425.
17. Grover S, Chakrabarti S, Sahoo S. Prevalence and clinical correlates of residual symptoms in remitted patients with bipolar disorder: an exploratory study. Indian J psychiatry. 2020;62(3):295–305. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_760_19.
18. Hart KL, McCoy TH Jr, Henry ME, Seiner SJ, Luccarelli J. Residual symptoms following electroconvulsive therapy: a retrospective cohort study. J Affect Disord. 2023;341:374–8. https://doi.org/10.1016/j.jad.2023.08.135.
19. Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol Med. 2010;40(1):41–50. https://doi.org/10.1017/S0033291709006011.
20. Pastuszak M, Cubała WJ, Kwaśny A. Treatment-emergent symptoms during short-term ketamine administration in treatment-resistant bipolar depression: A retrospective cross-sectional descriptive study. Asian J Psychiatry. 2024;99:104159. https://doi.org/10.1016/j.ajp.2024.104159.
21. Paykel ES, Abbott R, Morriss R, Hayhurst H, Scott J. Sub-syndromal and syndromal symptoms in the longitudinal course of bipolar disorder. Br J Psychiatry. 2006;189(2):118–23. https://doi.org/10.1192/bjp.bp.105.013870.
22. Joffe RT, MacQueen GM, Marriott M, Trevor Young L. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. Bipolar Disord. 2004;6(1):62–6. https://doi.org/10.1046/j.1399-5618.2003.00091.x.
23. Wang Y, Wang G, Zhang N, Huang J, Wu W, Jia F, Liu T, Gao C, Hu J, Hong W, Fang Y. Association between residual symptoms and social functioning in patients with depression. Compr Psychiatry. 2020;98:152164. https://doi.org/10.1016/j.comppsych.2020.152164.
24. Fava M, Ball S, Nelson JC, Sparks J, Konechnik T, Classi P, Dube S, Thase ME. Clinical relevance of fatigue as a residual symptom in major depressive disorder. Depress Anxiety. 2014;31(3):250–7. https://doi.org/10.1002/da.22199.
25. Rasmussen NA, Schrøder P, Olsen LR, Brødsgaard M, Undén M, Bech P. Modafinil augmentation in depressed patients with partial response to antidepressants: a pilot study on self-reported symptoms covered by the Major Depression Inventory (MDI) and the Symptom Checklist (SCL-92). Nord J Psychiatry. 2005;59(3):173–8.
26. European Medicines Agency, 2024. https://www.ema.europa.eu/en/events/ema-multi-stakeholder-workshop-psychedelics-towards-eu-regulatory-framework. Accessed 29 May 2024.