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ORIGINAL INVESTIGATION

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Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: Basic science, evidence-based knowledge and expert guidance

Siegfried Kasper[a], Wiesław J. Cubała[b], Andrea Fagiolini[c], Josep A. Ramos-Quiroga[d,e,f,g], Daniel Souery[h] and Allan H. Young[i]

[a]Center for Brain Research, Medical University of Vienna, Vienna, Austria; [b]Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; [c]Department of Molecular Medicine, University of Siena, Siena, Italy; [d]Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [e]Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; [f]Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain; [g]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; [h]European Centre of Psychological Medicine, Psy Pluriel, Brussels, Belgium; [i]Department of Psychological Medicine, King's College London, London, UK

ABSTRACT

Objectives: Despite the available therapies for treatment-resistant depression (TRD), there are a limited number that are evidence-based and effective in this hard-to-treat population. Esketamine nasal spray, an intranasal *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, is a novel, fast-acting option in this patient population. This manuscript provides expert guidance on the practicalities of using esketamine nasal spray.

Methods: A group of six European experts in major depressive disorder (MDD) and TRD, with clinical experience of treating patients with esketamine nasal spray, first generated practical recommendations, before editing and voting on these to develop consensus statements during an online meeting.

Results: The final consensus statements encompass not only pre-treatment considerations for patients with TRD, but also specific guidelines for clinicians to consider during and post-administration of esketamine nasal spray.

Conclusions: Esketamine nasal spray is a novel, fast-acting agent that provides an additional treatment option for patients with TRD who have previously failed several therapies. The guidance here is based on the authors' experience and the available literature; however, further real-world use of esketamine nasal spray will add to existing knowledge. The recommendations offer practical guidance to clinicians who are unfamiliar with esketamine nasal spray.

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Introduction

MDD is a complex and debilitating disease, affecting over 25.8 million people worldwide in 2017 (Liu et al. 2020). Despite the number of antidepressants available for MDD (Bauer et al. 2019), its complexity makes it difficult for many patients to reach remission (Trivedi and Daly 2008); approximately 30% of patients do not respond to antidepressant therapy (Al-Harbi 2012). Treatment options for MDD are limited by their delayed onset of action, early onset of adverse events (Kaur et al. 2019) and low response rates (Gaynes et al. 2008). Therefore, there is a need for fast-acting, efficacious therapies to treat patients with TRD (Duman et al. 2016).

Research into MDD pathophysiology has implicated abnormalities in glutamatergic transmission, with NMDA glutamate receptors identified as a potential pharmacotherapeutic target for MDD and other mood disorders (Mathews et al. 2012). Ketamine, a glutamate receptor antagonist, is a non-competitive, high-affinity NMDA receptor antagonist used 'off-label' for its rapid antidepressant effects (Kraus et al. 2017). However, ketamine as a therapy is limited due to recreational abuse among users who may develop dependency with repeated dosing (Kraus et al. 2017). Esketamine, the racemic *S*-enantiomer of ketamine, has a fourfold higher affinity for the NMDA receptor than the

CONTACT Siegfried Kasper Siegfried.kasper@meduniwien.ac.at Center for Brain Research, Medical University Vienna, Spitalgasse 4, Vienna, 1090, Austria

Table 1. Summary of Phase 3 studies of esketamine nasal spray in patients with TRD.

Clinical study	Study design	Esketamine nasal spray + oral AD, n	Placebo + oral AD, n	Key findings
ESKETINTRD3001 NCT02417064 (Fedgchin et al. 2019)	Randomised, double-blind, active-controlled study of adults (18–64 years) with TRD	231	113	No statistically significant change in MADRS score from baseline to Day 28 compared with placebo ($p = 0.088$)
ESKETINTRD3002 NCT02418585 (Popova et al. 2019)	Randomised, double-blind, active-controlled study of adults (18–64 years) with TRD	115	109	Rapid antidepressant effects 24 h post-first dose (least square mean change in MADRS score −3.3 [95% CI: −5.75, −0.85]). Change in MADRS score from baseline to Day 28 was significantly greater with esketamine nasal spray compared with placebo ($p = 0.020$)
ESKETINTRD3005 NCT02422186 (Ochs-Ross et al. 2020)	Randomised, double-blind, active-controlled study in elderly (≥65 years) patients with TRD	72	65	No statistically significant change in MADRS score from baseline to Day 28 ($p = 0.059$) in the esketamine nasal spray arm compared with placebo Response and remission rates were higher in the esketamine nasal spray arm compared with the placebo arm
ESKETINTRD3003 NCT02493868 (Daly et al. 2019)	Randomised, double-blind, withdrawal study of adults (18–64 years) with TRD	619[a]	145	Esketamine nasal spray treatment decreased the risk of relapse by 51% among patients who achieved stable remission ($p = 0.003$) and by 70% in patients who received stable response ($p \leq 0.001$) compared with placebo
ESKETINTRD3004 NCT02497287 (Wajs et al. 2020)	Open-label safety study of adults and elderly patients with TRD	802[b]	–	Long-term treatment with esketamine nasal spray was tolerated in adult and elderly patients The AE profile following up to 1 year of exposure was consistent with the short-term Phase 2 and 3 studies. Low rate of discontinuation due to AEs and low rate of severe AEs. Most AEs were mild-to-moderate in intensity

AD: antidepressant; AE: adverse event; CI: confidence interval; MADRS: Montgomery–Åsberg Depression Rating Scale; TRD: treatment-resistant depression.
[a]Included 182 patients from ESKETINTRD3001 and ESKETINTRD3002.
[b]Included 111 patients from ESKETINTRD3005 (55 patients in the esketamine nasal spray arm and 56 in the placebo arm; Doherty et al. 2020).

R-enantiomer (Muller et al. 2016). Esketamine nasal spray (Spravato®), a glutamate receptor antagonist, selectively blocks NMDA receptors expressed on gamma-aminobutyric acid-ergic inhibitory interneurons, leading to enhanced glutamatergic firing (Kadriu et al. 2019). Clinical studies showed esketamine nasal spray exerted rapid antidepressant effects (least square mean change in Montgomery–Åsberg Depression Rating Scale [MADRS] score −3.3 [95% confidence interval: −5.75, −0.85] 24 h after first dose) in patients with TRD (Table 1). In 2019, esketamine nasal spray was the first U.S. Food and Drug Administration (FDA)-approved therapy for TRD to target the glutamatergic system (Kaur et al. 2019). The European Medicines Agency (EMA) subsequently approved esketamine nasal spray, in combination with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), for adults with treatment-resistant MDD, who have not responded to at least two different treatments with antidepressants in the current moderate-to-severe depressive episode (EMA 2019). The initial recommended dose for adults <65 years is 56 mg and for adults ≥65 years or of Japanese ancestry is 28 mg (EMA 2019). This differs from the FDA indication, which does not specify the antidepressant class or define the number of treatment failures required for TRD and recommends a universal 56 mg starting dose in conjunction with an oral antidepressant (FDA 2019b).

In Europe, esketamine nasal spray is recognised as an efficacious treatment for patients with TRD, with a distinct safety profile and a different, intranasal method of administration (EMA 2019), compared with existing antidepressants (Carvalho et al. 2016). This manuscript aims to provide practical guidance on esketamine nasal spray to aid clinical treatment decision-making for patients with TRD.

Methods

Six European experts in MDD and TRD with clinical experience with esketamine nasal spray developed this manuscript. Collectively, at the time of writing, they had several years' experience with esketamine nasal spray, in treating over 120 patients.

The authors agreed to generate practical recommendations, in the form of consensus statements, on identifying and treating patients with esketamine nasal spray, based on their experience of treating patients with esketamine nasal spray and published data on TRD. All authors agreed on four themes to cover in the manuscript and draft statements were discussed, reviewed and approved by all authors.

The authors first discussed the practical recommendations at an online consensus meeting and over emails, before editing and voting on these to develop consensus statements (this process was not anonymous). The six voting options were 'strongly agree', 'mostly agree', 'somewhat agree', 'somewhat disagree', 'mostly disagree' and 'strongly disagree'. The authors were unanimous in 'strongly agreeing' with 5 of 11 statements. For the remaining statements, the authors voted either 'strongly agree' or 'mostly agree', and for only one statement, one author voted 'somewhat agree'. A meeting report summarising key discussion points and the amended consensus statements was reviewed and approved by all authors. The authors received support from a medical writing agency (funded by Janssen Pharmaceutica NV), which facilitated the process and drafted the consensus statements and manuscript, under the direction and guidance of all authors. This work was developed in alignment with Good Publications Practice (GPP3; Battisti et al. 2015). Janssen Pharmaceutica NV had no direct or indirect involvement in the development of the consensus statements, topics, or manuscript.

Results: Practical guidance for clinicians prescribing esketamine nasal spray

Here, we present consensus statements on pre-, during and post-treatment considerations for treating patients with TRD with esketamine nasal spray. Statements 1–4 provide advice on factors to consider prior to initiating treatment; statements 5–11 provide advice on during and post-administration clinical supervision and guidance.

Understanding the different facets of treatment-resistant depression

(1) TRD is a complex, multifaceted disorder with many contributing neurobiological, genetic, clinical and psychosocial factors

A number of molecular and structural neurobiological factors are implicated in TRD pathophysiology. A hyperactive hypothalamic–pituitary–adrenal axis was associated with an imbalance of the glucocorticoid and mineralocorticoid receptors and high levels of cortisol, in patients with TRD (Juruena et al. 2009). Additionally, patients with TRD have shown an upregulated pro-inflammatory response characterised by high levels of interleukin (IL)-6, IL-8, tumour necrosis factor, C-reactive protein and macrophage inflammatory protein-1 (Strawbridge et al. 2019). Structural characteristics of TRD might include white matter abnormalities in the cerebellum, which have been associated with symptoms of TRD, e.g. impaired cognitive function (Peng et al. 2013). Additionally, changes in functional connectivity (Hahn et al. 2019) within the default-mode network have been observed in TRD, related to symptom severity (Yan et al. 2019). Alterations in the putamen and parietal white matter tracts have also been associated with symptoms of TRD (Klok et al. 2019). These neurobiological characteristics and stress and inflammatory responses implicated in TRD illustrate its multifaceted pathophysiology.

Specific genes have been associated with an increased risk of TRD; however, studies investigating this association are limited in number and have varied findings. The short allele of the serotonin transporter promoter gene polymorphism is hypothesised to alter the serotonergic system, potentially leading to SSRI-treatment resistance (Coplan et al. 2014). More specifically, the short allele was shown to reduce transcription of the serotonin transporter gene (Lesch et al. 1996), the target for SSRIs. Additionally, several single nucleotide polymorphisms in genes implicated in the serotonergic system have been identified in TRD (Bartova et al. 2019), for example: *CREB1, BDNF* and *5HTR2A* (Schosser et al. 2012). There are few studies reporting the genetic complexity of TRD and its impact on overall antidepressant efficacy (Fabbri et al. 2019); further studies are needed.

Clinical characteristics are also associated with TRD, including comorbidities, characteristics and symptoms of the current depressive episode, and the patient's disease and treatment history. Psychiatric or somatic comorbidities of MDD can increase the risk of developing TRD (Kornstein and Schneider 2001), including anxiety, substance abuse and personality disorders, and neurodegenerative, neurovascular and autoimmune diseases (Bennabi et al. 2019). The characteristics and symptomatology of the current depressive episode can exacerbate the persistence and recurrence of TRD. These include the severity and duration of the

current depressive episode, early age of onset (Bennabi et al. 2019), melancholic features (Jaffe et al. 2019) or suicidal risk (Souery et al. 2007), the latter of which is thought to be associated with Val66Met and rs10501087 polymorphisms (Schosser et al. 2017). The patient's disease and treatment history may also impact the risk of TRD, for example, childhood adversity (Tunnard et al. 2014), number of prior depressive episodes (Bartova et al. 2019), traumatic or stressful life events, or previous non-remission or partial remission (Murphy et al. 2017). These clinical factors are thought to contribute to TRD, adding to its complexity.

(2) There are a number of different definitions of TRD; however, to inform clinical decisions in this context, the practical definition of TRD is 'the failure of at least two different treatments with antidepressants of adequate duration and dose in the current moderate-to-severe episode' (*EMA* 2019), in line with the EMA's definition of TRD (*EMA* 2013)

There is currently no universally accepted clinical definition for TRD. The most widely used definitions of TRD are based on at least two treatment failures, irrespective of drug class (Bartova et al. 2019; Brown et al. 2019). From the authors' experience, this may be because one treatment failure would place the threshold too low. Despite this, a recent systematic review identified 155 different definitions for TRD; however, many had overlapping criteria and/or were a clinician's opinion rather than a validated definition (Brown et al. 2019). Interestingly, the definition of TRD within clinical research is also variable; a systematic review found that only 17% of intervention studies defined TRD based on at least two treatment failures (Gaynes et al. 2020). These findings emphasise the variety of TRD definitions in both clinical practice and research.

Variability in the definition of TRD can be explained by many factors. Terminology can be confusing, for example, TRD and treatment-refractory depression; TRD often refers to two antidepressant failures, whereas treatment-refractory depression refers to three or more failures including electroconvulsive therapy (Kasper and Frazer 2019). Additionally, 'pseudo-resistance' can occur when treatment resistance arises due to misdiagnosis, individual clinician differences (Murphy et al. 2017), inadequate dose and duration of antidepressant treatment, or patient non-compliance (Dold et al. 2018). There are no international guidelines on the 'adequate duration and dose' of antidepressants; a suggested duration is 4 to 6 weeks (Bennabi et al. 2019), with a minimum of 2 to 3 weeks at the target dose (Dold and Kasper 2017). Poor tolerability may also limit a patient's ability to complete an adequate trial of antidepressants (Ashton et al. 2005).

Furthermore, clinicians should systematically evaluate improvement as early as possible as early improvement may optimise treatment (Oluboka et al. 2018)

Table 2. Examples of staging methods that can be applied to define TRD.

Staging method	Basic principles of the staging method used to define TRD
Thase and Rush Staging Model (Thase and Rush 1997)	Stage II of the model: Failure of a second adequate antidepressant trial. Second antidepressant must be of a distinctly different class from that used in Stage I As the stages progress, the therapies progress from simpler to more complex strategies, with ECT reserved for Stages III and IV of resistance
European Staging Model (ESM) (Souery et al. 1999)	Stage B of the model: Resistance to two or more adequate antidepressant trials of different classes (Ruhe et al. 2012; duration of treatment: 12 to 16 weeks) Proposed concept of CRD: Resistance to several antidepressant trials, including augmentation strategy (duration of treatment: at least 12 months)
Antidepressant Treatment History Form (ATHF) (Ruhe et al. 2012) (Sackeim et al. 2019)	Stage 1 of the form: Failure of any antidepressant trial of adequate dose and duration (less than 4 weeks or less than the minimum adequate daily dose) Provides detailed scores for each antidepressant trial during a depressive episode, considering duration and dose adequacy, treatment adherence, combination/augmentation and types of MDD
A 2-stage model to provide an operational definition of TRD (Conway et al. 2017)	Proposed definition for Stage I TRD: Failure of two antidepressant trials of adequate dose and duration, or psychotherapy, from different classes (either in combination or subsequently) in the current episode (STAR*D, level 3)
Maudsley Staging Model (MSM) (Fekadu et al. 2018)	An MSM score of 7–10: Failure of one antidepressant trial of adequate dose and duration for a minimum of 6 weeks Considers clinical factors associated with TRD, e.g. severity and duration of the episode
Sequential Treatment Optimisation Scheme (Kraus et al. 2019)	TRD stages correspond to treatment strategies Stage 1: Monotherapy/dose escalation; Stage 2: Augmentation/switch; Stage 3: ECT, VNS, TBS, ketamine, MAOI; Stage 4: Experimental treatments

CRD: chronic-resistant depression; ECT: electroconvulsive therapy; MAOI: monoamine oxidase inhibitor; MDD: major depressive disorder; MSM: Maudsley Staging Model; TBS: theta-burst stimulation; TRD: treatment-resistant depression; VNS: vagus nerve stimulation.

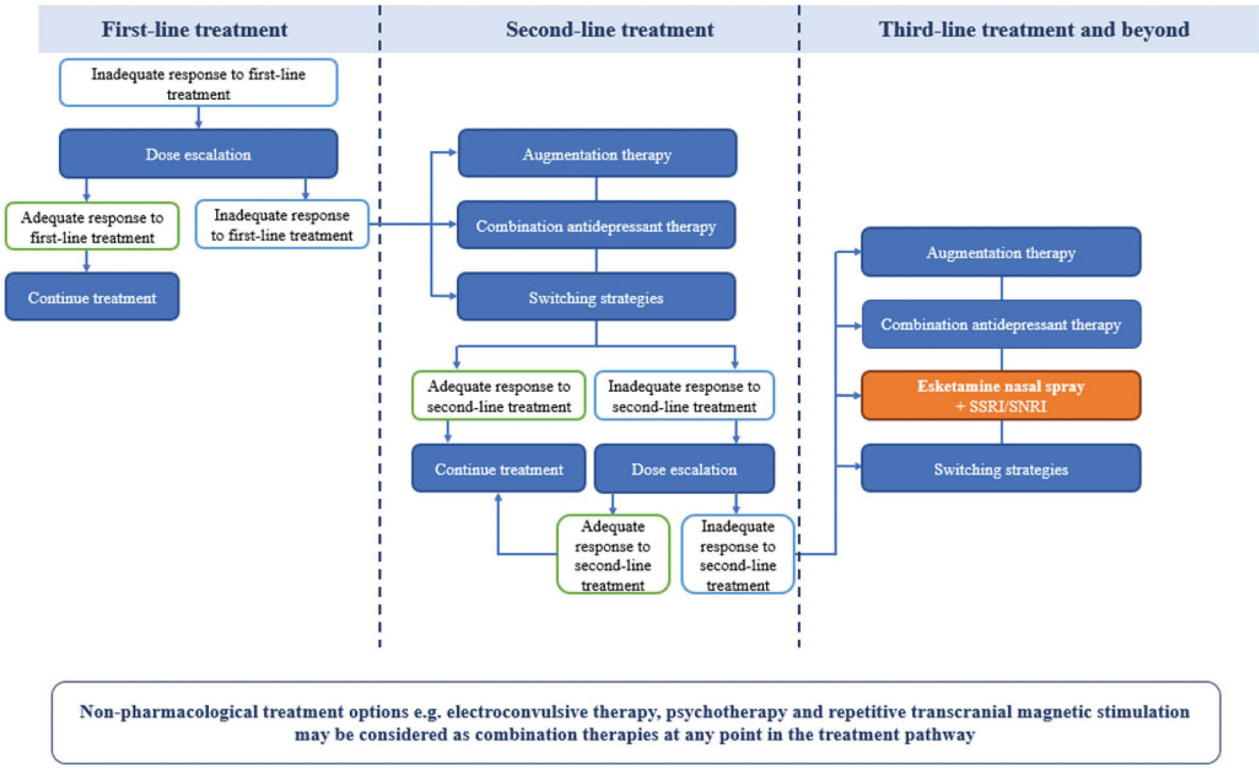


Figure 1. How esketamine nasal spray might fit into a proposed treatment pathway for patients with MDD. MDD: major depressive disorder; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

and is associated with treatment response and remission (Kraus et al. 2019). To evaluate treatment response, clinicians can consult various staging methods that define TRD alongside their own clinical judgement (Table 2). However, further studies are required to demonstrate the reliability and validity of these staging methods in determining treatment response (Gaynes et al. 2020). Alternative methods to determine treatment response include digital platforms such as HumanITcare (Jones 2019).

The recommendations for esketamine nasal spray are based on Phase 3 data (Table 1) where the study definition of TRD was 'non-response to an adequate trial (dosage, duration and adherence) of at least two antidepressants in the current episode (of which one was observed prospectively)' (Popova et al. 2019). As the study definition of TRD did not require the second antidepressant to be from a different class, a patient who had received two consecutive SSRIs or SNRIs was considered treatment resistant.

Despite the diversity of TRD definitions, European clinicians who decide to treat patients with TRD with esketamine nasal spray should always refer to the definition in the Summary of Product Characteristics (EMA 2019), based on the EMA's definition of TRD (EMA 2013).

Considerations prior to initiating treatment with esketamine nasal spray

(3) When deciding whether to initiate treatment with esketamine nasal spray or alternative third-line treatment options in patients with TRD, the prescribing clinician should carefully consider previous treatment history, comorbidities and current concomitant medication, as well as the individual patient's circumstances and treatment preferences

As well as esketamine nasal spray, there are a number of pharmacological and non-pharmacological treatment options available for patients with TRD (summarised in Figure 1). Pharmacological treatment options include switching strategies (Moret 2005), dose escalation with the current therapy, combination therapy and augmentation therapy (Dold et al. 2018). Currently, only olanzapine-fluoxetine combination therapy has received FDA approval for the acute treatment of TRD (Philip et al. 2010). Other atypical antipsychotics that have shown benefit as augmentation therapies in MDD include aripiprazole, quetiapine (Dold et al. 2018) and brexpiprazole (Wang et al. 2016). A recent meta-analysis indicated that esketamine nasal spray was nearly twice as efficacious in patients with TRD than these augmentation therapies (the meta-analysis included olanzapine monotherapy

rather than the olanzapine-fluoxetine combination; Dold et al. 2020). Analyses from the STAR*D study showed response rates of 16.2% in patients with TRD over 14 weeks with lithium augmentation (Gaynes et al. 2008). Despite these available augmentation therapies, evidence on antidepressant combination therapies is limited (Bennabi et al. 2019). Non-pharmacological treatment options for patients with TRD include cognitive behavioural therapy (CBT), vagus nerve stimulation, exercise (McAllister-Williams et al. 2020), bright light therapy (Camardese et al. 2015), electroconvulsive therapy and psychotherapy as combination therapies (Moret 2005). For example, a meta-analysis found that adjunctive CBT improved response compared with pharmacotherapy alone and sustained improvement for up to a year post-treatment (Li et al. 2018). While there are treatment options available for TRD, these are often limited by their delayed onset of antidepressant effects (Kaur et al. 2019) and lack of robust data for non-pharmacological options (Gartlehner et al. 2017).

Numerous factors can influence the treatment strategy for TRD, including the patient's preference and their medical and treatment history. Firstly, patient preference can be influenced by duration and onset of action of treatment, dosing schedule and symptom severity (Gelhorn et al. 2011). Given that esketamine nasal spray has a different method of administration via intranasal spray (EMA 2019) compared with oral antidepressants, this may also impact a patient's preference; the authors advise including patients in treatment decision-making. Comorbidities can also determine which treatment for TRD might be suitable. For example, esketamine nasal spray poses a risk to patients with cardiovascular and cerebrovascular conditions due to possible adverse events of elevated blood pressure (EMA 2019). If a patient presents with high blood pressure readings (>140/90 mmHg for patients <65 years of age and >150/90 mmHg for patients ≥65 years of age), consider delaying esketamine nasal spray treatment (EMA 2019). In summary, clinicians and patients should collaborate in assessing the risks and benefits of each treatment for TRD.

(4) Due to potential acute adverse events, clinical supervision is required for esketamine nasal spray post-administration, which may require additional logistical considerations and resource planning

There are important logistical factors to consider before initiating esketamine nasal spray treatment, summarised in Box 1. Esketamine nasal spray can transiently increase blood pressure; therefore, the EMA advises assessing blood pressure before and after administration. Additionally, appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation should be available when treating patients with clinically significant or unstable respiratory or cardiovascular conditions (EMA 2019). Esketamine nasal spray is also associated with other acute adverse events post-administration (EMA 2019); therefore, clinical supervision may be required for up to 3 h post-administration (Popova et al. 2019). A healthcare professional determines readiness to leave by observing the patient until they appear stable, based on clinical judgement; a supporting checklist is available (EMA 2019). In a Phase 3 study of adults (18–64 years) with TRD, 93% of patients treated with esketamine nasal spray were ready to leave at 1.5 h post-dose, with the remaining 7% ready to leave by 3 h (Popova et al. 2019). In the authors' experience, logistical planning becomes easier over time, building on experience from each administration session and reproducibility across sessions. In summary, esketamine nasal spray is associated with specific acute adverse events for which the administrating clinic must be fully equipped, including clinical supervision during and post-administration.

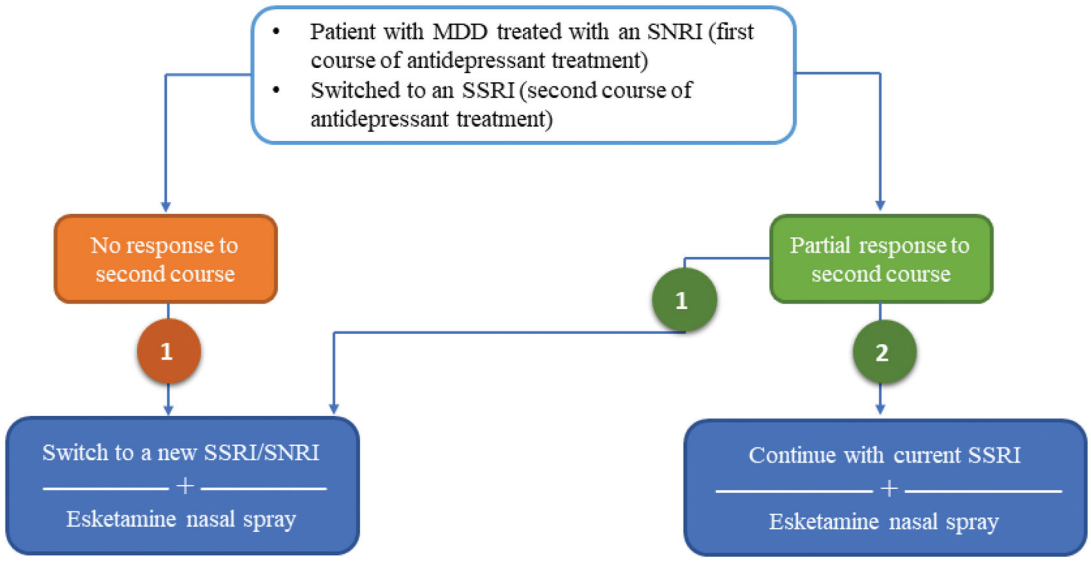
Box 1. Treatment room considerations for esketamine nasal spray treatment.

1. Provide patients with a comfortable seat that is able to recline to 45 degrees (EMA 2019)
2. In the authors' experience, a quiet room with minimal background noise and other distractions may help patients to feel calm
3. In the authors' experience, during the maintenance phase, cognitive stimuli (e.g. ambient lighting and/or imagery in the room) may be increased, based on clinical judgement
4. Resuscitation equipment should be available when treating patients with clinically significant or unstable cardiovascular or respiratory risk factors (EMA 2019)
5. In the authors' experience, it can be helpful for healthcare professionals to remain in proximity to the patient following administration, with easy access to specialised equipment if necessary

The practicalities of esketamine nasal spray administration

Statements 5–11 provide practical guidance on treatment of TRD with esketamine nasal spray in a clinical setting.

(5) Esketamine nasal spray is administered concomitantly with an SSRI/SNRI (EMA 2019); evaluate the patient's treatment response history to decide



MDD: major depressive disorder; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression.

Figure 2. An example of the different treatment options available when starting treatment of TRD with esketamine nasal spray. MDD: major depressive disorder; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression.

whether to continue with the current SSRI/SNRI, to begin treatment with a new antidepressant of the same class or to begin treatment with a new antidepressant of a different class (an SSRI/SNRI)

Esketamine nasal spray must be administered concomitantly with an SSRI/SNRI (EMA 2019); however, which particular drug depends on clinical judgement. Although it can make intuitive sense to change one treatment variable at a time, in clinical studies, esketamine nasal spray plus a new oral antidepressant showed clinical benefit in comparison with placebo plus a new oral antidepressant, supporting the choice to change two variables at once (Popova et al. 2019).

In the case of non-response, or an intolerable adverse-event profile, clinicians should consider switching the current antidepressant (Kudlow et al. 2014). In the case of a partial response, clinicians should ensure treatment compliance (QIDS 2009), before considering augmentation or combination therapy or medication switch. Please see Figure 2 for further guidance.

Current evidence from the STAR*D study suggests no difference in response when switching treatment to a new antidepressant of the same class or of a different class (Gaynes et al. 2008). For some patients it may be beneficial to choose a new antidepressant of the same class, as lack of tolerability to one SSRI or SNRI does not indicate intolerability to the whole class of antidepressants (Al-Harbi 2012). Taken together, these reports suggest that in some cases there may be no benefit to trying a new class compared with staying in the same class as the current antidepressant.

Future studies would be required to show if antidepressants of other classes, e.g. mirtazapine, could be an alternative to administer concomitantly with esketamine nasal spray for TRD. However, esketamine nasal spray is currently only indicated in combination with an SSRI or SNRI (EMA 2019).

(6) The dose of esketamine nasal spray is flexible throughout treatment, while the dosing schedule is flexible after the initial maintenance phase. The decision to change the dose or reduce the dosing frequency should be based on clinical evaluation supported by efficacy outcomes

The dosing schedule of esketamine nasal spray is different to previous treatments for TRD and should be regularly assessed. In the 4-week induction phase, esketamine nasal spray dose is flexible, with different twice-weekly doses recommended based on age and race (EMA 2019). After the initial 4 weeks, the EMA recommends that patients enter the maintenance phase

Table 3. Summary of some of the outcome measures available to support clinical judgement of efficacy.

Outcome measure	Description
Inventory of Depressive Symptomatology self-report (IDS-SR) (Rush et al. 2000)	• Patient-reported measure of depressive symptom severity and changes in depressive symptoms
Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) (Rush et al. 2000)	• Shortened version of the IDS-SR
Clinical Global Impression scale (CGI) (Kadouri et al. 2007)	• Physician questionnaire to measure the severity of illness, global improvement and efficacy index
Mental State Examination (MSE) (Snyderman and Rovner 2009)	• Includes a patient report and observational data gathered by the physician through a clinical interview • Assesses the patient's appearance, general behaviour, mood, thoughts and feelings
EuroQol-visual analogue scales (EQ-VAS) (Feng et al. 2014)	• Patient-reported vertical visual–analogue scale ranging from 0 (worst imaginable health) to 100 (best imaginable health)
Montgomery–Åsberg Depression Rating Scale-Self (MADRS-S) (Wikberg et al. 2015)	• 9-item patient-reported tool scored between 0 (minimum) and 6 (maximum)
Hamilton Depression Rating Scale (HDRS) (Kautzky et al. 2017)	• Physician-reported 17-item rating scale • Indicates the presence of moderate depressive symptoms after an adequate treatment period

where esketamine nasal spray can be administered flexibly: once weekly, or every other week (EMA 2019). For example, the long-term dosing schedule in the Phase 3 withdrawal study of esketamine nasal spray in adults (18–64 years) with TRD varied; the majority of patients in stable remission were treated every other week (68.9%) for most of the maintenance phase, whereas most of the stable responders were treated more frequently, once a week mostly (54.8%; Daly et al. 2019). Sustained or improved efficacy was reported with esketamine nasal spray in 76% of all responders, even at a lower dose frequency, supporting individualisation of treatment frequency (Nijs et al. 2020). Additionally, the initial dose from the induction phase can be increased to 84 mg if deemed appropriate (EMA 2019). For example, one of the authors' patients has received esketamine nasal spray, as part of a Phase 3 continuation of care study (ClinicalTrials.gov 2020a), since 2017 (3 years prior to the time of writing); they currently receive an 84-mg monthly dose (an investigational dosing regimen) alongside daily venlafaxine. From the authors' experience, if treatment is tolerable, the dose should be maintained. Clinicians should use their judgement and clinical experience, alongside patient- and clinician-reported outcomes (Table 3), to determine response to esketamine nasal spray within a certain timeframe.

Patient education can support compliance and adherence with the esketamine nasal spray dosing regimen; research suggests that patient non-compliance may occur as a result of poor therapy area understanding (Kornstein and Schneider 2001). The authors suggest that discussing the definition and causes of TRD, symptom recognition, and the practicalities of esketamine nasal spray treatment with patients could enhance patient adherence to the treatment regimen. The authors also found that reminder calls, SMS or digital calendars encouraged adherence. In case of non-compliance with pre-treatment recommendations – food and liquid avoidance and not using a nasally administered corticosteroid or decongestant – consider delaying or rescheduling administration. From the authors' experience, patient education measures aid patients' understanding of, and engagement with, the esketamine nasal spray treatment process.

Clinical considerations for managing treatment-emergent adverse events

(7) Due to the time course of adverse events, patients should be clinically monitored after administration of esketamine nasal spray, particularly for elevated blood pressure, dissociation and sedation (EMA 2019)

From the authors' experience, certain risk factors may be associated with esketamine nasal spray adverse events. The authors suggest that patients with comorbid borderline personality disorder, anxiety, post-traumatic stress disorder, or patients who experienced numerous adverse events with other antidepressants might be at higher risk. The authors therefore found it helpful to be aware of these factors when monitoring for adverse events associated with esketamine nasal spray.

Generally, in clinical studies, esketamine nasal spray adverse events followed a similar time course; most adverse events were transient, appeared shortly after dosing (during the first 30–40 minutes) and had resolved by 1.5 h after dosing (Popova et al. 2019). For example, most cardiovascular adverse events had an onset shortly after dosing and subsided by 1.5 h post-

dose (Doherty et al. 2020); this time course is consistent with the pharmacokinetic profile of esketamine nasal spray (FDA 2019a).

(8) Blood pressure elevation: If a patient's blood pressure is high or remains elevated for some time, continue to regularly monitor blood pressure and consider prescribing an antihypertensive medication based on your clinical judgement until the values normalise

To mitigate the risk of acute blood pressure elevation, any underlying hypertension (>140/90 mmHg for patients <65 years of age and >150/90 mmHg for patients ≥65 years of age) should be treated and stabilised prior to esketamine nasal spray administration (EMA 2019). Additionally, clinicians should check adherence and tolerability to current antihypertensive treatment. In esketamine nasal spray clinical studies, acute blood pressure elevation as an adverse event was more prevalent in patients with a history of hypertension (Doherty et al. 2020). This reinforces the importance of managing pre-existing hypertension before initiating esketamine nasal spray treatment.

The treating clinician and patient should be aware that most blood pressure adverse events appear shortly after dosing and are short-lived and self-resolving. In esketamine nasal spray clinical studies, blood pressure increases generally reached a maximum within 40 minutes of dosing and normalised within 1.5–2 h (Doherty et al. 2020). Most cases of increased blood pressure were not associated with symptoms, did not result in serious cardiovascular safety sequelae and had no clinically relevant effect on electrocardiogram parameters, and fewer than 2% of patients discontinued due to cardiovascular adverse events (Doherty et al. 2020). These data show that acute increases in blood pressure are generally transient and self-resolving.

In clinical studies of esketamine nasal spray, most cases of increased blood pressure were self-resolving without the need for medication (Popova et al. 2019; Doherty et al. 2020). However, in a short-term, double-blind study, a small proportion of patients without a history of hypertension required an antihypertensive (2.1% in the esketamine arm vs 1.2% in the placebo arm; Doherty et al. 2020). Antihypertensives prescribed in the esketamine arm included amlodipine, captopril, losartan, metoprolol and propranolol (Doherty et al. 2020). The decision to prescribe an antihypertensive following acute hypertension, and which to prescribe, is based on clinical judgement and the individual patient.

(9) Dissociation: In general, dissociation does not require specific intervention as it is transient and disappears over time; however, in rare cases of severe agitation or anxiety, consider prescribing a benzodiazepine, e.g. lorazepam

Dissociation has a large spectrum of symptoms, in which the severity of symptoms can be subjective; therefore, each patient experience is highly variable and could be positive or negative (Nijenhuis 2001). Dissociative symptoms include dissociative amnesia, depersonalisation, derealisation, identity confusion/identity fragmentation, the subjective feeling of being separated from the surrounding environment or one's body (Nijenhuis 2001), and the transient feeling of being disconnected from space and time (EMA 2019). While dissociation is experienced differently among patients, it is important to note that dissociation is an adverse event associated with esketamine nasal spray treatment and should *not* be used therapeutically to gain more insight into the 'unconscious world' of the patient.

Patient education is key to managing patient expectations of potential dissociation adverse events (Box 2). A vital aspect of patient education is regular supervision and reassurance from the treating clinician before and during treatment. From the authors' experience, it can be helpful to prompt patients to think about a positive moment from their life during administration, as this could potentially reduce their risk of experiencing a negative dissociative event. Additionally, it is important to emphasise that in esketamine nasal spray clinical studies, dissociation adverse events were transient and self-limiting, occurring on the day of dosing and in most cases disappearing within 1.5 h post-dose without the need for medical intervention (EMA 2019; Popova et al. 2019). No medications were utilised specifically for the management of dissociation in clinical trials; however, anxiety or agitation associated with dissociation could be treated with short-acting benzodiazepines; only 10 out of 1,601 patients treated with esketamine nasal spray in the Phase 3 TRD studies received such medication (unpublished data provided by Janssen Pharmaceutica NV). From the authors' experience, if necessary, medication for symptoms of dissociation can be beneficial. However, in the first instance, the authors found patient education most helpful (Box 2).

Box 2. Discussion topics for clinician-patient conversations around dissociation as an adverse event following esketamine nasal spray administration.

Evidence from the esketamine nasal spray clinical trials

- Professional supervision will be provided for the duration of treatment with esketamine nasal spray (EMA 2019)
- Dissociative adverse events will be monitored by the treating healthcare professional (EMA 2019)
- Dissociative symptoms vary and can be experienced in different ways; for example, they may be positive or negative (EMA 2019)
- In general, dissociation occurs shortly after esketamine nasal spray administration (EMA 2019; Popova et al. 2019)
- In general, symptoms of dissociation alleviate relatively quickly on their own (within 1.5 h post-dose; EMA 2019; Popova et al. 2019)
- In general, the severity of dissociative symptoms reduces over time with repeated treatment (EMA 2019; Popova et al. 2019)
- The incidence of severe dissociation in clinical studies was low (<4%; EMA 2019)
- Of 802 patients enrolled in the long-term safety study, discontinuation due to dissociation occurred in 5 patients (0.6%; Wajs et al. 2020)

Authors' suggestions

- It can be helpful to focus on positive and/or mindful thoughts before administration
- It can be helpful to focus on positive and/or mindful thoughts before administration
- Dissociative adverse events are not a form of therapy and should not be used to better understand the inner mind

(10) Sedation: If a patient experiences severe sedation or becomes unconscious, close monitoring for signs of respiratory depression and change in haemodynamic parameters is recommended

Several factors can help to manage the severity of sedation adverse events following esketamine nasal spray administration. Firstly, patient education helps to manage patient expectations. Clinicians may reassure their patients that cases of sedation are often transient and mild-to-moderate in severity. In clinical studies of esketamine nasal spray, no signs of respiratory distress were observed with sedation adverse events, and sedation was not associated with hypoxaemia (Popova et al. 2019). In addition, across all Phase 3 studies (Table 1), severe cases of sedation were infrequent (EMA 2019). For example, of 802 patients enrolled in the long-term safety study, 5 patients (<1%) experienced severe sedation, as demonstrated by a Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score of 0 (corresponding to no reaction to painful trapezius squeeze) or 1 (purposeful reflexive withdrawal in response to trapezius squeeze; Wajs et al. 2020). Secondly, the authors also found it helpful if the room was properly lit and if a comfortable seat was provided for administration. Thirdly, from the authors' experience, it was helpful to begin with a low esketamine nasal spray dose and then to only increase the dose as necessary, based on clinical judgement.

In the Phase 3 long-term safety study of esketamine nasal spray, in the cases of sedation (EMA 2019), vital signs and oxygen saturation were assessed, as well as any symptoms of respiratory distress (Wajs et al. 2020). Based on this, the authors advise regularly assessing vital signs to ensure no respiratory or hypotension problems arise during a potential sedation adverse event. Additionally, from the authors' experience, it is useful to assess cognitive function and alertness to determine when a patient is no longer experiencing sedation. Based on clinical judgement, consider limiting any concomitant benzodiazepines (Kaur et al. 2019) or certain antipsychotics (Miller 2004) as these can increase the risk of sedation (Kaur et al. 2019).

(11) Consider the frequency and severity of adverse events, dose adjustment, response, patient preference, concomitant medication use and psychiatric history when deciding to continue treatment with esketamine nasal spray

Across clinical studies of esketamine nasal spray, severe adverse events were infrequent (EMA 2019); however, regular monitoring is necessary to manage these events if they do occur. Rates of discontinuation due to adverse events in clinical studies were low; 7% of patients discontinued esketamine nasal spray treatment in the 4-week double-blind phase of the Phase 3 study of adults (18–64 years) with TRD (Popova et al. 2019), and 3.8% of patients discontinued in the 48-week open-label optimisation/maintenance phase of the long-term safety study (Wajs et al. 2020). Moreover, a post hoc analysis of the Phase 3 studies highlighted that, although adverse events such as dissociation were relatively common, they did not necessarily lead to discontinuation (Citrome et al. 2020).

The decision on whether to continue treatment with esketamine nasal spray following a severe adverse event is dependent on the type of adverse event and its intensity and duration, concomitant medication, patient preference, general clinical evaluation and presence of elevated blood pressure. For example, one of the authors' patients who was treated with esketamine nasal spray (56 mg) experienced a hypertensive crisis during their first administration,

Table 4. Summary of consensus recommendations for esketamine nasal spray.

No.	Consensus statement
Understanding the different facets of treatment-resistant depression	
1	TRD is a complex, multifaceted disorder with many contributing neurobiological, genetic, clinical and psychosocial factors
2	There are a number of different definitions of TRD; however, to inform clinical decisions in this context, the practical definition of TRD is 'the failure of at least two different treatments with antidepressants of adequate duration and dose in the current moderate-to-severe episode' (EMA 2019), in line with the EMA's definition of TRD (EMA 2013)
Considerations prior to initiating treatment with esketamine nasal spray	
3	When deciding whether to initiate treatment with esketamine nasal spray or alternative third-line treatment options in patients with TRD, the prescribing clinician should carefully consider previous treatment history, comorbidities and current concomitant medication, as well as the individual patient's circumstances and treatment preferences
4	Due to potential acute adverse events, clinical supervision is required for esketamine nasal spray post-administration, which may require additional logistical considerations and resource planning
The practicalities of esketamine nasal spray administration	
5	Esketamine nasal spray is administered concomitantly with an SSRI/SNRI (EMA 2019); evaluate the patient's treatment response history to decide whether to continue with the current SSRI/SNRI, to begin treatment with a new antidepressant of the same class or to begin treatment with a new antidepressant of a different class (an SSRI/SNRI)
6	The dose of esketamine nasal spray is flexible throughout treatment, while the dosing schedule is flexible after the initial maintenance phase. The decision to change the dose or reduce the dosing frequency should be based on clinical evaluation supported by efficacy outcomes
Clinical considerations for managing treatment-emergent adverse events	
7	Due to the time course of adverse events, patients should be clinically monitored after administration of esketamine nasal spray, particularly for elevated blood pressure, dissociation and sedation (EMA 2019)
8	Blood pressure elevation: If a patient's blood pressure is high or remains elevated for some time, continue to regularly monitor blood pressure and consider prescribing an antihypertensive medication based on your clinical judgement until the values normalise
9	Dissociation: In general, dissociation does not require specific intervention as it is transient and disappears over time; however, in rare cases of severe agitation or anxiety, consider prescribing a benzodiazepine, e.g. lorazepam
10	Sedation: If a patient experiences severe sedation or becomes unconscious, close monitoring for signs of respiratory depression and change in haemodynamic parameters is recommended
11	Consider the frequency and severity of adverse events, dose adjustment, response, patient preference, concomitant medication use and psychiatric history when deciding to continue treatment with esketamine nasal spray

EMA: European Medicines Agency; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression.

with their systolic blood pressure increasing to 210 mmHg. Despite being treated with captopril, the patient decided to discontinue esketamine nasal spray treatment (Wajs et al. 2020).

Although there is no specific guidance on treatment duration, the EMA recommends continuing treatment with esketamine nasal spray for at least 6 months after depressive symptoms improve. Additionally, clinicians should periodically re-evaluate treatment continuation during the maintenance phase (EMA 2013). Data from a withdrawal study (Daly et al. 2019) showed that esketamine nasal spray reduced the risk of relapse vs placebo by 70% in patients in stable response (hazard ratio, 0.30; 95% CI, 0.16–0.55). In addition, the median time to relapse was reduced in those patients who were treated with esketamine nasal spray for 20 months vs patients who were treated for only 4 months (635 days vs 88 days, respectively; Daly et al. 2019). Further guidance on treatment duration may emerge with additional real-world experience and potential insights from the ongoing long-term safety study (ClinicalTrials.gov 2020a). In summary, treatment continuation is a multifactorial and collaborative decision that should be made by the clinician and patient.

Conclusions

Based on the authors' clinical experience and data available in the literature, this manuscript provides guidance on the practical use of esketamine nasal spray, including treatment initiation and considerations pre-, during and post-administration (summarised in Table 4).

Esketamine nasal spray is a treatment for TRD, with a novel mechanism of action relative to existing therapies for TRD, which offers an additional option for patients who have already failed several lines of treatment. Current evidence highlights its rapid onset of antidepressant effects (Popova et al. 2019), beneficial response rates (Kaur et al. 2019), and its generally transient adverse events (Popova et al. 2019). Further studies of esketamine nasal spray in patients with TRD are ongoing: a long-term safety study (ClinicalTrials.gov 2020a) and a study investigating esketamine nasal spray versus quetiapine extended-release formulation (ClinicalTrials.gov 2020b). Esketamine nasal spray is also currently being investigated in patients with MDD who have active suicidal ideation with intent. In this population, esketamine nasal spray showed rapid improvement in depressive symptoms 24 h post-first dose; however, it did not demonstrate a significant improvement in the severity of suicidality compared with placebo (Fu et al. 2020; Ionescu et al. 2020). Based on these data, Janssen has applied to the EMA for a label extension (JNJ 2020).

Here, we provide guidance based on the authors' clinical experience and the available evidence. Future,

real-world use of esketamine nasal spray will add to our collective knowledge about this treatment for patients with TRD.

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ORCID

Josep A. Ramos-Quiroga http://orcid.org/0000-0003-1622-0350
Daniel Souery http://orcid.org/0000-0003-3434-5958
Allan H. Young http://orcid.org/0000-0003-2291-6952

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