Am J of Geriatric Psychiatry 31:12 (2023) 1032–1041

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Regular Research Article

Investigating the Effectiveness and Tolerability of Intranasal Esketamine Among Older Adults With Treatment-Resistant Depression (TRD): A Post-hoc Analysis from the REAL-ESK Study Group

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ARTICLE INFO

Article history:
Received May, 10 2023

ABSTRACT

Introduction: *Treatment-resistant depression (TRD) is a serious and debilitating psychiatric disorder that frequently affects older patients. Esketamine nasal spray (ESK-NS) has recently been approved as a treatment for TRD, with*

Editorial accompaniment, please see page 1042.

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https://doi.org/10.1016/j.jagp.2023.06.016

Revised June, 27 2023
Accepted June, 30 2023

Key Words:
Esketamine
geriatric psychiatry
real-world study
TRD

multiple studies establishing its efficacy and tolerability. However, the real-world effectiveness, tolerability, and safety of this treatment in older adults is still unclear. ***Objectives:*** *To evaluate the efficacy and tolerability of ESK-NS in older subjects with TRD.* ***Methods:*** *This is a post-hoc analysis of the REAL-ESK study, a multicenter, retrospective, observational study. Participants here selected were 65 years or older at baseline. The Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HAM-A) were used to assess depressive and anxiety symptoms, respectively. Data were collected at three-time points: baseline, 1 month after the start of treatment (T1), and 3 months after treatment (T2).* ***Results:*** *The sample included older adults with TRD (n = 30). MADRS and HAM-A values decreased significantly at T1 (T0 versus T1: p_{bolm} <0.001, Cohen's d = 0.840) and T2 follow-ups (T0 versus T2: p_{bolm} <0.001, Cohen's d = 1.419). At T2, 53.3% of subjects were responders (MADRS score reduced ≥50%), while 33.33% were in remission (MADRS<10). ESK-NS-related adverse effects were in order of frequency dizziness (50%), followed by dissociation (33.3%), sedation (30%), and hypertension (13.33%). Six out of 30 participants (20%) discontinued treatment.* ***Conclusions:*** *Our findings provide preliminary evidence of ESK-NS effectiveness in older adults with TRD, a highly debilitating depressive presentation. Furthermore, we observe high levels of treatment-emergent adverse events, which, in the majority of instances, did not require treatment suspension.* (Am J Geriatr Psychiatry 2023; 31:1032−1041)

Highlights

- **What is the primary question addressed by this study?**
  Treatment-resistant Depression (TRD) in older patients represents a severe condition characterized by more frequent treatment-related side effects and, globally, low response rates. Intranasal Esketamine (ESK-NS) has not been fully investigated in older subjects.
- **What is the main finding of this study?**
  In this post-hoc analysis of the REAL-ESK study, ESK-NS proved to be effective for older patients with TRD, although with greater side effects than for nonolder adults.
- **What is the meaning of the finding?**
  ESK-NS is effective for older patients, but clinicians should be aware of possible higher side effect rates; thus, precise treatment selection is crucial in this population to avoid their occurrence.

INTRODUCTION

Major depressive disorder (MDD) is a common and debilitating psychiatric disease affecting around 264 million people worldwide. In older patients, MDD is the second most common psychiatric disorder, encompassing about 30% of old adults.[1] A growing body of evidence suggests that MDD prognosis in these patients is even worse compared with nonolder subjects, in part due to the more prevalent comorbid and functional disability.[1,2] These subjects are also exposed to a reduced quality of life, together with disability, comorbid medical conditions, and risk of suicide, with impact on caregivers and increased demand on healthcare services and public health cost.[1] Indeed, older adults are frequently exposed to treatment-resistant depression (TRD), which is commonly defined as the absence of a therapeutic response following two adequate antidepressant trials.[3,4]

According to Whyte et al., more than 80% of older TRD adults may show either inadequate response to therapy or early relapse within the first 6–12 weeks, with comorbid anxiety symptoms being one of the most important factors associated with delayed treatment response.[5] In this special population, current treatment recommendations suggest integrated strategies of treatment, combining psychological and pharmacological intervention and physical therapies as second-line treatments (i.e., Transcranial Magnetic Stimulation/TMS, Electroconvulsive therapy/ECT).[6,7]

There is currently a growing body of evidence about the use of glutamatergic compounds (i.e., ketamine and intranasal esketamine/ESK-NS) as therapeutic strategies for TRD.[8] Both of them act as noncompetitive antagonists of N-Methyl-D-Aspartate (NMDA) glutamatergic, with a significant role as boosters of neurotropism and neuroplasticity, able to determine their antidepressant effect.[9] Furthermore, Ketamine and ESK-NS seems to be promising treatments in different psychiatric conditions, with good efficacy also in TRD patients with comorbidities, a frequent condition in older patients.[10]

Recently, ESK-NS has been approved as antidepressant therapy for TRD by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA),[11] based on the outcomes of several randomized controlled trials (RCTs) in nonolder populations[12–14] and is now considered an evidence-based therapeutic strategy for TRD.[15] Furthermore, RCTs have confirmed the drug's safety profile, also in older patients,[16] even though tolerability and effectiveness may be lower in the geriatric population.[12,16]

There is no current strong evidence of ESK-NS efficacy with respect to TRD in older adults, with a single RCT that indicates the significant antidepressant action of ESK-NS only among the younger patients affected (i.e., 65–74 years old).[16] Besides, consensus exists about the urgency of both RCTs and real-world data to assess effectiveness and tolerability of ESK-NS in older adults. Furthermore, real-world conditions may provide insight into the actual feasibility of ESK-NS among these patients, offering a further understanding of its effectiveness and tolerability in these subjects.

Based on the previously mentioned points, the current post-hoc analysis of the REAL-ESK study[17] aims to: 1) assess the effectiveness of ESK-NS among TRD patients aged 65 years and older and 2) evaluate the tolerability of this intervention by analyzing side effects and drop-out rates.

MATERIALS AND METHODS

Participants and Study Design

This study represents a post-hoc analysis of the REAL-ESK study,[17] a real-world, retrospective, observational, and multicenter study on the use of ESK-NS among TRD subjects. Subjects were enrolled across various Italian mental health facilities, as detailed in prior publications from the REAL-ESK study group.[17] Treatment was provided in an "early access" program that supplied esketamine to the major TRD centers in Italy.

In the present analysis, from the initial sample of 116 TRD patients only participants who were 65 or older at baseline were included (N=30).

Other inclusion criteria were: 1) experiencing a major depressive episode (MDE), 2) undergoing at least two conventional monoaminergic antidepressant trials in the absence of a clinical response (established by a qualified psychiatrist considering dose, duration, adherence, and the absence of a ≥50% decrease of depressive symptoms from baseline scale scores) following the common definition of TRD,[3] and being treated with an SSRI or SNRI for which ESK-NS treatment was considered appropriate, according to EMA indications and common clinical practice of TRD management.[11] Patients with comorbid medical disorders (i.e., untreated arterial hypertension or previous cerebrovascular disorders, myocardial infarction in the previous 6 weeks) that represented an absolute contraindication to esketamine according to EMA were excluded from the study.[11]

Study Procedures

Data from patients' anamnesis were gathered retrospectively, encompassing sociodemographic factors, depressive disease history, current MDE treatment history, comorbidities, previous antidepressant trials, augmentation approaches (including the use of mood stabilizers, benzodiazepines,

and antipsychotics), and other therapeutic modalities for TRD management. Information was also obtained for instances of early study withdrawal or clinically significant events such as hospital admission or discharge, symptom recurrence, or MDE remission.

The Montgomery−Åsberg Depression Rating Scale (MADRS)[18] was used to assess depressive symptoms. Hamilton Anxiety Rating Scale (HAM-A)[19] was used to assess anxious symptoms.

Anamnestic data and psychometric evaluations were obtained from patients' medical records at three-time points: baseline (T0), 1 month after initiating treatment (T1), and 3 months post-treatment commencement (T2).

Patients were classified as responders if they exhibited a 50% overall decrease in their MADRS or HAM-A scores relative to the baseline evaluation.[14] Furthermore, remission from the current MDE was identified by a MADRS score of less than 10.[20]

The study was approved by the local ethics committee of the Università degli studi di Brescia (Protocol Number: NP5331). All patient data were treated confidentially and anonymously, and the study was conducted in line with the Helsinki Declaration.[21]

Statistical Analysis

SPSS 20.0 software (SPSS Inc., Chicago, IL) and JASP for Mac (JASP version: 0.16.4; JASP Team, 2022) were used for statistical analysis. All tests were two-tailed, employing a statistical significance threshold of $p < 0.05$. Continuous variables are denoted as mean ± standard deviation (SD), while categorical variables are presented as mean values and proportions. The student's *t*-test was employed to evaluate continuous variables, while the Pearson χ^2 test was utilized for categorical variables.

Moreover, a generalized linear model methodology through a repeated measure ANOVA (rm-ANOVA) was adopted to evaluate the "within-factor" interaction effect (within factor, treatment duration: baseline/pretreatment/T0 versus the conclusion of the first month of treatment/T1 versus the termination of the third month of treatment/T2) on MADRS and HAM-A scales. The sphericity of the covariance matrix was assessed via Mauchly's test of sphericity; in instances of sphericity assumption infringement, Greenhouse-Geisser epsilon (ε) correction was employed. To stringently regulate Type I error, post-hoc pairwise comparison examinations were conducted utilizing Holm's method for multiple comparisons.

RESULTS

Sample Characteristics

The sample comprised a total of 30 TRD older adult subjects (age: 67.96 years ± 2.03). Comprehensively, subjects were experiencing a severe form of depression (MADRS score: 34.92 ± 8.85), with multiple antidepressant trials in the current episode (3.20 ± 0.85) and a long-lasting MDE (19.38 ± 10.83 months). Previous therapies included brain stimulation therapies (e.g., TMS, reported by 2/30 subjects, and ECT, reported by 1/30 subject); monoamine oxidase inhibitors (I-MAO) (in 1 subject); and dopamine agonists (e.g., pramipexole, used in 2/30 subjects as adjunctive antidepressant therapy), thus proving the complexity of the disorder. Socio-demographic and clinical data, as well as pharmacotherapies, are extensively reported in Tables 1 and 2. Specifically, with regard to the oral drug treatment administered to patients between T1 and T2, there was no variation. In reference, however, to ESK-

TABLE 1. Sociodemographic and Clinical Characteristics of the Study Sample (n = 30)

	TRD subjects (n = 30)
Sex ratio (M/F)	9/21
Age (years)	68.67 ± 3.43
Duration of MDE (months)	19.38 ± 10.83
Age at onset of depression (years)	47.24 ± 12.55
Number of previous depressive episodes (n)	5.28 ± 3.30
Number of adequate antidepressant trials (n)	3.20 ± 0.85
Illness Duration (years)	20.45 ± 12.28
Status	
Single	4 (13.33%)
Married	22 (73.33%)
Divorced /widowed	4 (13.33%)
Occupation (Unemployed/Employed)	19/11
Psychiatric Comorbidities	
General Anxiety Disorder	3 (10%)
Personality Disorder	3 (10%)
Obsessive Compulsive Disorder	2 (6.67%)
Eating Disorder	1 (3.33%)

Notes: F: female; M: male; MDE: major depressive episode; TRD: treatment-resistant depression.

TABLE 2. Current Pharmacotherapies and ESK-NS Administration in the Study Sample (n = 30)

Treatments	
Serotonin-norepinephrine reuptake inhibitors	10 (33.33%)
Duloxetine 60–120 mg	5
Venlafaxine 150–300 mg	5
Selective serotonin reuptake inhibitors	13 (43.33%)
Citalopram 20–40 mg	3
Fluoxetine 20 mg	1
Fluvoxamine 200 mg	2
Paroxetine 40–60 mg	3
Sertraline 100–150 mg	4
Other Antidepressants	19 (63.33%)
Bupropion 300 mg	1
Clomipramine 75–150 mg	4
Minocycline 200 mg	1
Mirtazapine 30–45 mg	3
Pramipexole 0.52 mg	1
Selegiline 10 mg	1
Trazodone 150–300 mg	4
Vortioxetine 10–20 mg	4
Mood Stabilizers	13 (43.33%)
Lamotrigine 200 mg	2
Lithium Carbonate 300–900 mg	5
Lithium Sulfate 83–166 mg	4
Valproic Acid 1,300 mg	2
Antipsychotics	20 (66.66%)
Aripiprazole 2.5 mg	2
Amisulpride 50 mg	1
Brexpiprazole 2 mg	2
Cariprazine 3 mg	1
Olanzapine 5 mg	1
Quetiapine XR 150–300 mg	8
Trifluoperazine 4 mg	1
Any Benzodiazepine	17 (56.66%)
Previous failed rTMS-approved therapy	2 (6.66%)
Previous failed ECT	1 (3.33%)
ESK-NS Administration	
Number of administrations during the study period (Mean ± SD)	14 ± 4.17
Average highest ESK-NS dosage: 28 mg	11 (36.66%)
Average highest ESK-NS dosage: 56 mg	13 (43.33%)
Average highest ESK-NS dosage: 84 mg	6 (20%)

Notes: ECT: electroconvulsive therapy; TMS: transcranial magnetic stimulation.

NS, most subjects were treated with low (28 mg, 36.66% of subjects) or medium (56 mg, 43.33%) doses of ESK-NS, while only 20% of subjects were treated with high doses of ESK-NS (84 mg). The administration regimen for ESK-NS adhered to the recommendations provided by the European Medicines Agency's Summary of Product Characteristics.[11] Given the age of the participants (over 65), all subjects started with a dosage of 28 mg, administered bi-weekly during the initial month (induction phase), followed by a transition to once-weekly administration for the subsequent 2 months. By EMA guidelines,[11] centers were allowed to increase dosages to 56 or 84 mg in case of limited response.

ESK-NS Antidepressant and Anxiolytic Effectiveness

After adjusting for age, rm-ANOVA shows a significant effect of time (i.e., "T0 versus T1 versus T2" interaction factor) on MADRS values ($F_{2.00,44.00}$ = 4.029, p = 0.025, ε = 0.892, η_p^2 = 0.155). Mauchly's test of sphericity was not significant: W = 0.879, χ_2^2 = 2.698, p = 0.2602.

MADRS values significantly decreased at both T1 (T0 versus T1: p_{holm} <0.001, Cohen'd = 0.840) and T2 follow-ups (T0 versus T2: p_{holm} <0.001, Cohen'd = 1.419; T1 versus T2: p_{holm} <0.001, Cohen'd = 0.579) (see Table 3 and Fig. 1).

Besides, considering the response, 8/30 subjects were responders at T1 (26.66%), while 16/30 were responders at T2 (53.3%) (χ_1^2= 0.375, p = 0.540). Remission rates significantly increased from T1 (3/30 subjects, 10%) to T2 follow-ups (10/30 subjects, 33.33%) (χ_1^2 = 4.800, p = 0.028).

Regarding ESK-NS anxiolytic action, after adjusting for age, rm-ANOVA indicates a significant effect of time (i.e., "T0 versus T1 versus T2" interaction factor) on HAM-A scores ($F_{2.00,34.00}$ = 8.875, p <0.001, ε = 0.765, η_p^2 = 0.262). Mauchly's test of sphericity was not significant: W = 0.692, χ_2^2 = 5.881, p = 0.083.

HAM-A values significantly decreased at both T1 (T0vsT1: p_{holm} <0.001, Cohen's d = 0.834) and T2 follow-ups (T0 versus T2: p_{holm} <0.001, Cohen's d = 1.409; T1 vs T2: p_{holm} = 0.003, Cohen's d = 0.575) (see Table 3 and Fig. 1).

Baseline Clinical Differences among T2 Remitters and Nonremitters

Patients not in remission at 3 months appear to have a higher frequency of depressive episodes (Remitters: 2.50 ± 1.96 versus nonremitters: 5.95 ± 3.274; Student's t = 3.040, dF = 27, p = 0.005), and to experience a longer duration of an ongoing depressive episode (Remitters: 7.00 4.99 versus nonremitters: 16.84 ± 12.751; Student's t_{27} = 2.332, p = 0.027) and a more severe depressive episode (MADRS baseline score, remitters: 30.10 ± 6.94 versus nonremitters: 37.17 ± 8.75; Student's t_{26} = 2.193, p = 0.037). Age and other baseline clinical variables (e.g., number of

TABLE 3. Mean (Standard Deviation) Values of MADRS and HAM-A in Older Adults with TRD at Baseline / Pretreatment (T0), at the End of the 1st Month of Treatment (T1), and at the End of the 3rd Month of Treatment (T2)

	MADRS			*HAM-A*		
	T0	**T1**	**T2**	**T0**	**T1**	**T2**
TRD subjects (n = 30)	34.91 (8.85)	22.91 (11.72)	15.25 (10.02)	29.89 (10.71)	20.89 (11.97)	14.68 (10.84)

Notes: HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; TRD: treatment-resistant depression.

previous antidepressant trials, duration of illness) were not significantly different between the two cohorts.

Treatment-Emergent Side Effects and Drop-Out Rates

Regarding drop-out rates and adverse effects, three participants withdrew at T1 (two due to ineffectiveness, one due to treatment-emergent adverse events/TEAE, specifically nausea, emesis, and vertigo), while three other participants discontinued at T2 (two due to ineffectiveness, one due to severe dizziness). In total, 6 out of 30 participants (20%) discontinued during the follow-up period. Adverse TEAEs related to ESK-NS were common in the entire cohort (19 out of 30 participants, 63.3%), with dizziness being the most common (15 out of 30, 50%, one case of severe dizziness), followed by dissociation (10 out of 30, 33.3%, two of whom reported intense dissociation), sedation (9 out of 30, 30%, one case of extreme sedation), and hypertension (4 out of 30, 13.33%).

The reported TEAEs were temporary and occurred immediately after administration, but they completely disappeared by the following day at the latest. There have been no reports of any persisting TEAEs.

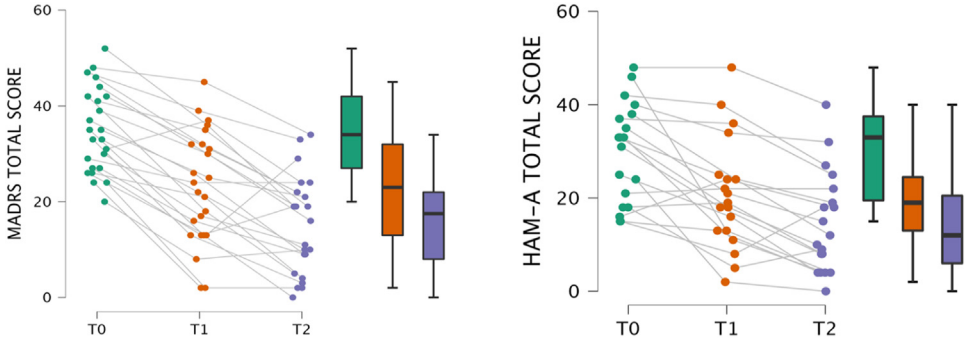
Besides, only 2/30 subjects experiencing TEAEs discontinued for excessive side effects.

No cases of psychomotor agitation or anxiety symptoms were documented.

DISCUSSION

Repeated doses of ESK-NS are associated with a significant reduction in depressive symptoms in real-world older adults with TRD, with large effect sizes (T0 versus T2 Cohen's d = 1.419). These results appear to be of great relevance considering the characteristics of the sample, with a proportion of subjects having tried other second- or third-line therapy strategies for TRD (e.g., I-MAO, dopamine-agonists, ECT, TMS) and considering the number of previous failed

FIGURE 1. MADRS and HAM-A scores variations across the different stages of the study, from baseline (T0), 1-month follow-up (T1) to 3-month follow-up (T2). Abbreviations: HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale.



antidepressant trials, which were even higher than those commonly necessary to define TRD (n = 3.20 ± 0.85).

Comparing these findings with regulatory trials on ESK-NS antidepressant efficacy in older patients, we found similar response and remissions rates at 1 month (T1) (Response Rates: 26.66% versus 27% reported by Ochs-Ross et al.; Remission Rates: 10% versus 17.5%), and also mean differences in the MADRS scores from baseline to 1 month were similar (-12 versus -12.70, respectively).[16] In the same way, our findings are also consistent with real-world data on intravenous ketamine effectiveness among older patients with respect to response rates at 1 month (i.e., 26.6% in our sample at T1 versus 27% observed with intravenous ketamine after acute administration).[22] Nonetheless, in comparison to both RCT on ESK-NS and real-world data on intravenous ketamine, our extended period of observation provides us with the chance to evaluate the overall impact of delayed response (which implies in our sample a significant increase of both response and remission rates). Furthermore, the observed response and remission rates at T2 are similar to those observed in the full sample previously reported by our research group,[17] suggesting that ESK-NS has clinically relevant effectiveness in older adults experiencing TRD.

Commonly, treatment strategies in older TRD adults involve augmentation with antipsychotic medication, as well as augmentation/switching with another antidepressant or physical therapy (i.e., TMS or ECT). A recent significant real-world study has directly compared antidepressant effectiveness of several treatment strategies in older TRD adults (i.e., aripiprazole augmentation, bupropion augmentation/switching, lithium augmentation, nortriptyline switch).[23] Interestingly, comparing our findings with those obtained by the aforementioned study, ESK-NS seems to show higher MADRS decrease and also higher remission rates with respect to all the treatment strategies studied (remission rates, ESK-NS: 33.33%, aripiprazole/augmentation: 28.9%, bupropion/augmentation: 28.2%, bupropion/switching: 19.3%, lithium/augmentation:18.9%, nortriptyline/switching:21.5%), even if our samples seem to be more difficult-to-treat, with higher failed antidepressant trials in the current episode (esk-ns: 3.20 ± 0.85, aripiprazole/augmentation: 2.3 ± 0.8, bupropion/augmentation: 2.20 ± 0.7, bupropion/switching: 2.4 ± 0.9, lithium/augmentation: 2.5 ± 0.9, nortriptyline/switching: 2.6 ± 1.1).[23] These data further highlight the significance of our preliminary results. However, It should be mentioned that reported TEAEs in our sample are higher than those reported with other augmentation strategies,[23] and this should be taken into account when considering ESK-NS as a potential augmentation strategies.

As regarding predictors able to affect response to ESK-NS, we found that patients with more severe manifestations of TRD (i.e., *more frequent recurrences, higher depression severity*, and l*onger duration of the depressive episode*) are less likely to achieve remission following treatment with ESK-NS. This aligns with larger cohort studies that designate depressive severity as a predictor of nonresponse to ketamine and esketamine.[24,25]

ESK-NS shows significant anxiolytic effectiveness among older TRD subjects. This further corroborates findings from literature of a significant efficacy on anxious symptoms of both ketamine and ESK-NS in TRD subjects.[26–28] Besides, anxious symptoms and co-occurring anxiety disorder during a depressive episode are often considered as predictors of treatment resistance.[29] In light of this, our finding of an anxiolytic effectiveness of ESK-NS in older TRD subjects is noteworthy.

Concerning safety and tolerability, TEAEs rates reported in our sample (i.e., 63.3%) are similar to those reported by RCT in older and nonolder TRD patients[12,14,16] and previous naturalistic studies on ESK-NS,[17,27] even though higher levels of dizziness (50%) and sedation (30%) seem to be experienced by these subjects compared to those reported in nonolder adults.[12,14,17] Intriguingly, unlike what has been observed in the RCT of ESK-NS conducted on older TRD adults, no serious adverse events have been reported in our sample.[15]

These findings are particularly interesting and, if replicated in larger real-world trials, should be considered when evaluating ESK-NS as therapeutic strategies in older patients: a higher probability of experiencing TEAEs related to ESK-NS, including dizziness and sedation, could be the trade-off for achieving remission in this group of patients. This should lead to a careful selection of older patients to undergo ESK-NS in practice, potentially avoiding individuals with concomitant therapies able to cause dizziness or sedation (e.g., benzodiazepines, antipsychotics).

However, the effectiveness of ESK-NS is still noteworthy and similar to outcomes obtained in nonolder adults, with the perspective of further therapeutic potential in this population.[10]

Furthermore, drop-out rates observed in our cohort (20%) appear to be higher compared to those documented in the full sample of adults previously reported by our group.[17]

As noted above, older patients often exhibit more resistant forms of TRD, characterized by prolonged episode durations and a greater number of prior antidepressant trials. This may account for the increased rates of inefficacy observed, leading to greater drop-out in this population.

Additionally, this is consistent with research demonstrating that brain in late life exhibits impaired neuroplasticity mechanisms (a key target for glutamatergic modulators such as ESK-NS),[9] which seem to be more challenging to ameliorate and are correlated with the typical neurodegenerative processes related to ageing.[30] This evidence could also explain the significant increase of response and remission rates from T1 to T2 in our sample (response rates: from 26.66% to 53.3%; remission rates: from 10% to 33.33%): from a neurobiological perspective, an aging brain characterized by prolonged brain damage could require longer exposure to neuroplasticity boosters (such as glutamatergic agents) to determine a real improvement in depressive symptoms.

Interpretation of our findings should consider further limitations, such as those related to the post-hoc analysis itself. For instance, the recruitment of participants was not age-based, and the absence of a control group prevents accounting for placebo/expectancy effects or regression to the mean due to repeated sampling. Additionally, the limited sample size, as well as the lack of data on co-occurrent medical conditions and on other medications used by the patients, precluded making robust conclusions regarding the safety and tolerability of ESK-NS in this population. Therefore, these factors necessitate further evaluation within the context of broader clinical studies.

Additionally, it's crucial to understand that the group of older adults with TRD studied here primarily consists of individuals aged between 65 and 71 years. This fact should be considered when interpreting our results. Specifically, the applicability of ESK-NS may not be as clear or feasible for even older patients, namely those aged over 75 years.

Moreover, this post-hoc analysis didn't include any measures of cognitive outcomes following the ESK-NS treatment, an aspect that could be significant, particularly in older adults with TRD, where cognitive impairment is a common occurrence. The lack of these measurements can be attributed to the fundamental design of the original study which did not primarily aim to assess the cognitive impacts of ESK-NS.[17] Future studies on ESK-NS in older individuals should properly evaluate cognitive effects to understand the treatment's full influence on this aspect, as well as to identify any potential safety risks related to cognitive function.

Despite the various limitations, the primary strength of this study is that it provides a real-world representation of ESK-NS use among older TRD patients, thereby offering an initial demonstration of its efficacy within this vulnerable population.

CONCLUSION

The results here presented preliminarily highlight the effectiveness of ESK-NS among older adults with TRD, who represent subjects with a long history of depression, as well as with numerous failures of previous antidepressant trials and several second-line and off-label therapies used for TRD (as in our sample represented by ECT, TMS, I-MAO, and dopamine agonists therapies), which further underscores the significance of our results. Indeed, older adults with TRD treated with ESK-NS tend to experience debilitating adverse events more frequently, and this should be taken into consideration when selecting patients to be treated with ESK-NS. Future prospective studies should evaluate the effectiveness of ESK-NS in well-characterized larger sample sizes, perhaps evaluating the overall impact of this treatment on cognitive symptoms.

AUTHOR CONTRIBUTIONS

All persons who meet the authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

DATA SHARING STATEMENT

Data are available upon request to the corresponding author.

DISCLOSURES

Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, Neuraxpharm, Rovi, and Recordati. Giorgio Di Lorenzo has been a speaker and / or a consultant for Angelini, Janssen-Cilag, Livanova, Lundbeck, Neuraxpharm, Otsuka, and Recordati. Dr. Roger McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, Atai Life Sciences. Dr. Roger McIntyre is the CEO of Braxia Scientific Corp. The remaining authors declare that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.

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