Eur J Psychiat. 39 (2025) 100313

Contents lists available at ScienceDirect

The European Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ejpsy

Original article

Treatment-resistant depression and intranasal esketamine: Spanish clinical consensus on practical aspects

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ARTICLE INFO

Keywords:
Intranasal esketamine
Spain
Consensus
Psychiatric comorbidities
Treatment algorithm

ABSTRACT

Background: Pharmacological management of major depressive disorder has traditionally relied on antidepressants targeting the monoaminergic pathway. Treatment-resistant depression (TRD) patients have been frequently excluded from registrational trials, resulting in a lack of clear clinical recommendations for an optimised management. In recent years, treatments based on other mechanisms of action have been developed and approved. Intranasal esketamine is a novel non-monoaminergic treatment directed to improve neuroplasticity through the modulation of the glutamatergic system. In this clinical consensus we aimed to provide expert guidance on the use of intranasal esketamine for TRD patients based in our clinical practice in Spain.

Methods: A scientific committee of nine psychiatrists, experts in TRD in Spain, reviewed the literature (grey literature and articles/scientific communications published in English or Spanish between January 2014 and January 2024 in PubMed). Statements on practical aspects of TRD management with intranasal esketamine were developed in a first meeting following a discussion group approach, refined in a second meeting with a nominal group technique, and finally drafted after consensus in a third meeting.

Results: We recommend a treatment algorithm for the management of TRD with intranasal esketamine. Recommendations were made for specific clinical profiles with other psychiatric comorbidities, which are not contraindications, and for patients who do not have at least a 50 % reduction in symptoms during the first induction phase (partial responders at the end of an induction phase). Treatment should be given in the same health centre where the patient normally receives mental care. The patient's clinical progress will determine early optimisation of intranasal esketamine dose during the induction phase, the need for flexible doses/repeating the induction treatment phase, customisation of management, and treatment duration. We described

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https://doi.org/10.1016/j.ejpsy.2025.100313
Received 27 February 2025; Accepted 23 April 2025
Available online 2 May 2025

factors impacting the use of intranasal esketamine and made recommendations on the characteristics of the ideal setting for its administration. Socio-economic aspects of intranasal esketamine were reviewed.
Conclusions: This is the first consensus developed in Spain regarding practical aspects of TRD management with intranasal esketamine, with a treatment algorithm for patients who are only partial responders at the end of the induction phase.

Introduction

Major depressive disorder (MDD) that has an inadequate response to at least two antidepressant treatments given at adequate dose and duration is known as treatment-resistant depression (TRD),[1] which is estimated to affect approximately a third of people receiving antidepressant treatment; however, epidemiology studies have reported up to 55 % of patients with MDD as having TRD.[2,3] Patients with depression may experience long-term symptoms and chronic episodes.[4–6] Compared to MDD, TRD imposes a higher burden on patients, mainly related to significantly higher comorbidity, mortality, and suicide-related behaviours.[7] TRD also severely impacts patients' quality of life and functionality.[8,9] Moreover, TRD is associated with increased direct and indirect costs compared with MDD, driven by greater healthcare utilisation, permanent disability, and productivity loss.[7,10–13]

Guidelines for treating MDD differ in their recommendations, and there is currently no consensus on the optimal approach for treating patients with TRD.[14–17] This leads to unoptimised use of a wide variety of both pharmacologic and non-pharmacologic strategies that have unsatisfactory results in over two-thirds of patients.[3,18] Indeed, a study assessing real-world treatment patterns of TRD in Europe found that the five most used approaches accounted for only 40 % of all treatments administered.[3] Beyond evidence from clinical trials, there are scarce data on treatment patterns and outcomes of patients with TRD.[18] Given the limited efficacy of conventional antidepressants, and the decreased likelihood of remission with increasing number of successive acute treatments,[19] there is an urgent need to adopt more effective treatment approaches for TRD.

Pharmacological management of MDD has traditionally consisted of antidepressants that target the monoaminergic pathway, which have not been evaluated in the TRD population.[20,21] For patients who do not achieve the desired results, alternative approaches, such as repetitive transcranial magnetic stimulation or electroconvulsive therapy have been utilised.[2] However, treatments relying on other mechanisms of action have been developed and approved in recent years.[21] In this context, intranasal esketamine has emerged as a novel non-monoaminergic treatment that improves neuroplasticity through the modulation of the glutamatergic system,[22] and it is the only antidepressant approved specifically for TRD in Europe.[23,24] It is also the only antidepressant in the European Medicines Agency (EMA)'s critical medicine list.[25] A robust clinical programme demonstrated the efficacy and safety of intranasal esketamine combined with an oral antidepressant in patients with TRD, rapidly improving depressive symptoms and delaying relapse compared with an antidepressant alone.[26] Intranasal esketamine also achieved better outcomes than augmentation with an antipsychotic in a head-to-head phase 3 trial,[27] and was found to be superior to currently used polypharmacy strategies in an indirect adjusted comparison of clinical trial and real-world data.[28]

In this clinical consensus, we aimed to provide expert guidance on the use of intranasal esketamine in clinical practice in Spain. This is particularly necessary, as a recent real-world study conducted in Spain evidenced a pattern of use of intranasal esketamine in routine clinical practice that differs from the recommendations of the Spanish Agency of Medicines and Medical Devices.[29] This highlights the lack of standardised protocols for the use of intranasal esketamine, which are necessary to achieve the best clinical response. Here, we also considered specific patient subgroups—such as patients with comorbidities and the small group of patients without a minimum 50 % reduction in symptoms at the end of the induction phase (partial responders)—and we reviewed aspects that may impact the use of this treatment.

Methods

Study design

A scientific committee was constituted, comprising nine experts in the management of TRD and intranasal esketamine in Spain. The inclusion criteria for the experts were: i) a minimum of 5 years of clinical experience in the management of TRD, and ii) proven experience with the intranasal esketamine encompassing all three stages of the development of this treatment (pre-clinical, compassionate use, and routine clinical practice). The scientific committee discussed the statements in three online meetings. First, a discussion session aimed to develop statements on clinical aspects related to the practical management of TRD with intranasal esketamine, specially in patients with comorbidities and small patient subgroups who are only partial responders at the end of an induction phase. Then, a second meeting followed a semi-structured nominal group technique, in which participants voted on the statements generated in the first session to achieve consensus. Finally, in a third meeting, the committee reviewed the final conclusions and validated the consensus. Key points were then defined based on these results.

Literature review

A targeted literature search was conducted in PubMed to identify articles and scientific communications published in English or Spanish between January 2014 and January 2024. Search terms regarded intranasal esketamine together with patient profiles, management and optimisation, response to treatment, and socioeconomic impact. Grey literature was also searched, focusing particularly on websites for medical associations of TRD. The 32 publications included were scientific articles, reviews, and meta-analyses. Letters to the editor, commentaries, books,were excluded.

Development of statements

The results of the literature review were used to identify topics that were unclear or on which the evaluated sources differed. The first meeting (April 2024) followed a discussion group approach and aimed to discuss statements.[30] After the first meeting, a list of statements was shared with the scientific committee to assess agreement or need for modifications. The committee refined and discussed the proposed statements at a second meeting (June 2024), following the nominal group technique. This methodology, commonly employed in consensus documents, is particularly suitable when the number of experts on a given topic is limited, facilitating achieving consensus.[31,32] Through this process, the panel elaborated a comprehensive list of statements, only including those that achieved unanimous consensus.[33] The consensus achieved, and the conclusions derived from the second meeting were discussed by the scientific committee in a third and final online meeting. A report summarising the consensus reached was reviewed by the scientific committee to confirm the adequacy of statements and their context. The final statements regarded three topics: management and optimisation of treatment with intranasal esketamine; clinical environment for administration of intranasal esketamine; and considerations

about access to intranasal esketamine. After seven manuscript drafts, the experts reached agreed on the content of the final manuscript version.

This study was funded by Johnson & Johnson, who did not participate in the study design or interpretation of the results.

Results

Topic 1. Management and optimisation of treatment with intranasal esketamine

Treatment algorithm

Consensus: We recommend a treatment algorithm for intranasal esketamine in TRD for the small patient subgroup who are only partial responders at the end of the induction phase (Fig. 1). Treatment should be optimised and personalised according to response, tolerability, patient's characteristics, and clinical progress.

Evidence/discussion: Initiating treatment with intranasal esketamine should be an informed and shared decision between the treating psychiatrist and the patient. Psychiatrists should educate their patients on the particularities of intranasal esketamine, its efficacy and safety profile, the route of administration, and the dosing schedule to optimise therapeutic management and ensure minimal impact on the patient's daily activities.[34]

Intranasal esketamine is indicated as concomitant treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI).[24] Expert guidance indicates that intranasal esketamine should be added to an SSRI/SNRI if a patient has had a partial response to the latter; however, if a patient has not responded to an SSRI/SNRI, a different oral antidepressant should be initiated together with intranasal esketamine.[34] Furthermore, new evidence suggests that intranasal esketamine may be useful as monotherapy.[35] The initial dose of intranasal esketamine is selected according to the patient's age.[24] After treatment initiation, the dose and frequency may be adjusted according to clinical progress varying between the induction and maintenance phases.[24,34,36] Form our perspective, the goal of the induction phase is to achieve a 50 % reduction of symptoms (responders) to achieve the best clinical progress. In our experience, symptoms improve more markedly when the maximum tolerated dose is used as soon as possible in the induction phase (generally, in the second or third administration, safety allowing).Esketamine has demonstrated favourable tolerability and a robust safety profile.[37] Furthermore, the side effects are brief and do not became a problem for the patient with long-term treatment.[38,39] Consequently, increasing the dosage may be considered as soon as possible, with the aim of significantly enhancing the efficacy of the treatment in reducing symptoms. The goal of the maintenance phase is to consolidate a stable clinical progress, either stable response or stable remission. The approved posology for intranasal esketamine considers a 4-week induction phase with twice-weekly administrations.[24] However, given the severe profile and poor prognosis of patients with TRD, in a small subgroup of patients with only a partial response at the end of the induction phase (especially those with psychiatric comorbidities, a history of relapse, high number of failed antidepressants, or those who are rapid or ultra-rapid metabolisers), we advocate for a flexible approach at the end of an induction phase, evaluating response after 4 weeks, and potentially performing 1–2 additional 4-week induction phases if only a partial response is observed at the end of the induction phase and the patients are benefiting from therapy. However, management in the case of partial response should be individualised. The EMA label for intranasal esketamine indicates the dosing in the maintenance phase should be individualised to the lowest frequency to maintain remission/response[24]; based on our clinical experience, during the maintenance phase, most patients are treated with weekly doses of intranasal esketamine to avoid fluctuating symptoms and ensure clinical stabilisation and good prognosis.[34,40–42] There is no consensus on when and how to discontinue intranasal esketamine either because of a slow response (or lack thereof) or because the patient has recovered from depression and the treatment is completed. Regarding delayed response, a head-to-head clinical trial demonstrated

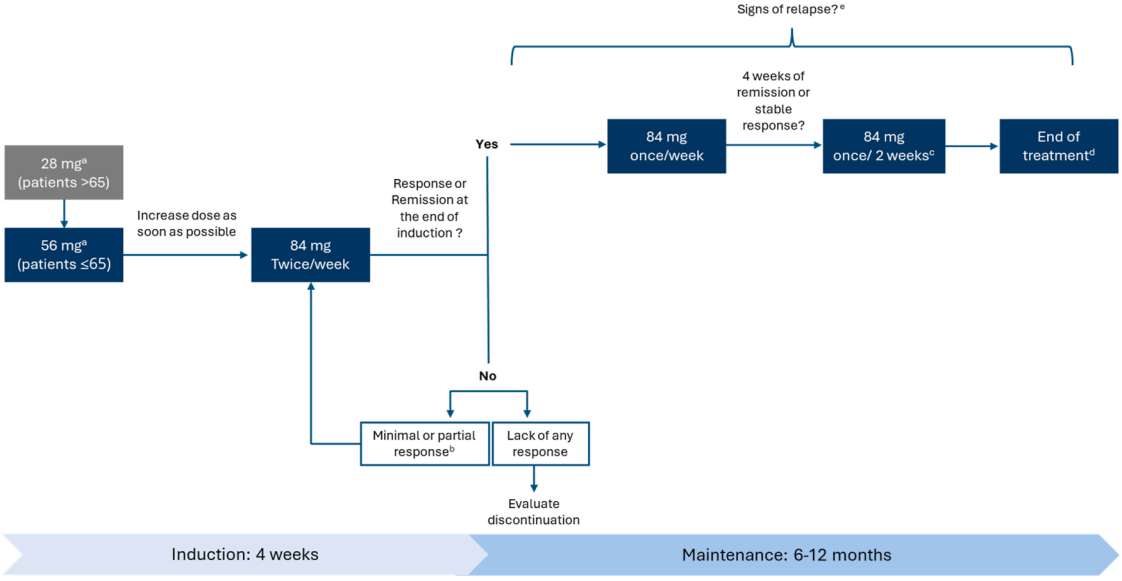

Fig. 1. Treatment algorithm for intranasal esketamine. [a]Doses of 28 mg and 56 mg are the first doses given, according to patient's age. If good tolerability, initial dose should be escalated in the next session. Maximum tolerated dose should be reached as soon as possible (safety allowing) to optimize the treatment outcomes. [b]In complex patients/patients with risk factors (frequent/recurring episodes, history of relapse, chronic episodes, with presence of psychiatric comorbidities, presence of residual symptoms), or rapid/ultra-rapid metabolisers, 84 mg twice/week may be maintained potentially for 1–2 additional 4 week induction phases for partial responders who continue to improve on therapy, if good tolerability and progressive response are observed. Other optimization strategies (addition of other antidepressants or augmentation strategies) may be evaluated as well. [c]Symptom stability evaluated regularly every 4 weeks. [d]Total treatment duration should be personalised according to clinical stability. Intranasal esketamine dose and frequency of administration should be personalized when treatment cessation due to clinical stability is planned. [e]Relapses during treatment with intranasal esketamine should be managed based on symptom severity: for mild symptoms, we recommend reverting the dose and frequency used during the patient's stable period; for severe symptoms, restarting the treatment from the induction phase is advisable.

that both response and remission rates increase during treatment with intranasal esketamine.[27] Also, a real-world study pointed to a significant increase in both the response and remission rates 1–3 months after intranasal esketamine initiation (the rate of remission increased from 11.2 % to 40.6 %).[43] Also, 38 % of non-responders and partial-responders at month 1 were remitters at month 3.[43] Regarding clinical recovery, the EMA label indicates that treatment should be maintained for at least 6 months after symptoms improve, but no maximum treatment duration is established.[24] In our experience, the average treatment time spans 6–12 months, but there are patients who show a clear benefit-risk ratio beyond that timeline, wich is consistent with the findings of a recent study.[39] Hence, since the main goal of the maintenance is to resolve the depressive episode and prevent relapses, treatment duration should be sufficient to achieve this and should be tailored to the specific characteristics of each patient.

Suspending the treatment after a complete course should be decided with the patient, who should be informed about the next steps. Discontinuation should be personalised to each patient's case, aiming for remission, sustained response, and prevention of future relapses. We advocate for a gradual reduction of intranasal esketamine treatment while evaluating response; the patient should be monitored regularly (followed-up at least once every 6 months) to detect potential symptom fluctuations.

Relapses during treatment with intranasal esketamine should be managed based on symptom severity: for mild symptoms, we recommend reverting the dose and frequency used during the patient's stable period; for severe symptoms, restarting the treatment from the induction phase is advisable.

Relapses after completing and responding to treatment with intranasal esketamine should be addressed by repeating the entire treatment course, starting with the induction phase and following the same steps that proved to be effective previously.

As highlighted by Buchmayer et al.,[38] if no noticeable improvement is evident, the treatment may be discontinued.[38] Additional factors, although infrequent, should be also be considered such as adverse events and alterations in scheduling.

Intranasal esketamine for specific patient profiles

Consensus: Psychiatric comorbidities are not contraindications for intranasal esketamine; however, the risk-benefit must be considered for each patient, and comorbidities should be treated. We developed recommendations for selected patient profiles (Table 1).

Evidence/discussion: A multicentre study found no difference in efficacy of intranasal esketamine between patients with and without psychiatric comorbidities.[43] Di Vincenzo et al[44] suggested that no psychiatric comorbidity should lead to the contraindication of esketamine treatment, as it has been extensively employed in patients with different comorbidities such as anxiety, attention deficit hyperactivity disorder, substance use disroder, obsessive–compulsive disorder, fatigue, self-harm, chronic pain, insommnia, post-traumatic stress disorder, and anorexia nervosa. Also, the U.S. Food and Drug Administration (FDA) and the EMA labels did not point to contraindications.[45,46]

Regarding patients with substance abuse, no reports of intranasal esketamine abuse or misuse were reported in the INtegrate and REAL-ESK studies.[47,48] A study evaluating the World Health Organization Pharmacovigilance Database also reported no association of esketamine with substance abuse.[49] Further, the risk of abuse or misuse of intranasal esketamine may be negligible, given the controlled setting in which it is administered. Also, no abuse of intranasal esketamine was reported in a clinical trial with a design that permitted estimating abuse.[50] As long as these regulatory measures remain in place, the likelihood of substance abuse associated with esketamine remains very low. Besides these regulatory measures, It is recommended that the pattern of addiction be monitored prior to the initiation of intranasal esketamine.[51]

Evidence for patients with psychotic features derives from case reports, which showed intranasal esketamine led to an improvement of symptoms in patients with psychotic features.[52,53] The management of psychotic depression is not currently based on strong evidence, as stated by Oliva et al[54] Hence, newer options, such as adjunctive esketamine, may have a role. Moreover, real-world studies have demonstrated the effectiveness of intranasal esketamine in treatment-resistant bipolar depression.[55–57] Data from two studies (one of them a phase 3 trial) showed that intranasal esketamine improved the severity of depressive symptoms, including suicidal ideation in a population with suicidality.[58,59] A review of 18 randomised clinical trials also concluded that intranasal esketamine was effective and more practical treatment than more invasive alternatives.[60] Retrospective studies showed intranasal esketamine improved symptoms of depression and achieved a response in patients with post-traumatic stress disorder.[61,62] However, further high-quality studies are required to confirm these findings. Finally, anxiety has been associated with treatment resistance in patients with major depressive disorder.[63] However, a clinical trial and a real-world study demonstrated that intranasal esketamine improved symptoms in patients with TRD and anxiety.[64,65]

Clemens et al[66] evaluated the costs associated with intranasal esketamine treatment logistics, and observed the burden might vary between regions depending on access to healthcare institutions, clearly evidencing the potential benefit of increasing access to healthcare.

Table 1
Recommendations for intranasal esketamine in selected patient profiles.

Psychiatric comorbidities	Recommendation
TRD and history of substance abuse	Address substance abuse with psychological treatment (and specific pharmacological treatment, if needed) while also using intranasal esketamine.
TRD and psychotic features	Close monitoring to assess progress of psychotic symptoms.
TRD and history of bipolar disorder	Maintain treatment with mood stabilisers and monitor closely to evaluate euthymia.
TRD and history of suicidal ideation	Optimise dose to reach maximum dose of intranasal esketamine as soon as possible and monitor closely for suicidal ideation. If needed, initiate treatment at a dose of 84 mg.
TRD and history of trauma/PTSD	Close monitoring for potential flashbacks, especially during the induction period of intranasal esketamine. If flashbacks or dissociation occur, intranasal esketamine doses should be spaced out. It may be useful for the same healthcare professional to administer the first doses so that the patient feels calm and safe. The patient should also undergo psychological treatment to prepare the patient for treatment and redefine dissociative symptoms.
TRD and history of anxiety	Use relaxation techniques before and after the administration of intranasal esketamine. If anxiety is not controlled, temporary use of benzodiazepines may be useful. Generally, a good response to intranasal esketamine may help reduce treatment with benzodiazepines.

PTSD, post-traumatic stress disorder; TRD, treatment-resistant depression.

Factors that impact the use of intranasal esketamine

Consensus: Factors that constrain the use of intranasal esketamine include: i) lack of knowledge of the drug by psychiatrists; ii) therapeutic inertia; iii) administration logistics; and iv) healthcare cost containment (Fig. 2).

Facilitators to the use of intranasal esketamine include: i) studies that reflect clinical practice; ii) real-world socioeconomic studies that consider indirect costs; iii) adapting patient care pathways to new therapies and patient needs; iv) training and education of healthcare professionals on adequate management of TRD; and v) development of a treatment algorithm for TRD that positions intranasal esketamine (Fig. 2).

Evidence/discussion: This recommendation was based on expert opinion.

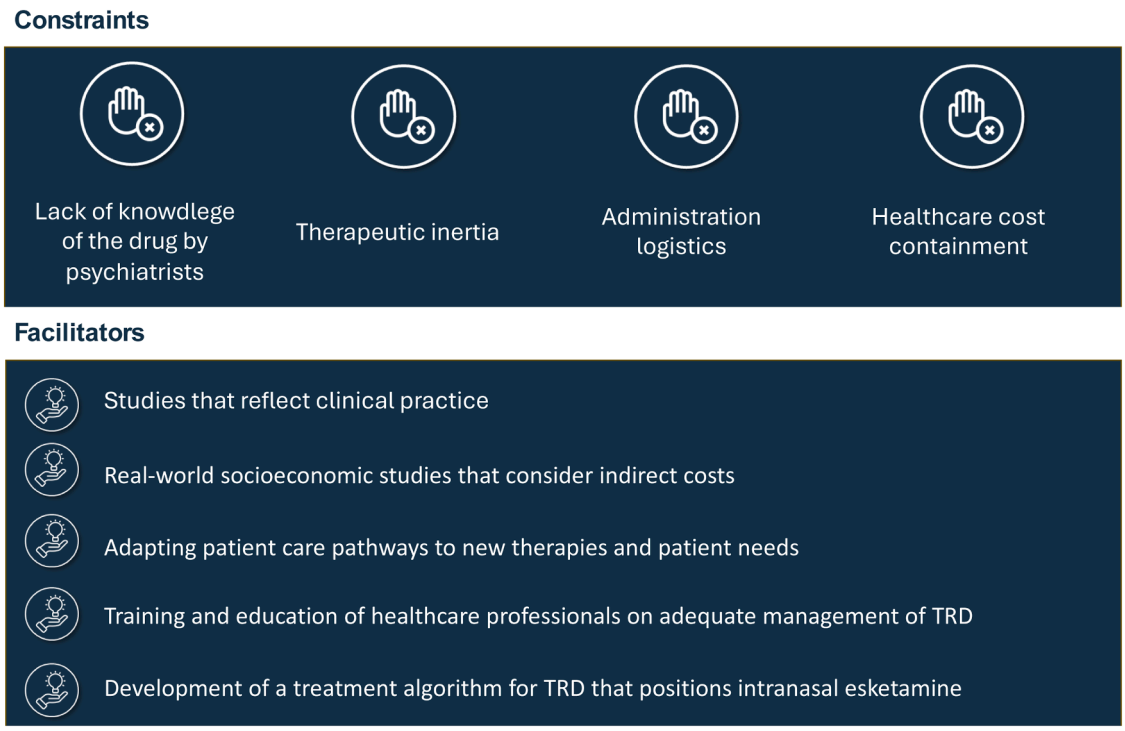

Fig. 2. Factors that impact the use of intranasal esketamine.

Topic 2. Organisation of clinical environment for administration of intranasal esketamine

Environment for administration

Consensus: Intranasal esketamine should be administered at the same health centre where the patient habitually receives mental health care, guaranteeing safety, close supervision, and trained staff. Patients may be treated in a hospital setting if they have comorbidities or clinical characteristics that might require specific resources.

Evidence/discussion: Intranasal esketamine is self-administered under the supervision of a healthcare professional,[24] which may limit its use, since patients must visit a health centre. On this note, the INtegrate study found no difference in the rate of adverse events reported by several health centres (mental health clinic, day hospital, outpatient clinic, hospital, emergency room) when using intranasal esketamine in the induction and maintenance phases.[67]

Characteristics of the location where intranasal esketamine is administered

Consensus: Intranasal esketamine should be administered in a setting that minimises patient stress. The setting should have minimal background noise, low lighting, and presence of nursing staff; patients may also listen to music (Fig. 3).

Evidence/discussion: This recommendation was based on expert opinion and previous international practical recommendations.[34] An observational study showed that patients who listened to their own music while receiving treatment with intranasal esketamine experienced better tolerability and reduced anxiety.[68]

Fig. 3. Characteristics of the location where intranasal esketamine is administered.

Patient preparation

Consensus: Before administering intranasal esketamine, physicians should inform patients about what constitutes a routine treatment session, describing the steps involved and the type and duration of potential adverse events they may experience. Vital signs should be monitored before and after administration. Physicians should also inform patients that they will be accompanied during the entire process.

Evidence/discussion: This recommendation was based on expert opinion and previous international practical recommendations.[34] Intranasal esketamine has a well-documented safety profile, and any possible side effects must be treated on an individual basis to ensure the best possible outcomes.[37]

Topic 3. Considerations about access to intranasal esketamine

Consensus: There is a need for studies that evaluate the impact of intranasal esketamine on indirect non-healthcare costs.

Evidence/discussion: The economic impact of TRD has been thoroughly researched, with particular attention given to its indirect costs, wich account for over 50 % of the total cost of the disease. Furthermore, the duration of absence from work and disability from mental health disorders has been shown to extend up to approximately six months, which is approximately four times the optimal duration.[69] Several studies emphasise that the primary costs of TRD are societal, particularly those arising from increased work loss and absenteeism. In Spain, Pérez-Sola et al. reported higher total costs of TRD vs non-TRD (€6096 vs. €3846; $p < 0.001$) and higher direct costs (€1341 vs. €624; $p < 0.001$), greater lost productivity (€1274 vs. €821; $p < 0.001$) and increased permanent disability (€3481 vs. €2401; $p < 0.001$).[7]

Intranasal esketamine is the only antidepressant approved specifically for TRD; it is also the only antidepressant included in the EMA's critical medicine list.[25] In Spain, the public healthcare system reimburses intranasal esketamine in combination with selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors in adults with TRD who, in the current severe major depressive episode, have not responded to, at least, three antidepressant strategies, one of them being a combination or an augmentation strategy. In a

budget-conscious setting, the widespread availability of generic oral antidepressants has placed intranasal esketamine at a disadvantage because of its cost. However, from a patient- and community-focused perspective, intranasal esketamine has demonstrated unprecedented clinical and functional benefits,[27,70] and a positive impact on quality of life[71] and ability to work,[72] all of which are objectives of special relevance to a population with poor prognosis and a severe condition, such as TRD.

A systematic review found that greater treatment resistance (i.e., increasing number of treatments that achieved no response) was linked to higher direct and indirect costs, along with a reduced quality of life.[73] Studies of both European and Spanish cohorts have also revealed that TRD was associated with higher direct and indirect costs compared to non-TRD.[7,11] Moreover, an economic study of intranasal esketamine in Italy found the treatment was cost-effective from a societal perspective but not from a healthcare system perspective.[74] Additionally, intranasal esketamine has been associated with significantly larger improvements in work productivity loss and related costs compared to other alternatives.[66] A recent study in Spain found that 7.5 million euro were saved in indirect costs related to productivity loss when patients with TRD treated with intranasal esketamine returned to work.[75] In contrast, one study indicate that electroconvulsive therapy may be a more cost-effective option than esketamine.[76] However, other evidence has identified intranasal esketamine as a cost-effective strategy,[77] demonstrating short- and long-term efficacy while reducing medical costs and improving presenteeism,[66] particularly in severe TRD cases.[78]

Discussion

Management of TRD is challenging, as there are multiple treatment options available, yet clinical guidelines do not establish a clear preference for one versus another.[14–17] Pharmacologic approaches with mechanisms of action different from the classic one focusing on the monoaminergic pathway have been approved in recent years, including intranasal esketamine.[21] In Europe, however, intranasal esketamine is the only treatment approved for depression in the last 50 years that has a truly new mechanism of action. Considering the improved clinical benefit achieved with intranasal esketamine,[26–28] the fact that it is the only antidepressant approved for TRD in Europe, and its distinctive mechanism of action that directly addresses neuroplasticity, we developed a consensus document. The aim of this document is to provide a treatment algorithm for use of intranasal esketamine in patients with TRD, based on our experience using it in clinical practice in Spain. Several consensus documents have been recently published on the use of intranasal esketamine for TRD, made by experts from various world regions.[34,38,42,79–81] A recent meta-analysis concluded that intranasal esketamine has modest efficacy as an add-on to antidepressants in TRD.[82] However, this meta-analysis combined studies with different trial designs, patient populations, study durations, and timing of the primary endpoint, and it included a dose determined to be sub-therapeutic; all of this may have contributed to misleading or erroneous interpretations. For example, the article concludes that esketamine's effect is similar to that of augmentation with oral antipsychotics, providing no supporting evidence. Of note, with the exception of olanzapine (Zyprexa)–fluoxetine combination, antipsychotics have not been studied in TRD and are not approved by the FDA for this indication.[2] Moreover, the authors' statement is contrary to findings of the rater-blinded ESCAPE-TRD head-to-head comparative study, in which intranasal esketamine was superior to extended-release quetiapinebased on remission at week 8 (the primary endpoint)[27] and was better tolerated.[36]

Our recommendations largely align with those made by others in terms of the importance of informing the patient on the procedure and the efficacy and tolerability of the treatment, administering the treatment in a simple and practical space that allows for the patient to be accompanied and monitored while ensuring a calm and satisfactory treatment administration, the need for flexible dose/repetition of the induction treatment phase, and customisation of management and duration of treatment based on the patient's clinical progress.

We acknowledge that the EMA prescribing information for intranasal esketamine has flexible posology.[24] Overall, we reckon that early effective management of TRD is key to improve clinical prognosis. Therefore, considering the severity and poor prognosis of real-world patients with TRD, we propose an early optimisation of intranasal esketamine dose during the induction phase and a prudent evaluation of clinical stability during the maintenance phase before extending the frequency of administration. Treatment management must be contingent on efficacy and tolerability for each patient's case to ensure the best clinical progress possible, aiming for recovery from depression, and avoiding the common problem of therapeutic inertia observed with monoaminergic antidepressants.[83] We, therefore, advocate for a flexible approach based on the characteristics and clinical course of each patient. For instance, in the event of an initial partial response at the end of the 4-week induction phase, treatment should be continued with potentially 1–2 additional 4-week induction phases for partial responders who continue to improve on therapy, and reassessed periodically to determine if partial responders have converted to responders and may move into the maintenance phase. Intranasal esketamine treatment should be discontinued if there is no response within 4 weeks of its initiation. The EMA prescribing information for intranasal esketamine stipulates as well a minimum treatment duration of 6 months when depressive symptoms improve but does not specify a maximum treatment duration.[24] Since there are patients who clearly benefit beyond that timeline, we advocate for continuing intranasal esketamine and regularly evaluating response for 4 weeks during treatment maintenance before deciding next steps, such as spacing treatment administrations or discontinuing the treatment. When finalising the treatment due to a recovery or stabilisation, an agreement with the patient about times and next steps is of vital importance to prepare them psychologically and therapeutically for the after-treatment period. A cornerstone of treatment with intranasal esketamine is the implementation of a plan for regular clinical monitoring to ensure that the clinical stability achieved during treatment is maintained. On another note, patients with TRD have a higher prevalence of psychiatric comorbidities than patients with non-resistant MDD.[84] Here, we made recommendations for specific profiles of patients with other psychiatric comorbidities, underscoring the need for these to be adequately managed in addition to using intranasal esketamine. Recommendations made by others generally did not discuss specific patient profiles, although patients with psychosis were ruled out as amenable to intranasal esketamine in one of the studies.[34,38,42,79] Overall, we consider that treatment with intranasal esketamine should be tailored to each patient to maximise response and remission.

We identified a set of factors that impact the use of intranasal esketamine. Acknowledging these factors and understanding how to address them can facilitate the use of this treatment to, ultimately, benefit patients with TRD. The use of a comfortable, quiet, and familiar space to conduct intranasal esketamine administration is key to optimising the patient's therapeutic experience. One of the main factors affecting a more ubiquitous use of intranasal esketamine is the logistics related to its administration. For example, a study in the U.S. found that initiation of intranasal esketamine decreased with longer travel distance to the treatment centre; greater travel distance was also associated with increased likelihood of treatment interruption.[85] Cost of treatment is another constraint; however, given the considerable total expenditure derived from TRD, partly driven by indirect costs,[7,10,12,13] and the demonstrated clinical benefit of intranasal esketamine for TRD,[26] we believe that it is key that psychiatrists and the clinical community support innovative treatments with strong evidence in the pursuit of providing patients with the best possible outcome. Depression is a leading cause of disability, and its chronification must be addressed to alleviate the clinical, social, and economic burden associated with it.

The main strength of this study lies in establishing the first consensus on the use of intranasal esketamine for TRD in Spain, guided by experts who considered the socio-cultural context and specific characteristics of its healthcare system. A structured methodology was used to seek consensus with the nominal group technique, which ensured that all experts weighed in on each topic, and the consensus statements were revised and modified, if needed, by all members of the scientific committee. A limitation of this study is the non-systematic literature review, which may have resulted in some relevant sources being missed. In addition, the absence of detailed information and the lack of rigour in certain published studies may have limited the scope of the discussion. However, the consensus reached on many topics was based solely on expert opinion, and all the relevant data from the clinical program for intranasal esketamine were considered.

Conclusions

In this study, a committee of psychiatrists from Spain who are experts in TRD reviewed the literature and provided guidance on the management of TRD with intranasal esketamine, proposing an algorithm for its use, making recommendations for specific patient profiles, identifying factors impacting its use and acceptance, suggesting setting characteristics for its administration, and evaluating socio-economic aspects. Since intranasal esketamine is the first treatment for depression with a unique mechanism of action developed in the last 50 years, we have entered a promising era where new approaches can be implemented to improve patient outcomes.

Ethical considerations

This study did not involve any procedures or data collection that required ethical approval. No human participants were involved in the research. Therefore, no ethical concerns were identified.

Funding

The study was funded by Johnson & Johnson, who did not participate in the study design or interpretation of the results.

CRediT authorship contribution statement

J. Antoni Ramos-Quiroga: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Fernando Mora:** Conceptualization, Funding acquisition, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Silvia Arostegui:** Investigation, Writing – review & editing. **Narcís Cardoner:** Investigation, Writing – review & editing. **Jon-Inaki Etxeandia-Pradera:** Investigation, Writing – review & editing. **Rocío Gómez-Juanes:** Investigation, Writing – review & editing. **Marcos Gómez-Revuelta:** Investigation, Writing – review & editing. **José Manuel Montes:** Investigation, Writing – review & editing. **Eduard Vieta:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

JARQ was on the speakers' bureau and/or acted as consultant for Biogen, Idorsia, Casen-Recordati, Johnson & Johnson, Novartis, Takeda, Bial, Sincrolab, Neuraxpharm, Novartis, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Idorsia, Janssen-Cilag, Rubió, Takeda, Bial and Medice. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 3 years: Exeltis, Idorsia, Janssen- Cilag, Neuraxpharm, Oryzon, Roche, Probitas and Rubió.

FM declares the following conflicts of interest: Honoraria from Amarin; participation in speaking engagements and advisory boards for Adamed, Alter, Baxter, Biogen, BMS, GSK, Janssen (Johnson & Johnson), Lilly, Lundbeck, MSD, Mundipharma, Neuraxpharm, Novartis, Otsuka, Pfizer, SOBI, Takeda, Teva and Vantive; consultancy for Angelini, Baxter, GSK, Janssen (Johnson & Johnson), Lilly, Lundbeck, and Neuraxpharm. He has also received funding from the European Regional Development Fund (Plan Estatal de Investigación Científica y Técnica y de Innovación y del ISCIII).

SA has received financial support from Johnson & Johnson to attend or participate as a speaker at various medical training events related to esketamine. In addition, she has participated in medical meetings and has received payments for presentations, consulting, and research studies organized or funded by Lundbeck, Pfizer, AstraZeneca, Lilly, Wyeth, Rovi, Esteve, GSK, and Adamed, as well as training support from Lundbeck and Adamed.

NC served on advisory boards and received speaker's honoraria from Angelini, Esteve, Johnson & Johnson, Lundbeck, Novartis, Pfizer and Viatris. Furthermore, they have been awarded research grants from the Ministry of Health, Ministry of Science and Innovation (CIBERSAM) and the Strategic Plan for Research and Innovation in Health (PERIS) for the period 2016–2020, as well as from Marato TV3 and Recercaixa.

JIEP has received consulting or speaking fees from Johnson & Johnson and Lundbeck.

RGJ has had agreements or received fees as a speaker from Johnson & Johnson.

MGR had consulting agreements and received speaker's honoraria from Johnson & Johnson, Otsuka-Lundbeck, Angelini Pharma, Casen Recordati, Italfarmaco and Boehringer Ingelheim.

JMM has received Research funding from Johnson & Johnson, Carlos III Health Institute and Otsuka-Lundbeck. In the las 5 years, he has had agreements or received fees as a speaker from Exeltis, Lundbeck, Angelini, Johnson and Johnson, Neuraxfarm, Otsuka, Pfizer, Rovi, Servier and Recordati.

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Alcediag, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, Medincell, Merck, MindMed, Neuraxpharm, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, outside the submitted work.

Acknowledgements

The authors also thank Nadia Pires, Angela Rynne Vidal, PhD, Irene Huerga, PhD, and Héctor de Paz, PhD, for providing writing support, funded by Outcomes10.

This work was supported by the Spanish Society of Psychiatry and Mental Health (SEPSM).

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