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Case report

Results of esketamine administration in a Greek population; A case series

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ABSTRACT

Esketamine is a non-selective, competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor in the brain. Through NMDA receptor antagonism, esketamine causes a transient increase in glutamate release, leading to increases in neurotrophic signaling and restoration of synaptic function in brain regions involved in mood regulation and emotional behavior. Several randomized clinical trials have shown its effectiveness in reducing the symptoms of depression in some people, despite its short-term side effects that include mainly disorientation, dizziness, nausea, and increased blood pressure. In 2019, the United States Food and Drug Administration (FDA) as well as the European Medicines Agency approved the use of esketamine nasal spray in combination with an oral antidepressant for treatment-resistant depression in adults. Our study aimed to evaluate the effectiveness of this new therapeutic proposal in a case series of five Greek patients with treatment-resistant depression. Intranasal esketamine was administered under medical supervision in combination with an oral antidepressant. Depressive symptoms were evaluated at three-time points (baseline, end of treatment, and one-year post-treatment) using the Montgomery–Åsberg Depression Rating Scale (MADRS), the Patient Health Questionnaire (PHQ-9), the CGI Clinical Global Impression Scale, and the Perceived Deficits Questionnaire for Depression (PDQ-D). Possible side effects were assessed using the Richmond Suppression Agitation Scale (RASS), the Sheehan Disability Scale (SDS), the CADSS Disruptive States Scale, and a predefined list of adverse events (AEs) and serious adverse events (SAEs). Patients followed an individualized treatment plan for seven to twelve months depending on the achievement of an adequate response. Statistical analysis of the results revealed a significant improvement ($p<0.05$) on all scales used. All participants maintained their level of improvement at follow-up after twelve months. Adverse effects were found to be mild and tolerable. It is worth noting that significant side effects were reported only by the two patients with comorbid personality disorder. The results, despite being limited to a small sample, indicate the positive effect of esketamine on the stable reduction of depressive symptoms among patients with resistant depression, even after the completion of treatment.

KEYWORDS: Esketamine, treatment-resistant depression, mood disorders, therapeutic intervention, fast-acting antidepressant.

Introduction

Depression remains the leading cause of disability worldwide.[1] It is estimated that 10–20% of people with major depressive disorder are resistant to treatment.[1] Treatment-resistant depression (TRD) is defined as the failure to achieve remission with two or more adequate trials of antidepressants.[2] In 2019, both the European Medicines Agency and the United States Food and Drug Administration (FDA) approved the use of esketamine in combination with an oral antidepressant for treat-

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ment-resistant depression in adults.[3–5] Escetamine is administered as a nasal spray under medical supervision and works by targeting N- methyl -D-aspartic acid (NMDA) receptors in the brain.[3,6] Escetamine is effective in reducing depressive symptoms, despite potential side effects.[7–9] Among the most common side effects are nausea, dizziness, drowsiness, sedation, and dysgeusia (taste distortion).[10,11]

The present study provides the first results of esketamine administration in a case series of five Greek patients diagnosed with TRD. Study participants received esketamine along with an oral antidepressant for 7 to 12 months and were followed up to one year after treatment.

Materials and Method

Participants

Purposive sampling was applied to collect eligible participants. Participants had to meet the following criteria: (1) meet the diagnostic criteria for the major depressive disorder of moderate to severe intensity at clinical judgment, as defined by the ICD-10-GrM (Greek Modification), version 2017, version 2 (code F32.2, F32.3 or F33) confirmed by Mini International Neuropsychiatric Interview (MINI version 7.0.0, Greek), medical history, and/or prescription records, (2) meet the criteria for TRD, i.e., as a non-responder to two "adequate" cycles of treatment 3 (3) have a total score of 28 or higher on the Montgomery – Åsberg Depression Scale (MADRS), (4) be at least 18 years old, (5) feel comfortable with self-administration of intranasal medication, (6) be willing and able to adhere to prohibitions and restrictions established for esketamine, (7) be medically stable based on physical examination, medical history, and vital signs. Key exclusion criteria were a history of bipolar or psychotic features, suicidal behavior in the last year, and the presence of a serious health condition overshadowing the depressive clinical picture.

All patients underwent a basic psychiatric evaluation to confirm the diagnosis of TRD and certain medical tests (blood, urine, and electrocardiogram) to determine medical stability and rule out substance abuse. Written informed consent was obtained from all participants after the risks and benefits associated with esketamine treatment were discussed with them.

Tools

The Montgomery – Åsberg Depression Rating Scale (MADRS),[12] the Patient Health Questionnaire (PHQ -9),[13] the Clinical Global Impression Scale (CGI)[14] and the Perceived Deficit Depression Questionnaire (PDQ)[15] were used to assess symptom severity and treatment efficacy.[16]

The MADRS is a widely used depression severity scale completed by clinicians. It is often used in the investigation of treatment responses to antidepressant drugs. The PHQ is a self-administered questionnaire that assesses the severity of depression. The CGI includes two scores that assess (a) severity of psychopathology from 1 to 7 (CGI-S) and (b) change since treatment initiation on a similar seven-point scale (CGI-I). After a clinical assessment, the CGI form can be completed in less than a minute by an experienced rater. The Perceived Deficits–Depression Questionnaire (PDQ-D) is a short rating scale completed by depressed patients to assess subjective cognitive dysfunction.

Adverse symptoms were recorded within the first hour after dosing using the Richmond Agitation Suppression Scale (RASS),[17] the Sheehan Disability Scale (SDS),[18] the CADSS Disruptive States Scale[19] and a list of predefined adverse events (AEs) and serious adverse events (SAE).[20] The Richmond Suppression Agitation Scale (RASS) is an instrument designed to assess the level of alertness and agitated behavior in critically ill patients. The Sheehan Disability Scale (SDS) measures impairment in functionality. The scale has four scores: a work disability score, a social life disability score, a family life disability score, and a total score. The "toxicity data" or "side effects" of a drug can generally be divided into two types of events: adverse events (AEs) and serious adverse events (SAEs).

Adverse events (AEs) are defined as "any untoward medical event in a patient administered a medicinal product that does not necessarily have to be causally related to that treatment". Serious AEs (SAEs) are defined by the Food and Drug Administration as AEs that result in death, are life-threatening, require hospitalization, or prolong an existing hospitalization, result in persistent or significant disability, cause a congenital abnormality/ birth defect, or require special intervention to prevent permanent harm or damage.

The intervention

The study was carried out in an outpatient psychiatric setting at a tertiary military hospital in Northern Greece. All participants received esketamine along with an oral antidepressant. Participants self-administered esketamine under the direct supervision of a responsible healthcare professional. The initial dose of esketamine was 56 mg. Dose and frequency were later adjusted on an individual basis according to treatment guidelines and patient response (table 1).

Tool scores were collected at three different time points (baseline, end of intervention, and one year later). At the end of treatment, patients who achieved a

Table 1. Analysis of sample and treatment intervention.

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Male	Female	Female	Female	Female
Age	28	32	45	51	35
Years since the diagnosis of Major Depressive Disorder	2	7	15	21	2
Oral antidepressant Dosage of oral antidepressant	Vortioxetine 20 mg	Paroxetine 20 mg	Velafaxine 150 mg	Duloxetine 60 mg	Escitalopram 30 mg
Total treatment duration	44 Eβδ	52 Eβδ	52 Eβδ	29 Eβδ	32 Eβδ
Start day	56 mg	56 mg	56 mg	56 mg	56 mg
Induction Phase (1rst- 4th week)	2x84 mg/week	2x84 mg/week	2x84 mg/week	2x84 mg/week	2x84 mg/week
Maintenance Phase (5th- 8th week)	84 mg/week		84 mg/week	84 mg/week	84 mg/week
Escetamine Dosage					
Next Step Phase (from 9th week)	84 mg/2 weeks	84 mg/week	84 mg/week	84 mg/week	84 mg/week
Termination Phase (one month before end of treatment)	56 mg/2 weeks	84 mg/2 weeks	84 mg/2 weeks	84 mg/week	84 mg/week

50% or greater reduction in MADRS scores were considered "responders."

Statistical data analysis

The statistical analysis of the data was completed using SPSS software version 15. The Wilcoxon signed rank test and the Student's t-test were applied depending on the normality of the distribution. The level of statistical significance was set at $p<0.05$.

Results

Case 1

The first patient was a 28-year-old man, single, with no medical comorbidities. Two years ago, he was diagnosed with major depressive disorder. At the time of evaluation, the patient was depressed, with a loss of sexual interest, anhedonia, pessimistic thoughts, concentration deficits, and social isolation. During the third esketamine infusion, the patient complained of mild dissociative symptoms, photosensitivity, and dizziness. These side effects disappeared completely within the next hour. Four weeks later, the patient had mild depressive symptoms (MARDS=15 points), improved libido, and organized a vacation. At the end of the treatment (after six months), the improvement was evident. The patient reported an 85 % remission of depressive symptoms. One year later, the patient had returned to his previous functioning in his social, work, and love life. From the 4th month to the 18th, the patient showed no symptoms of depression. A picture of continuous improvement was observed. There was a complete recession.

Case 2

The second patient was a 32-year-old woman. Since 2017, she has been experiencing depressed mood, loss of interest, blunted emotion, and anxiety. Despite several antidepressant treatments, the patient had frequent relapses. She received esketamine 84 mg weekly for six months. The patient had no side effects during treatment. Her MADRS score dropped from 41 to 16 after 12 infusions of esketamine. At follow-up after one year, her MADRS score was 12 (mild depression score) and her PHQ-9 was 2.

Case 3

The third patient was a 45-year-old woman who was diagnosed with resistant depression about 15 years ago. During this time, she was severely depressed, with previous suicidal thoughts, anxiety, insomnia, and cognitive deficits. Over the past 10 years, she has tried various drug combinations, but her symptoms have not improved. After 12 administrations of esketamine, the patient reported a significant reduction in depressive symptoms. Throughout the induction phase, the patient continued to report benefits from esketamine treatment, as evidenced by the PHQ-9 self-report scale. By the end of the induction phase (week 4), the patient's PHQ-9 score had decreased to 5, indicating no depressive symptoms. The MARDS score also decreased from

49 to 16. The MARDS score at the follow-up was 9 (mild depression). The patient reported functional recovery after a long time.

Case 4

The fourth patient, age 51, in her mid-thirties, developed major depressive symptoms with persistent low mood, anhedonia, poor concentration, and excessive guilt. Previous adequate drug trials were not effective. The psychiatric evaluation added borderline personality features to the diagnosis (F60.3). The dose of esketamine reached 84 mg twice weekly. During the third week of esketamine administration, the patient reported dizziness and suicidal thoughts. Twenty-four hours later, the patient had no suicidal ideation. In the maintenance phase, the frequency was reduced to once per week. The treatment lasted 7 months. The improvement was slow but steady. At follow-up, the MADRS had decreased to 20 (moderate depression) from 40 (severe depression).

Case 5

The fifth patient was 35 years old and for the last 2 years, she has suffered from anhedonia, social withdrawal, feelings of worthlessness, fear of abandonment, and a significant decline in her functionality. She had been treated with different antidepressants in combination with anxiolytics, showing a partial response only to the phobic symptoms. A diagnosis of resistant depression with dependent and paranoid features was given (F.32, F.61). During the induction phase, the patient experienced nausea, dizziness, and moderate dissociative symptoms, which resolved within the next hour. The patient developed a cardiac arrhythmia within the second month of treatment and esketamine treatment was discontinued for six months. After the six months and having a negative organic control, the patient started taking esketamine again from the beginning. She completed treatment within six months with no further adverse effects. As hypothesized, the cardiac arrhythmia was not attributable to esketamine itself. At the follow-up, depressive symptoms and cognitive deficits had improved significantly as shown by the MADRS, PHQ-9 and PDQ-D scores.

Overall result

Five patients with a mean age of 39.5±11.5 years, four women and one man participated in our study (table 1). Comparisons of pre-and post-treatment scores revealed significant improvement ($p<0.05$) on all scales used. Improvement ranged from 10 to 30 points on each scale. The results indicate a significant reduction in the MADRS score in all our patients. At follow-up, MADRS scores reached minimal levels, with a variation between 20 and 6 points among our patients (figure 1). After the intervention ended, depressive symptoms continued to decrease. Patient 1 achieved full recovery (MADRS score: 6), while patients 2,3,4,5 achieved mild depression scores. Similarly, PHQ-9 and PDQ-D scores decreased as treatment continued (table 2).

Adverse events were found to be mild and tolerable (table 3). The reported side effects did not occur

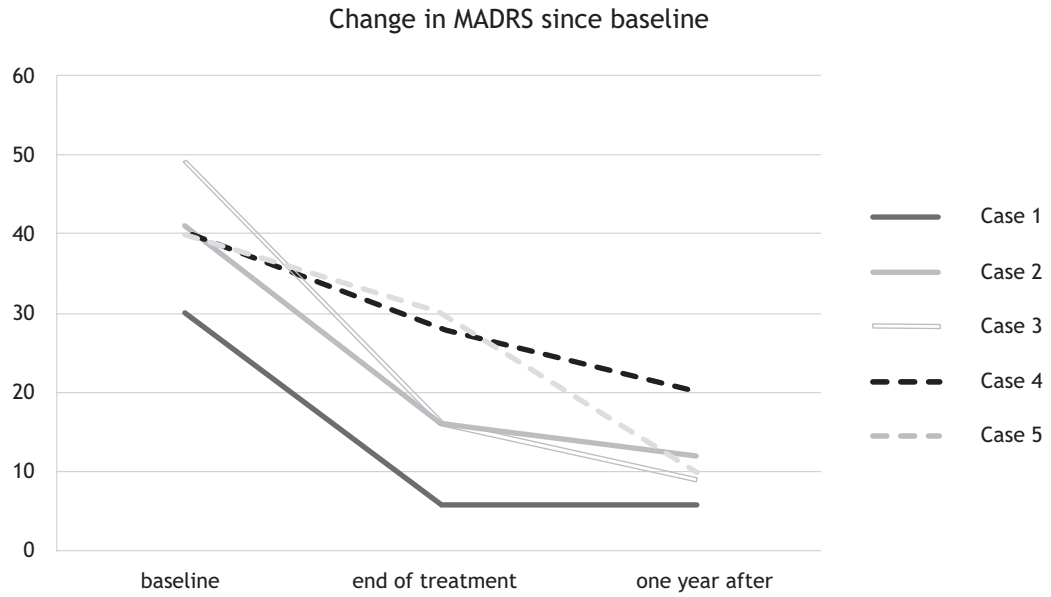

Figure 1. MADRS score change

Table 2. Course of depressive symptoms for each patient during treatment.

	Case 1				Case 2				Case 3				Case 4				Case 5			
Time points	T0	Tm	T1	T2	T0	Tm	T1	T2	T0	Tm	T1	T2	T0	Tm	T1	T2	T0	Tm	T1	T2
MARDS (Highest score 60)	30	9	6	6	41	20	16	12	49	21	16	9	40	31	28	20	40	32	30	10
PHQ-9 (Highest score 27)	20	–	4	2	23	–	6	2	25	–	5	3	23	–	22	15	23	–	20	8
CGI (S-I) (Highest score 7-7)	6–4	–	1–1	0–0	6–4	–	2–1	1–0	6–4	–	2–1	0–0	7–4	–	4–3	2–0	6–4	–	4–3	2–2
PDQ-D (Highest score 80)	9	–	0	0	55	–	13	8	55	–	20	10	22	–	14	15	52	–	35	10

Abbreviations. MADRS: Montgomery-Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; CGI: Clinical Global Impression Scale; PDQ-D: Perceived Deficits Questionnaire- Depression; T0: start of treatment; Tm: one month later; T1: end of treatment; T2: one year after treatment

Table 3. Adverse events during treatment.

Variables	Case 1			Case 2			Case 3			Case 4			Case 5		
Time points	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
CADSS (Highest score 92)	0	0	0	0	0	0	0	0	0	0	6	0	1	4	0
RASS (Highest score 30)	+	0	0	+	0	0	+	0	0	+	++	+	+	+	0
SDS	7–8-5	0-0-0	0-0-0	9-8-10	4-1-2	2-1-1	10-10-5	4-4-1	3-3-1	9-9-8	8-7-7	8-7-7	9-9-10	7-6-6	4-4-4
AE		0			0			0		Dizziness			Dizziness, nausea, vomits, weakness		
SAE		0			0			0		Suicidal thoughts			Heart problem		

Abbreviations. CADSS: Clinician-Administered Dissociative States Scale, RASS: Richmond Agitation Sedation Scale, SDS: Sheehan Disability Scale; T0: start of treatment; T1: end of treatment; T2: one year after treatment.

after each dose but appeared to occur infrequently within the first four weeks of treatment and lasted for a maximum of two hours. Side effects did not deter any of the participants from discontinuing treatment. Comparisons of scale scores between the time points of the study are shown in table 4.

Discussion

This case series provides the first evidence for the safety and long-term efficacy of esketamine in a Greek population sample of patients with resistant depression. Our study found that nasal esketamine together with an oral antidepressant, was an effective combination for reducing the depressive symptoms of patients with resistant depression. Our results are consistent with those of previous studies regarding the efficacy of esketamine in reducing depressive symptoms and preventing relapse.[8,9,21,22]

Several studies have examined the side effects associated with the intake of esketamine.[21,23,24] Our patients experienced mild and transient side effects, mainly in the first hour after the infusion and during the induction phase. Side effects became less frequent as the treatment continued. In contrast to previous studies, the participants in our study did not feel "overwhelmed" by the "side effects" of esketamine.[25] Only one participant experienced a major complication (heart problem) that was treated by temporarily stopping the treatment and restarting the treatment protocol six months later. Zhang and Hassimoto commented on the addictive potential of (S)-norketamine.[26] No addiction was found in our patients.

This study has limitations. Firstly, our small sample does not allow generalizations. Secondly, participants were followed up one year after treatment. Longer-term clinical trials and "real-world" efficacy data are needed to conclude long-term efficacy and the best treatment regimen. Thirdly, the tests used can be applied to a small sample. More practical tools could be selected in studies of more patients. Despite these limitations, the present study presents the first results from the administration of esketamine to a Greek population. Undoubtedly, the sample is too small to conclude efficacy and tolerability. Nevertheless, we can conclude that the patients in our sample showed good cooperation and compliance and achieved an improvement in their overall clinical picture and functionality. We believe that esketamine, despite the conditions and limitations it poses (financial access, abuse potential, time commitment, and REMS requirements), is a clinically applicable and promising option in the treatment of patients with treatment-resistant depression.

Table 4. Scales' total scores.

Scales	T0	Tm	T1	T2	Statistic	Comparison baseline – a month after (p)	Comparison baseline – a year after (p)
MADRS	40,00 (6,75)	22,60 (9,40)	19,20 (9,86)	10,00 (3,54)	3.25 (start-month) 4.83 (start-year)	0,011[a]	0.008[a]
PHQ-9	22,80 (1,79)	–	11,40 (8,82)	6,00 (5,61)	2.92	–	0.043[a]
PDQ-D	38,60 (21,62)	–	16,40 (12,70)	8,60 (5,46)	3.21	–	0.033[a]
CGI-S	6,20 (0,45)	–	2,60 (1,34)	1,00 (1,00)	7.06	–	0.002[a]
CGI-I	4,00 (0,00)	–	1,80 (1,10)	0,40 (0,89)	0.00	–	0.053[b]
SDS a	8,80 (1,10)	–	4,60 (3,13)	3,40 (2,97)	3.16	–	0.034[a]
SDS b	8,80 (0,84)	–	3,60 (3,05)	3,00 (2,74)	3.95	–	0.017[a]
SDS c	7,60 (2,51)	–	3,20 (3,11)	2,60 (2,88)	3.92	–	0.017[a]

Abbreviations. MADRS: Montgomery-Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; PDQ-D: Perceived Deficits Questionnaire- Depression; CGI: Clinical Global Impression Scale; SDS: Sheehan Disability Scale; a Student's test b Wilcoxon signed-rank test, T0: start of treatment; Tm: one month after; T1: end of treatment; T2: one year after treatment.

Values in columns T0, Tm, T1 and T2 are means (standard deviations). A p-value of less than 0.05 is considered statistically significant

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Παρουσίαση περίπτωσης

Αποτελέσματα χορήγησης εσκεταμίνης σε Ελληνικό πληθυσμό: Παρουσίαση σειράς περιστατικών

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 27 Σεπτεμβρίου 2023/Αναθεωρήθηκε 31 Δεκεμβρίου 2023/Δημοσιεύθηκε Διαδικτυακά 29 Μαΐου 2024

ΠΕΡΙΛΗΨΗ

Η εσκεταμίνη είναι ένας μη εκλεκτικός, συναγωνιστικός ανταγωνιστής του N-μεθυλ-D-ασπαρτικού (NMDA) υποδοχέα στον εγκέφαλο. Μέσω του ανταγωνισμού για τον υποδοχέα NMDA, η εσκεταμίνη προκαλεί παροδική αύξηση στην έκλυση γλουταμινικού, οδηγώντας σε αυξήσεις της νευροτροφικής σηματοδότησης και αποκατάσταση της συναπτικής λειτουργίας στις περιοχές του εγκεφάλου που εμπλέκονται στη ρύθμιση της διάθεσης και τη συναισθηματική συμπεριφορά. Αρκετές τυχαιοποιημένες κλινικές δοκιμές έχουν δείξει την αποτελεσματικότητά της στη μείωση των συμπτωμάτων της κατάθλιψης σε ορισμένα άτομα, παρά τις βραχυπρόθεσμες παρενέργειές της που περιλαμβάνουν κυρίως διάσχιση, ζάλη, ναυτία και αύξηση της αρτηριακής πίεσης. Το 2019, ο Οργανισμός Τροφίμων και Φαρμάκων των Ηνωμένων Πολιτειών (FDA) καθώς και ο Ευρωπαϊκός Οργανισμός Φαρμάκων ενέκριναν τη χρήση ρινικού εκνεφώματος εσκεταμίνης σε συνδυασμό με ένα από του στόματος αντικαταθλιπτικό φάρμακο για την ανθεκτική στη θεραπεία κατάθλιψη σε ενήλικες. Η μελέτη μας είχε ως στόχο να αξιολογήσει την αποτελεσματικότητά αυτής της νέας θεραπευτικής πρότασης σε μια σειρά περιπτώσεων πέντε Ελλήνων ασθενών με ανθεκτική κατάθλιψη. Το ρινικό εκνέφωμα εσκεταμίνης χορηγήθηκε υπό ιατρική επίβλεψη σε συνδυασμό με ένα από του στόματος αντικαταθλιπτικό. Τα συμπτώματα της κατάθλιψης αξιολογήθηκαν σε τρία χρονικά σημεία (έναρξη θεραπευτικής παρέμβασης, λήξη θεραπείας, ένα έτος μετά τη θεραπεία) χρησιμοποιώντας τηη κλίμακα αξιολόγησης κατάθλιψης Montgomery–Åsberg (MADRS), το ερωτηματολόγιο υγείας ασθενών PHQ-9, την κλίμακα κλινικής παγκόσμιας εντύπωσης CGI, και το ερωτηματολόγιο αντιληπτών ελλειμμάτων για την κατάθλιψη (PDQ-D). Πιθανές παρενέργειες εκτιμήθηκαν χρησιμοποιώντας την κλίμακα καταστολής διέγερσης Richmond (RASS), την κλίμακα αναπηρίας Sheehan (SDS), την κλίμακα διασπαστικών καταστάσεων CADSS και έναν προκαθορισμένο κατάλογο ανεπιθύμητων (AE) και σοβαρών ανεπιθύμητων ενεργειών (SAE). Οι ασθενείς ακολούθησαν ένα εξατομικευμένο θεραπευτικό πρόγραμμα για 7 έως 12 μήνες, αναλόγως της επίτευξης επαρκούς ανταπόκρισης. Η στατιστική ανάλυση των αποτελεσμάτων αποκάλυψε σημαντική βελτίωση ($p<0,05$) σε όλες τις κλίμακες που χρησιμοποιήθηκαν. Όλοι οι συμμετέχοντες διατήρησαν το επίπεδο βελτίωσης στο follow-up μετά από 12 μήνες. Οι ανεπιθύμητες ενέργειες βρέθηκαν να είναι ήπιες και ανεκτές. Αξίζει να σημειωθεί ότι σημαντικές παρενέργειες αναφέρθηκαν μόνο από τους δύο ασθενείς με συννοσηρά στοιχεία προσωπικότητας. Τα αποτελέσματα, παρόλο που προέκυψαν από μικρό δείγμα ασθενών, υποδεικνύουν τη θετική επίδραση της εσκεταμίνης στη σταθερή μείωση των καταθλιπτικών συμπτωμάτων ασθενών με ανθεκτική κατάθλιψη, ακόμη και μετά την ολοκλήρωση της θεραπείας.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Εσκεταμίνη, ανθεκτική κατάθλιψη, διαταραχές διάθεσης, θεραπευτική παρέμβαση, αντικαταθλιπτικό ταχείας δράσης.

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