Treatment-Resistant Depression: Expert Consensus Identified Real-World Experience and Individualized Care as Key Considerations for Novel Treatments in Major Depressive Disorder

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INTRODUCTION

- Treatment-resistant depression (TRD) is defined as major depressive disorder (MDD) in adults who have not responded (i.e., have not attained significant clinical improvement) to ≥2 antidepressant therapies of adequate dose and duration in the current major depressive episode (MDE); up to one-third of patients with MDD have TRD[1,2]
- Esketamine nasal spray (ESK), a novel antidepressant therapy, was initially approved in the United States in 2019, in conjunction with an oral antidepressant, for adults with TRD[3]
- Although newly approved treatments are supported by clinical trial data, they generally enter the market without real-word data or experience, particularly regarding long-term use

OBJECTIVES

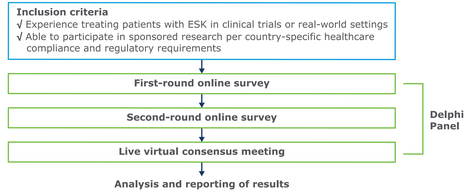
- To obtain expert clinical opinion on the appropriate duration of continuation treatment with ESK in individual patients with TRD who have remained in remission (i.e., are symptom-free or have only minimal symptoms) for ≥2 months based on physician opinion
- To determine when patients may appropriately discontinue ESK without resulting in a worsening of symptom severity or an increased risk of relapse or the occurrence of a new episode

METHODS

Delphi Panel

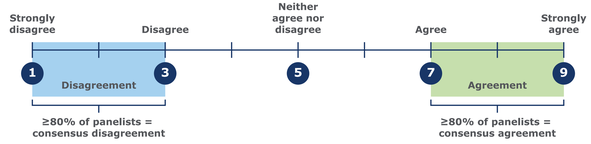
- The study was conducted between July and December 2020 and utilized the Delphi method: a structured communication method to elicit or identify consensus from a range of opinions[4]
- Eligible psychiatrists from the European Union, United Kingdom, and United States were recruited to participate (**Figure 1**). Invitations were sent via email through a third-party vendor; all participants signed an informed consent form and were compensated for their time
- The study sponsor was blinded to the identity of the participants and had no direct contact with them at any stage
- Before the first-round survey, participants were provided with a study brief that included background information and an overview of study rationale, the Delphi panel process, and their roles and responsibilities
- The panel followed a modified Delphi process consisting of 3 parts:
  - First-round survey: Participants completed an online questionnaire that included a series of questions regarding duration of treatment with ESK in patients with TRD
  - Second-round survey: In a follow-up online questionnaire, participants were asked to review, give their level of agreement, and comment on several statements derived from consolidated first-round outputs
  - Live, anonymized discussion: A virtual panel discussion was held to reach consensus on statements derived from the prior 2 rounds

Figure 1. Overview of study methodology



- Consensus was defined as ≥80% of participants expressing either their "agreement" or "disagreement" with a statement on a 9-point Likert scale (i.e., rating a statement from 7-9 or 1-3, respectively) (**Figure 2**)

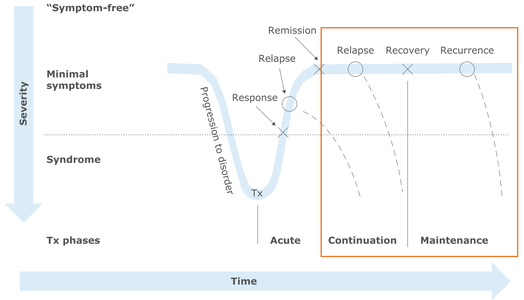
Figure 2. Likert scale used to assess consensus



Definitions of Health States of Interest and Treatment Phases in MDD

- Health states of interest were defined as follows[5,6] (**Figure 3**)
  - **Remission**: the period during which a patient is either symptom-free or has only minimal symptoms for ≥2 months
  - **Relapse**: the return of an MDE following the achievement of remission but before fulfilling criteria for recovery from the current episode
  - **Recovery**: the period when the current MDE has ended based on clinical judgment and the patient has minimal to no depressive symptoms; recovery typically entails an extended time period following the achievement of remission (e.g., 4-12 months based on current US and European treatment guidelines[7-9])
  - **Recurrence**: the development of a new MDE after a patient achieves recovery from the current MDE
- Treatment phases were defined as follows[5,6] (**Figure 3**)
  - **Acute**: the initial phase of treatment that aims to achieve remission
  - **Continuation**: the phase of treatment that aims to sustain the remission achieved acutely until such time that the current MDE would have ended (based on clinical judgment). At that point, recovery from the current MDE can be declared. An MDE that returns during continuation phase treatment is regarded as a relapse of the current episode
  - **Maintenance**: the phase of treatment that aims to prevent the onset of a new MDE (recurrence) following recovery from the current episode

Figure 3. Visual representation of health states of interest and phases of treatment in MDD[5,a]



MDD, major depressive disorder; Tx, treatment.
[a]The box delineates treatment phases discussed in the Delphi panel.
From *Annals of Internal Medicine*. Qaseem A et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Volume 164, Number 5. Pages 350-359.

RESULTS

Psychiatrist Participation

- Of the 77 psychiatrists contacted, 11 agreed to participate and completed the first survey (**Table 1**). Of these 11 participants, 10 subsequently completed the second survey and 9 (European Union, 3; United Kingdom, 1; United States, 5) participated in the final consensus discussion
- Of the 10 participants who completed the second-round survey, 50% had experience with ESK through clinical trials only, 10% through real-world clinical practice alone, and 40% through both clinical trials and real-world clinical practice

Table 1. Psychiatrist Participation Across Delphi Rounds

Country of Residence	Participants N = 11
Belgium	1
France	1
Italy	1[a]
Spain	1[b]
Sweden	1
United Kingdom	1
United States	5[c,d]

[a]One psychiatrist in Italy withdrew from the Delphi panel between the second round and the consensus meeting due to time conflicts.
[b]One psychiatrist in Spain withdrew from the Delphi panel between the second round and the consensus meeting due to time conflicts.
[c]One psychiatrist in the United States withdrew from the Delphi panel between the first and second rounds due to time conflicts.
[d]One additional psychiatrist in the United States took part in the final consensus meeting due to limited availability of respondents. This participant was provided with all study documents, including the brief, and prior questionnaires for context.

Delphi Panel Recommendations

- Overall, panelists reached general alignment or consensus on several principles regarding ESK treatment; however, panelists were unable to reach consensus regarding most aspects of ESK treatment duration (**Table 2**)

Table 2. Summary of Delphi Panel Final Recommendations

MDD and TRD Treatment Phases	• Panelists agreed that the treatment phases in **Figure 3** apply to most patients with TRD and nontreatment-resistant MDD (TRD, mode response: 90-100% of patients; agreement: 90%; MDD, mode response: 81-100% of patients; agreement: 100%) • After further discussion, panelists emphasized that for patients with TRD, the identification and application of treatment phases is much less clear than for patients with nontreatment-resistant MDD • The estimated duration of the continuation phase was considered to be longer for TRD versus nontreatment-resistant MDD, although consensus on timeframe was not reached (TRD, mode response: 12-24 months' duration; agreement: 20%; nontreatment-resistant MDD, mode response: 6-12 months' duration; agreement: 60%)
ESK Treatment Duration	**Total:** • The minimum total treatment duration (from initiation) with ESK plus oral AD for TRD is considered to be 6 months (mode response: 6 months' duration; agreement: 80%) **Continuation:** • Panelists were unable to reach consensus regarding continuation treatment duration for ESK in patients with TRD who had attained remission (mode response: 6-12 months' duration; agreement: 50%) **Maintenance:** • Most patients who achieve recovery with ESK require extended oral AD therapy as maintenance treatment to prevent recurrence (mode response: 80-100% of patients; agreement: 80%) • Panelists reported that they consider multiple factors, including the number and severity of a patient's prior MDEs (80% agreement), in maintenance therapy decisions • Panelists agreed that a patient's previous history of treatment failures was predictive of the need for extended treatment with oral ADs for recurrence prevention; panelists speculated that if a patient initiated a therapy with high efficacy, the impact of the number of prior treatment failures would be reduced • The minimum duration of maintenance treatment (following recovery) was recommended to be 6 months (100% agreement) • Panelists felt they could not provide a recommended maximum duration of maintenance treatment with ESK, emphasizing that there is insufficient evidence to provide a time estimate (mode response: 24 months' duration; agreement: 60%)
Impact of ESK Treatment Discontinuation	• Panelists agreed that treatment decisions regarding ESK discontinuation should be decided on an individual patient basis, per clinical judgment (80% agreement)

AD, antidepressant; ESK, esketamine nasal spray; MDD, major depressive disorder; MDE, major depressive episode; TRD, treatment-resistant depression.

TAKE-HOME MESSAGES

- There was general recognition that TRD is more difficult to treat and may require a longer treatment duration than nontreatment-resistant MDD. Panelists agreed that treatment with ESK plus an oral AD for TRD should be continued for a minimum of 6 months
- Because ESK is a recently approved, novel therapy, there are limited data from real-world practice or clinical trial settings to inform treatment-duration decisions, and there are no similar products from which to draw comparisons. Therefore, the panel was reluctant to recommend a maximum treatment duration and expressed concern regarding restrictions on ESK treatment in the absence of real-world or substantive data. These findings speak to the need for additional real-world evidence and clinician experience to inform treatment decisions
- Panelists considered multiple factors when making treatment decisions (e.g., response to treatment, severity of depression, fluctuations in depressive symptoms) and highlighted the need to treat each patient individually due to heterogeneity within the population with TRD
- Panelists highly valued the ability to make treatment decisions independently, without pressure from outside forces (i.e., payors). Panelists acknowledged that real-world data and experience will take time to acquire but feel that such information is necessary before formal treatment recommendations and guidelines can be developed

CONCLUSIONS

- **Psychiatrists with expertise in treating patients with TRD recognize the need for, and place a high value on, individualized treatment and real-world data specific to patients with TRD and TRD treatment**
- **Recommendations on restrictions on the clinically appropriate duration of treatment with esketamine nasal spray are viewed as premature and inappropriate at this time, with panelists agreeing that treatment decisions are best left in the hands of the clinicians who can account for the multiple patient-specific factors that inform their clinical decision-making**

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