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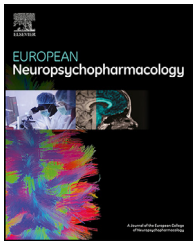

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SHORT COMMUNICATION

Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: A viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study

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Abstract
Esketamine, the S-enantiomer of ketamine, has recently emerged as a therapy for treatment-resistant depression (TRD), showing both rapid antidepressant action and good efficacy and high safety. It is also indicated for the acute short-term treatment of psychiatric emergency due to major depressive disorder (MDD) and for depressive symptoms in adults with MDD with acute suicidal thoughts/behavior. We here provide preliminary insights on esketamine nasal spray (ESK-NS) effectiveness and safety among patients with a substance use disorder (SUD) within the sample of patients with TRD collected for the observational, retrospective, multicentre REAL-ESK study. Twenty-six subjects were retrospectively selected according to the presence of a SUD in comorbidity. Subjects enrolled completed the three different follow-up phases (T0/baseline, T1/after one month, and T2/after three months) and there were no dropouts. A decrease in Montgomery-Asberg depression rating scale (MADRS) scores was recorded, thus highlighting the antidepressant efficacy of ESK-NS (MADRS decreased from T0 to T1, $t = 6.533$, df=23, $p<0.001$, and from T1 to T2, $t = 2.029$, df=20, $p = 0.056$). Considering tolerability and safety issues, one or more side effects were reported by 19/26 subjects (73%) after treatment administration. All reported side effects were time-dependent and did not cause significant sequelae; among them, dissociative symptoms (38%) and sedation (26%) were the most frequently reported. Finally, no cases of abuse or misuse of ESK-NS were reported. Despite study limitations related to the inherent nature of the study, a limited number of patients, and a short follow-up period, ESK-NS showed to be effective and safe in patients diagnosed with TRD comorbid with a SUD.

1. Introduction

The concept of treatment-resistant depression (TRD) came from the clinical observation of patients who do not respond to treatment, and it is unquestionably clinically relevant, although difficult to define (Brown et al., 2019; Rybak et al., 2021; Wilkowska and Cubała, 2022). The definition adopted by the multinational European research consortium 'Group for the Study of Resistant Depression' (GSRD) requires at least two failed trials, either consecutive or as combination or augmentation therapy, resulting in a comparably high degree of severely ill and resistant patients (Kautzky et al., 2019). Symptom severity, psychotic and melancholic features, suicidality, comorbid anxiety and personality disorders, higher number of antidepressants administered previously, and lifetime depressive episodes as well as longer duration of the current episode, previous hospitalisations, positive family history of depression, and early age of onset are considered the most prominent risk factors for TRD (Kautzky et al., 2019; Bartova et al., 2019).

Depression and other mental disorders may precede the presentation of a substance use disorder (SUD), irrespective of the substance used (Brenner et al., 2019). Conversely, alcohol and drug dependence can often lead to various negative mental, physical, and economic outcomes, being the 12-month prevalence of alcohol or drug dependence in major depressive disorder (MDD) patients estimated at about 12–30% (Brenner et al., 2019). In a population-based cohort study on 121 669 MDD patients, TRD patients had an elevated risk of subsequent SUD diagnosis compared to other MDD patients both $\leq$ 1 and $>$ 1 year after antidepressant initiation, respectively 51% during the first year after starting antidepressants and 39% thereafter, with risks more elevated for the subcategories involving opioid and sedative use disorders (Brenner et al., 2019). In a subsequent study by the same authors, the results were replicated, finding that SUD before or during treatment increases the risk for subsequent TRD in antidepressant-treated patients with depression (Brenner et al., 2020) leading to worse treatment outcomes due to a generally lower effect of antidepressants in the presence of comorbidity with SUD (Brenner et al., 2019; Brenner et al., 2020; Nunes and Levin, 2004).

Intranasal esketamine (ESK-NS), the S-enantiomer of ketamine, has recently emerged as a treatment for TRD, showing both rapid antidepressant action and good efficacy and high safety not only in experimental but also in naturalistic settings (McIntyre et al., 2021; Martinotti et al., 2022; Martinotti et al., 2023; Lengvenyte et al., 2022) It is also indicated for the acute short-term treatment of psychiatric emergency due to (MDD-PE) and for depressive symptoms in adults with MDD with acute suicidal thoughts or behavior (MDSI) (Lengvenyte et al., 2022). Considering that ketamine infused in a sub-anesthetic dose, integrated with behavioral treatment, has been shown to reduce alcohol and cocaine use (Lengvenyte et al., 2022), and in view of the presence of patients with a SUD within the sample of TRD patients collected for the observational, retrospective, multicentre REAL-ESK study (Martinotti et al., 2022; Martinotti et al., 2023) and treated with ESK-NS, we provide here a prelimi-

Table 1 Dose schedule of Esketamine-Nasal Spray (ESK-NS) according to the Summary of Product Characteristics (SPC).

INDUCTION PHASE	MAINTENANCE PHASE	
WEEKS 1–4	WEEKS 5–8	FROM WEEK 9
Starting day 1 dose: 56 mg	56 mg or 84 mg once weekly	56 mg or 84 mg every 2 weeks or once weekly
Subsequent doses: 56 mg or 84 mg twice a week	During the maintenance phase, ESK-NS dosing should be individualized to the lowest frequency to maintain remission/response The need for continued treatment should be re-examined periodically	

nary overview of its effectiveness and safety in this category of patients.

2. Materials and methods

This analysis represents a post-hoc analysis of the REAL-ESK study (Martinotti et al., 2022; Martinotti et al., 2023), focusing primarily on the effectiveness and safety of ESK-NS in subjects with TRD and SUD. Consequently, twenty-six subjects were retrospectively selected according to the presence of a SUD in comorbidity. The centres involved in the REAL-ESK study, as well as the inclusion and exclusion criteria were extensively described in our previous work by the REAL-ESK study group (Martinotti et al., 2022; Martinotti et al., 2023). Dose schedule followed the Summary of Product Characteristics (SPC) (Spravato 2023) according to Table 1.

Retrospective anamnestic data were collected to include information on sociodemographic factors, history of the disease, treatment history of the current episode of depression, antidepressant trials experienced during the current episode, augmentation strategies (e.g., the combined use of mood stabilizers or antipsychotic medications), and other therapeutic tools used to treat TRD. Data collection also covered premature study withdrawal or the occurrence of clinically relevant events, such as hospitalizations or discharge from hospital care, relapse of symptoms, or remission of major depressive episodes. Anamnestic data were obtained from the patients' medical records at baseline (T0), while psychometric assessments were collected at T0, one month (T1) and three months (T2) after the start of treatment. Thus, at least, treatment duration was of three months, periodically re-examining the need for continued treatment from week 9, as reported in the SPC. During the maintenance phase, ESK-NS dosing was individualized to the lowest frequency to maintain remission/response. Where discontinued, esketamine did not cause withdrawal symptoms or require supportive pharmacological treatment. Clinicians used the Montgomery-Asberg depression rating scale (MADRS) to characterize depressive symptoms. Patients were defined as responders with an overall 50% reduction in the MADRS score from baseline assessment (Popova et al., 1), while remission was defined as a MADRS score <10 (Frank et al., 1991). Statistical analyses were performed using SPSS 20.0 software (SPSS Inc.) and JASP for Mac (JASP version: 0.16.4; JASP Team, 2022). All tests were two-tailed, with a level of statistical significance set at $p < 0.05$. Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are reported as mean numbers and percentages. Student's *t*-test was conducted to assess changes in continuous variables, whereas the Pearson $\chi 2$ test was performed for categorical variables. Furthermore, a general linear model approach using repeated-measure ANOVA (rm-ANOVA) was used to analyze the "between factor" × "within factor" interaction effect (between factor: alcohol vs benzodiazepine vs cannabis vs cocaine use; within factor, treatment time: base- line/T0 vs. at the end of the 1st month of treatment/ T1 vs. at the end of the 3rd month of treatment/T2) on MADRS total scores.

3. Results

Of the 26 subjects with TRD and comorbid SUD included, 13 had an alcohol use disorder, 5 a benzodiazepine use disorder, 4 a cannabis use disorder and 4 a cocaine use disorder. The subjects enrolled completed the three different follow-up phases (T0, T1, T2) and there were no dropouts. The sample consisted mainly of subjects presenting with a severe form of depression (MADRS score: 33.72±8.32), recurrent (number of previous MDEs: 4.34±3) and with several failed antidepressant attempts (3.57±0.98), with some subjects experiencing physical antidepressant therapies (i.e., repetitive transcranial magnetic stimulation/rTMS and electroconvulsive therapy/ECT) as part of their treatment algorithms. All socio-demographic and clinical characteristics are detailed in Table 2.

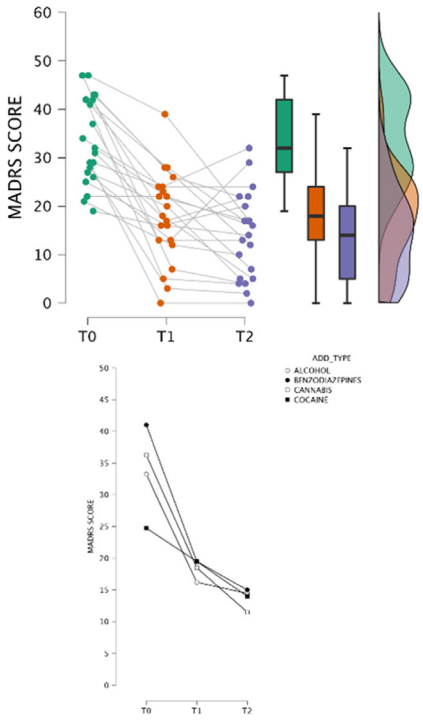
The Paired Student T-test showed a significant effect of time in determining the decrease in MADRS scores, thus highlighting the antidepressant efficacy of ESK-NS. Specifically, MADRS values decreased significantly from T0 to T1 ($t = 6.533$, df=23, $p<0.001$), but not significantly from T1 to T2, although a trend towards significance was evident ($t = 2.029$, df=20, $p = 0.056$) (Fig. 1).

Response and remitters levels exhibited a significant increase when moving from T1 to T2 evaluations after treatment with ESK-NS. Indeed, responders were 7/26 (27%) subjects at one-month and 13/26 (50%) at three-months, with a statistically significant increase (T1 responders vs. T2 responders: $\chi 2 = 3.962$ df $= 1$ $p = 0.047$). With regard to remitters from the current depressive episode, 4/26 subjects were early remitters after one month of ESK-NS (15.4%), while 8/26 were remitters at three month (30.8%), with a significant increase from T1 to T2 (T1 remitters vs. T2 remitters: $\chi 2 = 9.600$ df $= 1$ $p = 0.002$). Stratifying the sample according to the different comorbidities, a higher severity of depressive symptoms at baseline is observed in the group with benzodiazepine abuse (41 ± 6.93) compared to cannabis users (36.25 ± 7.89), AUD (33.17 ± 8.06) and patients with cocaine use disorder (24.75 ± 3.86), with the latter showing the lowest severity of depressive symptoms ($F = 3.564$, df=3, $p = 0.032$). In the rm-ANOVA model, the multivariate test showed a non-significant effect of the interaction factor "alcohol vs. benzodiazepine vs. cannabis vs. cocaine use" X "T0vsT1vsT2″ ($F = 1.137$, df=4.83, $p = 0.364$), thus indicating the absence of a statistically significant between-group variation (Fig. 1). Considering tolerability and safety issues, one or more side effects were reported by 19/26 subjects (73%) after treatment administration. Among them, dissociative symptoms (10/26 subjects, 38%), sedation (7/26 subjects,

Table 2 Sociodemographic and clinical characteristics of the sample.

	TRD subjects with comorbid SUD ($n = 26$)
Sex ratio (M/F)	15/11
Age (years)	48.88± 11.82
Depression episodes duration (months)	13.16 ± 9.71
Age at onset of depression (years)	29.15 ± 4.35
Number of previous depressive episodes (n)	4.34 ± 3.06
Number of adequate antidepressant trials (n)	3.57 ± 0.98
Status	
Single	11 (42%)
Married	10 (38%)
Divorced /widowed	5 (19%)
Occupation	
Unemployed/Employed	13/13 (50%)
Comorbid SUD	
Alcohol Use Disorder	13 (50%)
Benzodiazepine misuse	5 (19%)
Cannabis Use Disorder	4 (15%)
Cocaine Use Disorder	4 (16%)
Treatments	
Serotonin-norepinephrine reuptake inhibitors	13 (50%)
Duloxetine 60-120 mg	6
Venlafaxine 150-300 mg	7
Selective serotonin reuptake inhibitors	12 (46%)
Citalopram 20-40 mg	3
Escitalopram 20 mg	1
Fluoxetine 20 mg	2
Fluvoxamine 200 mg	1
Paroxetine 40-60 mg	3
Sertraline 100-150 mg	2
Other Antidepressants	20 (77%)
Bupropion 150-300 mg	7
Mirtazapine 30-45 mg	2
Minocycline 200 mg	1
Trazodone 50-100 mg	3
Trazodone 150-300 mg	3
Vortioxetine 10-20 mg	4
Mood Stabilizers	15 (57%)
Lamotrigine 200 mg	3
Lithium Carbonate 300-900 mg	6
Lithium Sulfate 83-166 mg	5
Valproic Acid 1300 mg	1
Antipsychotics	12 (46%)
Aripiprazole 10-20 mg	2
Asenapine 10 mg	1
Brexpiprazole 2 mg	2
Levosulpride 75 mg	1
Quetiapine IR 25-100 mg	3
Quetiapine XR 150-300 mg	3
Previous failed rTMS approved therapy	3 (11%)
Previous failed ECT	3 (11%)
Esketamine dosage: 28 mg	2 (8%)
Esketamine dosage: 56 mg	6 (23%)
Esketamine dosage: 84 mg	18 (69%)

Abbreviations: ECT: Electroconvulsive therapy; F: female; IR: immediate release; M: male; SUD: substance use disorder; rTMS: repetitive Transcranial Magnetic Stimulation; TRD: treatment-resistant depression; XR: extended release.



	MADRS		
	T0	T1	T2
Overall sample	33.72 (8.32)	17.90 (9.41)	13.91 (8.99)
TRD subjects with AUD	33.22 (8.95)	16.22 (8.36)	14.44 (10.99)
TRD subjects with benzodiazepine misuse	41 (6.93)	19.5 (9.60)	15 (8.72)
TRD subjects with cannabis use disorder	36.25 (7.89)	18.5 (16.38)	11.5 (7.85)
TRD subjects with cocaine use disorder	24.75 (3.86)	19.5 (5.26)	14 (8.28)

Fig. 1 MADRS score reduction between baseline (T0), one-month (T1) and three-month (T2) observations after ESK-NS introduction in the overall sample and considering the addiction-type (alcohol vs benzodiazepine vs cannabis vs cocaine use) interaction factor
Abbreviations: AUD: alcohol use disorder; ESK-NS: esketamine nasal spray; MADRS: Montgomery-Asberg depression rating scale; TRD: treatment-resistant depression.

26%), increased blood pressure (3/26 subjects, 11%), hypomanic symptoms (3/26 subjects, 11%), psychomotor agitation (1/26 subjects, 4%), and anxiety (1/26 subjects, 4%) were the most frequently reported. All reported side effects were time-dependent and did not cause significant sequelae. Finally, no cases of abuse or misuse of ESK-NS were reported.

4. Discussion

To the very best of our understanding, findings presented provide preliminary insights on the antidepressant action and safety of ESK-NS for the treatment of TRD patients comorbid with a SUD, which, differently from common experimental trials, were included in our naturalistic sample. As previously recorded in the REAL-ESK study (Martinotti et al., 2022; Martinotti et al., 2023), although the limitations related to the number of patients involved, MADRS score reduction was here recorded from the baseline. Notably, the baseline score was higher in subjects with a SUD involving a central nervous system (CNS) depressant, such as alcohol or benzodiazepines, while it was lower in subjects with a cocaine use disorder, hypothetically distinguishing between a depressive condition synergistically conditioned by a depressive agent and a depressive condition sustained by a stimulating agent. Moreover, in being no statistically significant between-group variation in the antidepressant action of ESK-NS (Fig. 1), the efficacy of ESK-NS is here confirmed in all groups of SUD, speculating on promising effects of esketamine on glutamatergic dysregulation and altered functioning of the prefrontal cortex and mesolimbic regions commonly occurring in SUD, independently from the type of substance used (Martinotti et al., 2021). This is consistent with previous studies demonstrating ESK-NS potential benefits in the management of post-traumatic stress disorder, suicidal ideation, pain relief, obsessive-compulsive disorder, eating disorders, and SUD (Gutiérrez and Vázquez, 2022). An important finding of the study concerns the safety of ESK-NS for the treatment of patients with SUD, who have shown neither moderate nor severe adverse events related to pharmacological interactions of ESK-NS with any other substance. Typical side effects were dissociation and sedation, as previously recorded in both clinical and pharmacovigilance studies (McIntyre et al., 2021; Guo et al., 2022; Wajs et al., 2020); specifically, side effects monitoring was limited to two hours as requested by the SPC, and they did not require any major medical intervention. Moreover, consistently with previous data, in the time of observation there were no reports of new-onset drug or alcohol misuse (Wajs et al., 2020). Similarly, craving occurrence was not reported. Finally, no misuse nor diversion of ESK-NS were here recorded.

5. Conclusion

Despite study limitations related to the inherent nature of the study, a limited number of patients, and a short follow-up period (3 months), ESK-NS showed to be effective and safe in patients diagnosed with TRD comorbid with a SUD.

Although research efforts are needed to clarify the many unknowns associated with the long-term use of ESK-NS, including a specific assessment of substance abuse related issues, e.g. relapse of substance use, craving, etc., which were out of the aims of the REAL-ESK study, the results presented, albeit preliminary, allow the option of ESK-NS to be safely offered in rather complex clinical conditions to be treated, e.g. in relation to comorbidity with SUD.

Authors' statement

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. Specifically, GM, SC, and GdA conceptualized the hypothesis and the design of the study. AVi, GM, SC, GdA, SDF, MDN, IA, RB, SB, MP, MC, and BDO were responsible for the patient recruitment and the collection of clinical data. GM, SC and GdA performed the statistical analysis, carried out data interpretation, and wrote the first draft of the manuscript. AVi, SDF, MDN, IA, RB, SB, MP, MC, SS, and BDO revised the manuscript and provided substantial comments. All authors contributed and approved the final manuscript.

Declaration of Competing Interest

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, and Recordati.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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References

Bartova, L., Dold, M., Kautzky, A., Fabbri, C., Spies, M., Serretti, A., Souery, D., Mendlewicz, J., Zohar, J., Montgomery, S., Schosser, A., Kasper, S., 2019 Jul. Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice. World J. Biol. Psychiatry 20 (6), 427–448. doi:10.1080/15622975.2019.1635270.

Brenner, P., Brandt, L., Li, G., DiBernardo, A., Bodén, R., Reutfors, J., 2019 Jul. Treatment-resistant depression as risk factor for substance use disorders-a nation-wide register-based cohort study. Addiction 114 (7), 1274–1282. doi:10.1111/add.14596.

Brenner, P., Brandt, L., Li, G., DiBernardo, A., Bodén, R., Reutfors, J., 2020 Apr. Substance use disorders and risk for treatment resistant depression: a population-based, nested case-control study. Addiction 115 (4), 768–777. doi:10.1111/add.14866.

Brown, S., Rittenbach, K., Cheung, S., McKean, G., MacMaster, F.P., Clement, F., 2019 Jun. Current and common definitions of treatment-resistant depression: findings from a systematic review and qualitative interviews. Can. J. Psychiatry 64 (6), 380-387. doi:10.1177/0706743719828965.

Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., Weissman, M.M., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch. Gen. Psychiatry 48 (9), 851–855. doi:10.1001/archpsyc.1991.01810330075011.

Guo, H., Wang, B., Yuan, S., Wu, S., Liu, J., He, M., Wang, J., 2022 Apr 8. Neurological adverse events associated with esketamine: a disproportionality analysis for signal detection leveraging the FDA adverse event reporting system. Front. Pharmacol. 13, 849758. doi:10.3389/fphar.2022.849758, Erratum in-Front Pharmacol2022 Nov 09131075966.

Gutiérrez, G., Vázquez, G., 2022 Dec. Pros and cons of esketamine treatment in psychiatry. Eur. Neuropsychopharmacol. 65, 12–14. doi:10.1016/j.euroneuro.2022.09.003.

Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G.S., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Fabbri, C., Serretti, A., Lanzenberger, R., Dikeos, D., Rujescu, D., Kasper, S., 2019 Jan. Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. Acta Psychiatr. Scand. 139 (1), 78–88. doi:10.1111/acps.12959.

Lengvenyte, A., Strumila, R., Olié, E., Courtet, P., 2022 Apr. Ketamine and esketamine for crisis management in patients with depression: why, whom, and how? Eur Neuropsychopharmacol 57, 88–104. doi:10.1016/j.euroneuro.2022.02.004.

Martinotti, G., Chiappini, S., Pettorruso, M., Mosca, A., Miuli, A., Di Carlo, F., D'Andrea, G., Collevecchio, R., Di Muzio, I., Sensi, S.L., Di Giannantonio, M, 2021 Jun 27. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. Brain Sci. 11 (7), 856. doi:10.3390/brainsci11070856.

Martinotti, G., Vita, A., Fagiolini, A., Maina, G., Bertolino, A., Dell'Osso, B., Siracusano, A., Clerici, M., Bellomo, A., Sani, G., d'Andrea, G., Chiaie, R.D., Conca, A., Barlati, S., Di Lorenzo, G., De Fazio, P., De Filippis, S., Nicolò, G., Rosso, G., Valchera, A., Nucifora, D., Di Mauro, S., Bassetti, R., Martiadis, V., Olivola, M., Belletti, S., Andriola, I., Di Nicola, M., Pettorruso, M., McIntyre, R.S., di Giannantonio, M.REAL-ESK Study Group, 2022 Dec 15. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). J. Affect. Disord. 319, 646–654. doi:10.1016/j.jad.2022.09.043.

Martinotti, G., Dell'Osso, B., Di Lorenzo, G., Maina, G., Bertolino, A., Clerici, M., Barlati, S., Rosso, G., Di Nicola, M., Marcatili, M., d'Andrea, G., Cavallotto, C., Chiappini, S., De Filippis, S., Nicolò, G., De Fazio, P., Andriola, I., Zanardi, R., Nucifora, D., Di Mauro, S., Bassetti, R., Pettorruso, M., McIntyre, R.S., Sensi, S.L., di Giannantonio, M., Vita, A.REAL-ESK Study Group, 2023 Jan 13. Treating bipolar depression with

esketamine: safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. Bipolar Disord. doi:10.1111/bdi.13296.

McIntyre, R.S., Rosenblat, J.D., Nemeroff, C.B., Sanacora, G., Murrough, J.W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D.V., Lopez Jaramillo, C., Kasper, S., Kratiuk, K., Lee, J.G., Lee, Y., Lui, L.M.W., Mansur, R.B., Papakostas, G.I., Subramaniapillai, M., Thase, M., Vieta, E., Young, A.H., Zarate Jr, C.A., Stahl, S, 2021 May 1. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am. J. Psychiatry 178 (5), 383–399. doi:10.1176/appi.ajp.2020.20081251.

Nunes, E.V., Levin, F.R., 2004. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA 291 (15), 1887–1896. doi:10.1001/jama.291.15.1887.

Popova, V., Daly, E.J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M.E., Shelton, R.C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W.C., Singh, J.B., 2019 Jun 1. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry 176 (6), 428–438. doi:10.1176/appi.ajp.2019.19020172, Epub 2019 May 21Erratum in: Am J Psychiatry2019 Aug 1176(8)669.

Rybak, Y.E., Lai, K.S.P., Ramasubbu, R., Vila-Rodriguez, F., Blumberger, D.M., Chan, P., Delva, N., Giacobbe, P., Gosselin, C., Kennedy, S.H., Iskandar, H., McInerney, S., Ravitz, P., Sharma, V., Zaretsky, A., Burhan, A.M., 2021 Apr. Treatment-resistant major depressive disorder: canadian expert consensus on definition and assessment. Depress Anxiety 38 (4), 456–467. doi:10.1002/da.23135.

Spravato, INN-esketamine-Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf (Assessed 5th April 2023).

Wajs, E., Aluisio, L., Holder, R., et al., 2020. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). J. Clin. Psychiatry 81, 19m12891.

Wilkowska, A., Cubała, W.J., 2022 Nov 23. The downstaging concept in treatment-resistant depression: spotlight on ketamine. Int. J. Mol. Sci. 23 (23), 14605. doi:10.3390/ijms232314605.