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Management of treatment-resistant depression with esketamine nasal spray: clinical questions for daily practice in Gulf Cooperation Council countries

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Abstract

Background There is a high unmet need among patients with treatment-resistant depression (TRD) as treatment with standard therapies is associated with low response and remission rates and high rates of relapse. Esketamine nasal spray, an *N*-methyl-D-aspartate receptor antagonist, is a novel, fast-acting treatment option for TRD. This article addresses common questions in Gulf Cooperation Council (GCC) countries regarding esketamine nasal spray by discussing the latest clinical evidence and by providing expert opinions.

Methods Six expert psychiatrists from the GCC region with clinical experience in TRD reviewed and critically appraised published evidence on esketamine nasal spray for TRD and considered clinical guidelines, expert opinions and consensus statements. Consensus views were reached on clinical questions pertinent to implementing esketamine nasal spray for TRD in the GCC region.

Results Clinical questions on patient identification, selection of serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors, treatment duration, management of adverse events and clinical requirements for the safe administration of esketamine nasal spray were addressed.

Conclusions Esketamine nasal spray represents a new treatment paradigm for TRD. This article provides clinical guidance based on the latest evidence and clinical experience to help mental health practitioners implement esketamine nasal spray into everyday clinical practice.

Keywords Esketamine nasal spray, Treatment-resistant depression, Major depressive disorder, Gulf Cooperation Council

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Background

The Gulf Cooperation Council (GCC) consists of six contiguous countries (the United Arab Emirates [UAE], Kingdom of Bahrain, Kingdom of Saudi Arabia, Sultanate of Oman, State of Qatar and State of Kuwait) that share similar cultural, religious, political and social values, as well as unique demographics, shaped by large expatriate populations [1–3]. GCC countries have similar chronic non-communicable disease patterns and healthcare systems and, in recognition of the considerable burden of chronic mental health disorders, have prioritized mental health in their national healthcare strategies [2, 3].

Major depressive disorder (MDD) was the fourth leading cause of disability worldwide in 2002 and is projected to be the second leading cause of disability by 2030 [4]. Disability-adjusted life years, which measure years of healthy life lost to either mortality or disability, are estimated to be ~ 800–1100 per 100,000 persons for MDD in GCC countries [5]. Moreover, the prevalence of MDD in GCC countries has increased by up to 38% since the start of the coronavirus 2019 (COVID-19) pandemic [5].

Globally, ~ 20–40% of patients with MDD develop treatment-resistant depression (TRD) [6–10], commonly defined as failure to respond to or achieve remission after ≥ 2 different pharmacological antidepressant courses of adequate dose and duration [7, 8, 10–14]. Guideline-recommended strategies for managing TRD include switching to another antidepressant, combining two antidepressants, or augmentation of an antidepressant with another pharmacological agent (e.g., quetiapine or lithium) or another modality that may include psychotherapy such as cognitive behavioural therapy, transcranial magnetic stimulation or electroconvulsive therapy [15–20].

There is a high unmet need among patients with TRD as treatment with standard pharmacological, psychotherapeutic and neurostimulation therapies is associated with low 6- and 12-month response (~ 27% and ~ 31%, respectively) and remission (~ 17% and ~ 19%, respectively) rates [13]. Furthermore, ~ 52–66% of patients with TRD who achieve response or remission relapse within 6 months [6, 13]. Compared with patients with non–treatment-resistant MDD, patients with TRD are twice as likely to experience suicide ideation (~ 8% and 17%, respectively; $p < 0.001$) and have significantly greater work impairment ($p = 0.001$), activity impairment ($p < 0.001$) and healthcare utilisation ($p = 0.002$) [9].

Patients with TRD account for a disproportionate amount of the economic burden of MDD, both in terms of direct healthcare costs and indirect costs through loss of productivity [8]. A White Paper published in 2020 estimated the overall direct burden of TRD to be SAR 14,997 million, KWD 304 million and AED 2,461 million in Saudi Arabia, Kuwait and the UAE, respectively, representing a substantial healthcare expenditure in GCC countries [21].

Esketamine nasal spray (Spravato®, Janssen-Cilag International NV) in combination with either a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) was initially approved by the US Food and Drug Administration (FDA) in 2019 as a treatment option for adults with TRD [22]. Esketamine nasal spray consists of the *S*-enantiomer of racemic ketamine, a glutamate receptor antagonist that selectively blocks *N*-methyl-D-aspartate (NMDA) receptors expressed on γ-aminobutyric acid (GABA)-ergic inhibitory interneurons, leading to enhanced glutamatergic firing [22, 23]. This, in turn, stimulates α-amin o-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R)-mediated neurotrophic signalling [22, 23], which may restore synaptic function in areas of the brain that control mood and emotional behaviour [22] (Fig. 1). In the registrational, Phase 3 TRANSFORM 2 trial of esketamine nasal spray 56/84 mg plus an SSRI/SNRI versus placebo plus an SSRI/SNRI, the difference in the least square mean (LSM) Montgomery–Åsberg Depression Rating Scale (MADRS) score between treatment groups was –3.3 (95% confidence interval [CI] –5.75, –0.85) points 24 h after administration of the first dose, suggesting rapid onset of clinically meaningful efficacy [24].

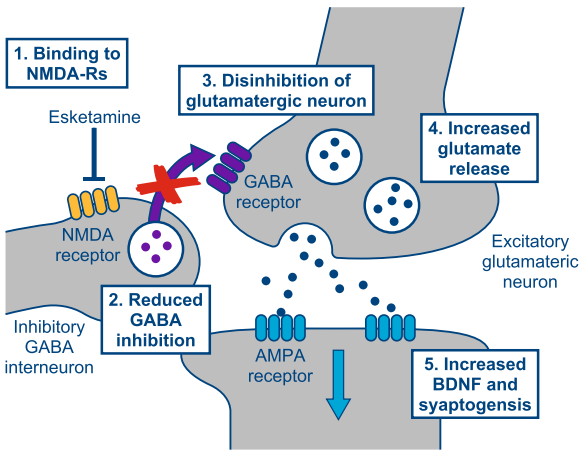

Fig. 1 Mechanism of action of esketamine nasal spray. Figure adapted from Duman, R.S., Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide. F1000Res, 2018. 7(F1000 Faculty Rev):659 [22, 25]. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *BDNF* brain-derived neurotrophic factor, *GABA* γ-aminobutyric acid, *NMDA-R N*-methyl-D-aspartate receptor

Current TRD guidelines for GCC countries require updating with recent treatment approvals, such as esketamine nasal spray [15–20]. This, in turn, has led to a delay in uptake of esketamine nasal spray among healthcare professionals who may have relevant clinical questions that they feel remain to be answered. These may include questions regarding patient identification, SSRI/SNRI selection, treatment duration, the risks of misuse and dependency, and clinic requirements for the safe administration of esketamine nasal spray, as well as how to communicate the efficacy and safety of esketamine nasal spray to their patients. Recent expert opinions and consensus publications guiding the implementation of esketamine nasal spray in TRD have focused on Europe and the USA [11, 26]. Mental health practitioners in GCC countries face region-specific challenges, including religious and cultural considerations, as well as unique demographics [2, 15]. We address common questions on esketamine nasal spray in TRD in the GCC region by discussing the latest clinical evidence and by providing expert opinions. This clinical article is intended as a practical tool to help mental health practitioners implement esketamine nasal spray into everyday clinical practice. Practical guidance is focused on the GCC region; however, this clinical practice tool is relevant to mental health professionals globally when used alongside local guidelines and the local esketamine nasal spray prescribing information.

Methods

Six expert psychiatrists from the GCC region with clinical experience in MDD and TRD, including two experts with experience prescribing esketamine nasal spray, developed this clinical article. We considered MDD and TRD clinical guidelines [15–20], as well as expert opinions [26], consensus statements [11] and local clinical practice guidelines [27] on esketamine nasal spray. We reviewed published evidence on esketamine nasal spray in TRD using the PubMed database to search for English language publications. Keywords in literature searches included "esketamine", "ketamine", "MDD", "major depressive disorder", "treatment-resistant depression", "TRD", "efficacy", "safety", "Gulf Cooperation Council", "GCC", "Arab", "United Arab Emirates", "UAE", "Bahrain", "Saudi Arabia", "Oman", "Qatar" and "Kuwait". We critically appraised the identified evidence to achieve consensus views on clinical questions pertinent to implementing esketamine nasal spray for TRD in the GCC region.

Results

Patient identification

What patient criteria must be met before considering esketamine nasal spray in TRD?

Esketamine nasal spray combined with an SSRI/SNRI is indicated for treating TRD in adults who have not responded adequately to ≥ 2 separate courses of antidepressants, each of adequate dose and duration, in a moderate-to-severe depressive episode [22].

Patient evaluation for esketamine nasal spray treatment should include psychiatric assessment, physical examination, and review of prior antidepressant treatment adherence and response, alongside clinical judgment [11, 26]. Treatment response tools (e.g., the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [ATRQ], Antidepressant Treatment History Form [ATHF] and Maudsley Treatment Inventory [MTI] [28]) can be useful for assessing treatment adherence and response; such tools generally consider a treatment duration of 4 to ≥ 6 weeks to be an adequate treatment duration [29–32], and a < 25% improvement in MDD symptoms is considered by the ATRQ to demonstrate non-response to an antidepressant treatment course [29–31]. MDD severity can be assessed using a standard severity rating tool such as the 17-item Hamilton Depression Rating Scale (HDRS17), Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-C) version or 30-item Inventory of Depressive Symptomatology-Clinician Rating ($IDS\text{-}C_{30}$) [28]. It is also essential to consider differential diagnoses, e.g., bipolar disorder or a major depressive episode secondary to dementia or a cerebrovascular accident, when evaluating patients for possible TRD [33]. A proposed MDD treatment algorithm, showing where esketamine nasal spray fits in the treatment pathway, is shown in Fig. 2.

To minimize the risk of potential adverse events (AEs) with esketamine nasal spray, patients with clinically significant or unstable cardiovascular or respiratory conditions, as well as certain other comorbidities (Table 1), should be carefully assessed before initiating esketamine nasal spray in order to determine if the benefits of treatment outweigh the potential risks [22]. Furthermore, esketamine nasal spray should only be initiated in patients with hypertension if blood pressure is adequately controlled [22]. Blood pressure should be measured before administration of esketamine nasal spray, and a delay in the administration should be considered if blood pressure is elevated (> 140/90 and > 150/90 mmHg for patients < 65 years old and ≥ 65 years old, respectively) [22].

Although ketamine, a racemic mixture of (*R*)-ketamine and (*S*)-ketamine [22], is known for its susceptibility to recreational abuse [34], misuse and diversion related to esketamine nasal spray is limited by the requirement to administer it under the supervision of a healthcare professional [22]. Furthermore, there were no reports of drug seeking or abuse of esketamine nasal spray, including requests for an increase in dose or dosing frequency, in Phase 3 clinical trials or a real-world French cohort

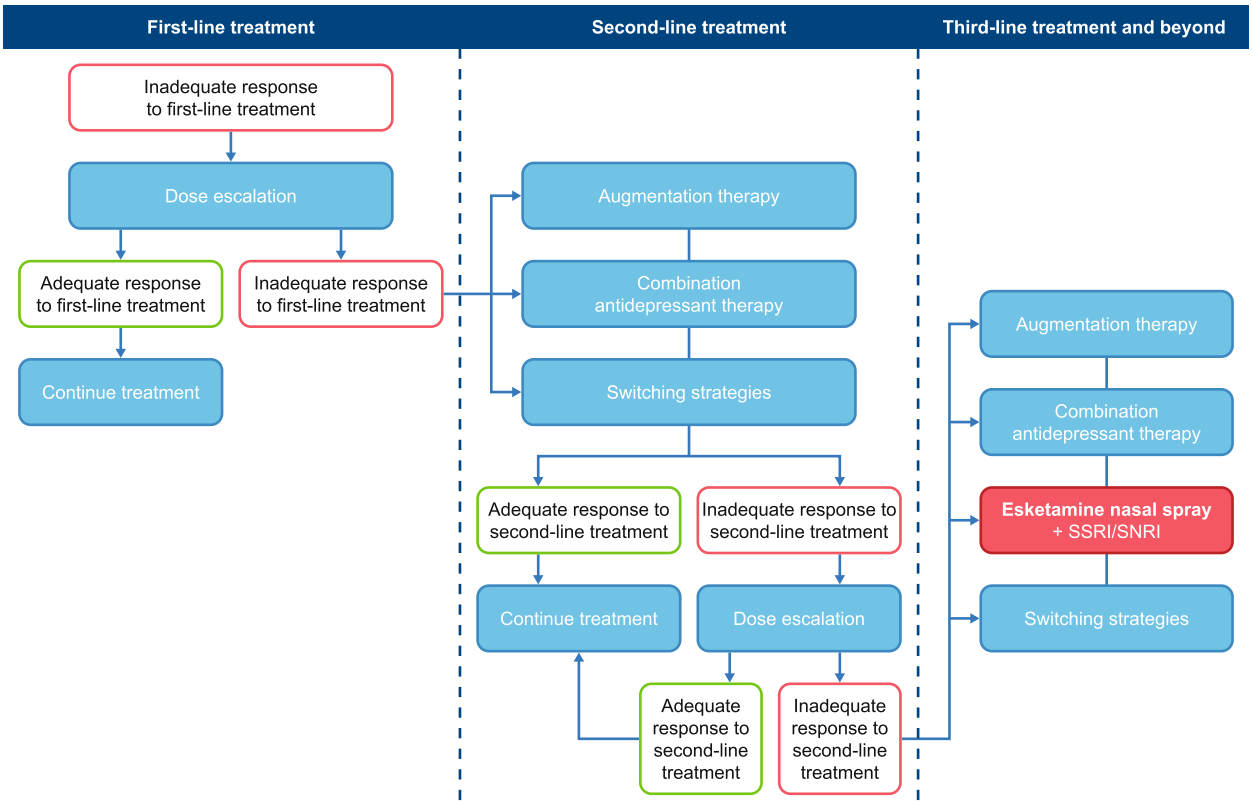

Fig. 2 Proposed MDD treatment algorithm. Figure adapted from Kasper S, et al. 2021 [11]. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way

MDD major depressive disorder, *SNRI* serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

Table 1 Clinical conditions in patients with TRD that require precaution when initiating esketamine nasal spray [22]

Clinically significant or unstable cardiovascular or respiratory conditions
COPD or other significant pulmonary insufficiency
Sleep apnoea with morbid obesity[a]
Uncontrolled bradyarrhythmias or tachyarrhythmias, leading to haemodynamic instability
History of MI
Haemodynamically significant valvular heart disease or heart failure[b]
Other comorbidities
Presence or history of psychosis
Presence or history of mania or bipolar disorder
Hyperthyroidism that has not been sufficiently treated
Conditions associated with increased intracranial pressure[c]

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *MI* myocardial infarction, *NYHA* New York Heart Association, *TRD* treatment related depression

[a] BMI ≥ 35 kg/m^2

[b] NYHA Class III–IV

[c] Including history of brain injury, hypertensive encephalopathy and intrathecal therapy with ventricular shunts

study of esketamine nasal spray in TRD [24, 35–37]. Nevertheless, each patient should have their risk for drug abuse and misuse assessed before initiating esketamine nasal spray [22].

An example case of a patient with TRD who meets the clinical criteria for esketamine nasal spray is shown in Table 2.

Clinical criteria for esketamine nasal spray for TRD are based partly on inclusion and exclusion criteria used in Phase 3 studies of esketamine nasal spray in patients with TRD [24, 35, 36, 38, 39]. In Phase 3 clinical trials, eligible patients had Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)-diagnosed, recurrent MDD or single-episode MDD for ≥ 2 years, without psychotic features [24, 35, 36, 38, 39], that was moderate-to-severe in severity (IDS-C_{30} scores of ≥ 34 and ≥ 31 in patients 18–64 years old and ≥ 65 years old, respectively) [24, 38, 39]. Included patients also met the study definition of TRD, defined as ATRQ-assessed non-response (a < 25% symptom improvement following an adequate dose of antidepressant for ≥ 6 weeks)

Table 2 Case of a patient with TRD who meets the clinical criteria for treatment with esketamine nasal spray plus an SSRI/SNRI

- Fifty-year-old male
- Three previous episodes of depression; currently experiencing a relapse that has not responded to treatment with three different antidepressants, including an SSRI and an SNRI, and augmentation with quetiapine
- Current depressive symptoms are moderate-to-severe in nature and are impacting the patient's functioning
- No clinically significant or unstable cardiovascular or respiratory conditions
- No other relevant comorbidities

SNRI serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TRD* treatment-resistant depression

to ≥ 2 antidepressants in the current depressive episode, and were medically stable [24, 38, 39]. Excluded patients included those with significant psychiatric comorbidities (e.g., psychotic, bipolar, borderline, antisocial, histrionic, narcissistic, autism spectrum or obsessive–compulsive personality disorders) or medical comorbidities (uncontrolled hypertension, significant pulmonary insufficiency, cerebrovascular disease, coronary artery disease with myocardial infarction, unstable angina, aneurysmal vascular disease or revascularisation surgery in the last year, New York Heart Association Class III–IV heart failure, or seizures) [24, 38, 39].

What clinical factors disqualify a patient with TRD from receiving esketamine nasal spray?

Esketamine nasal spray is contraindicated in patients with comorbidities for whom an increase in blood pressure or intracranial pressure poses a serious risk (Table 3) [22]. Additionally, esketamine nasal spray should not be administered in patients with uncontrolled hypertension [22].

Table 3 Comorbidities that are contraindications to esketamine nasal spray [23]

- Aneurysmal vascular disease[a]
- History of intracerebral haemorrhage
- Recent[b] cardiovascular event[c]

[a] Including intracranial, thoracic, abdominal aorta and peripheral arterial vessels

[b] Within 6 weeks

[c] Including myocardial infarction

Practicalities of administering esketamine nasal spray in GCC countries

What are the prescribing requirements for esketamine nasal spray in GCC countries?

Esketamine nasal spray must be prescribed by a psychiatrist and self-administered under medical supervision at clinics licensed to provide psychiatric care [22]. Esketamine nasal spray must not be taken home by patients for self-administration. Additionally, there are specific clinical monitoring requirements immediately after administration, which are discussed in detail in this article.

How is esketamine dosed?

Esketamine nasal spray dosing consists of a 4-week induction phase of twice-weekly administration and a maintenance phase of weekly administration for 4 weeks, followed by flexible, weekly or every-other-week administration to maintain remission/response [22, 27] (Fig. 3). Dose level is flexible and directed by treatment response and tolerability [11, 22, 27]. Recommended starting doses for TRD are 56 mg and 28 mg for adults < 65 years old and ≥ 65 years old, respectively [22, 27].

In the long-term, Phase 3 SUSTAIN-2 trial of esketamine nasal spray plus an SSRI/SNRI for up to 1 year in patients ≥ 18 years old with TRD, higher proportions of patients received a final maintenance dose of 56 mg (45.6%) or 84 mg (50.2%) compared with 28 mg (4.0%) [36]. Furthermore, 38.1% of patients continued with dosing every 2 weeks while 37.8% switched more than once between weekly and every 2 weeks dosing [36]. In a *post-hoc* analysis of dosing frequency, most patients (68.0%) who switched from weekly to every-other-week dosing experienced further symptom improvement or

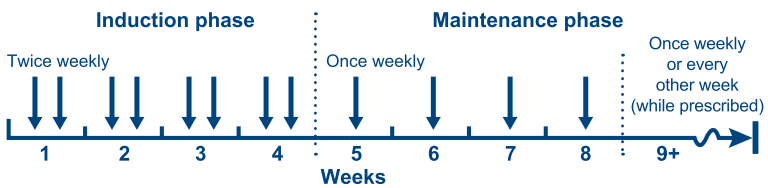

Fig. 3 Esketamine nasal spray dosing [22]

maintained clinical benefit, while most (90.0%) remaining patients either improved or remained unchanged following an increase in dosing frequency from every other week back to weekly [40]. Collectively, these findings support individualization of esketamine nasal spray dose and dosing frequency [36, 40].

Clinicians should regularly assess treatment response [11] using treatment response tools such as the ATRQ alongside clinical judgment and experience. During the maintenance phase, esketamine nasal spray dosing should be individualised to the lowest frequency required to maintain remission/response [22].

Should patients initiating esketamine nasal spray continue with their existing antidepressant or initiate a new SSRI/SNRI?

A switch in antidepressants should be considered in patients with a non-response to their SSRI/SNRI at the initiation of esketamine nasal spray (Fig. 4) [11]. The decision to switch a patient's antidepressant at the initiation of esketamine nasal spray should be based on clinical judgement and should consider adherence, tolerability and treatment response [11].

In Phase 3 clinical trials of esketamine nasal spray in TRD, all patients had a non-response (a ≤ 25% improvement in MDD symptoms as measured by the ATRQ) to their antidepressant at entry and were initiated on a new SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine extended release) in combination with esketamine nasal spray or placebo [24, 35, 36, 38, 39]. Clinical benefit was demonstrated for patients treated with esketamine nasal spray versus those treated with placebo, supporting a switch in antidepressant at initiation of esketamine nasal spray [24, 35, 36, 38, 39]. Further supporting data for a switch in antidepressant come from a Phase 2, dose-escalation trial of esketamine nasal spray plus an SSRI/SNRI in TRD [41]. In this Phase 2 trial, patients randomized to esketamine nasal spray 28/56/84 mg or placebo continued treatment with the same antidepressant they were receiving at enrolment. In the esketamine nasal spray arm, decreases from baseline in mean MADRS total score plateaued by approximately Day 39 and were maintained at –7.2 at Day 74 [41]. By contrast, among patients in Phase 3 trials who initiated a new SSRI/SNRI at the same time as initiation of esketamine nasal spray, the mean decrease in MADRS score at Day 28 was –10.0 for esketamine nasal spray 28/56/84 mg in patients ≥ 65 years old (TRANSFORM-3) and –21.4 for esketamine nasal spray 56/84 mg in patients 18–64 years old (TRANSFORM-2) [24, 39].

What are the logistical considerations for prescribing esketamine nasal spray?

Administration of esketamine nasal spray is associated with potential transient AEs: blood pressure elevation, dissociative symptoms and sedation [22, 24, 35, 36, 38, 39].

Patients must therefore be monitored by a healthcare professional after administration of esketamine nasal spray until clinically stable [11, 22, 27, 42, 43], which is generally ~ 1.5 h after administration, but may take up to 3 h [11, 22, 24, 35, 36, 38, 39, 42]. In accordance with SEHA guidelines, a minimum of 2 h of monitoring is required in

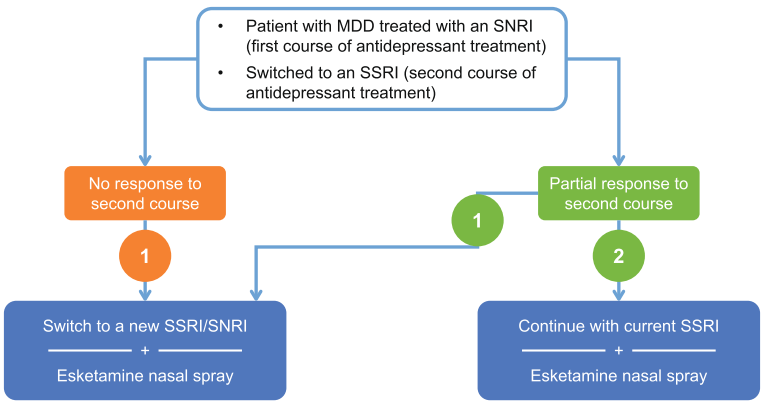

Fig. 4 Example of patient pathway when starting treatment of TRD with esketamine nasal spray. Figure adapted from Kasper S, et al. 2021 [11]. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way

MDD major depressive disorder, *SNRI* serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TRD* treatment-resistant depression

the authors' clinical practice [27]. Additionally, esketamine nasal spray should only be administered at clinics with blood pressure monitoring equipment [42] and appropriate resuscitation equipment, and healthcare professionals with cardiopulmonary training must be available when administering esketamine nasal spray to patients with clinically significant or unstable cardiovascular or respiratory conditions (see Table 1).

A practical checklist of treatment room considerations for esketamine nasal spray is provided in Table 4. In addition to equipment and facility considerations, monitoring requirements during the post-administration observation period require adequate resource planning [11]. In a real-world French cohort study of esketamine nasal spray in TRD, post-administration monitoring was performed by nurses familiar with esketamine AEs and their management, suggesting that continuous monitoring by the treating psychiatrist may not be required and that post-administration monitoring can be safely performed by other well-trained healthcare professionals [37].

What are the clinical supervision requirements during the treatment observation period?

A treatment session for esketamine nasal spray consists of medically supervised self-administration of esketamine nasal spray followed by a post-administration observation period during which the patient is monitored for transient AEs, particularly increases in blood pressure, dissociative symptoms and sedation [11, 22, 26, 27, 42].

During the post-administration observation period, blood pressure should be assessed ~ 40 min after administration of esketamine nasal spray by a healthcare provider with expertise in blood pressure monitoring [22, 27, 42]. If blood pressure is elevated, it should be monitored until it has returned to clinically acceptable levels [22, 27, 42, 43]. Additionally, patients should undergo monitoring for signs of sedation, dissociation, respiratory depression and other AEs [11, 22, 26, 27, 42].

Close monitoring during the post-administration observation period should be performed for patients with clinically significant or unstable cardiovascular or respiratory conditions (Table 1) [27, 42]. Additionally, patients ≥ 65 years old should be carefully monitored, as they may be at increased risk of falling once mobile following treatment [22, 27, 42].

Patients should leave the clinic only when assessed by the treating psychiatrist as clinically stable [22, 27, 42, 43]. In the Phase 3 TRANSFORM-2 trial of esketamine nasal spray 56/84 mg plus an SSRI/SNRI in patients with TRD aged 18–64 years, 93.2% of patients treated with esketamine nasal spray were deemed suitable for discharge by 1.5 h after administration, with all patients being cleared for discharge within 3 h post-administration [24]. Among patients with TRD aged ≥ 65 years who were treated with esketamine nasal spray 28/56/84 mg in the Phase 3 TRANSFORM-3 trial, the majority (90.0%) were deemed suitable for discharge by 1.5 h after administration, with all patients being cleared for discharge within 3 h post-administration [39]. A 'Readiness-to-leave Checklist for Healthcare Professionals', approved by the Saudi Food and Drug Authority, is available to aid clinical decision-making [42].

What COVID-19 protocols should be considered?

Clinicians should follow clinic procedures and protocols in place to limit the spread of COVID-19. General infection control measures should be employed, including hand washing and wearing of masks, to limit transmission by droplets and aerosols. Healthcare professionals supervising administration of esketamine nasal spray should wear protective gloves when handling and holding the esketamine nasal spray device [27]. Additionally, patients should test negative for COVID-19 before administration of esketamine nasal spray.

How can AEs associated with esketamine nasal spray be managed?

Most common AEs associated with esketamine nasal spray (elevations in blood pressure, sedation/somnolence and dissociative symptoms) are mild-to-moderate in intensity, transient, self-limiting and resolve within 1.5 h [22, 24, 35–39, 42]. Specific measures can be implemented to manage AEs, if judged clinically necessary. A clinical tool (the Ketamine Side Effect Tool) is available to download to help clinicians assess patients for risks of AEs associated with esketamine nasal spray and to monitor for treatment-related AEs after administration [44].

Table 4 Checklist of treatment room considerations for administration of esketamine nasal spray [12, 23, 27, 43]

☐ Blood pressure monitoring equipment
☐ Resuscitation equipment[a]
☐ Calm environment, without bright lights, too much noise or other distracting stimuli
☐ Comfortable patient bed that is adjustable, permitting esketamine nasal spray administration and monitoring
☐ Close proximity to nurses' station, permitting frequent check-ins during postadministration observation period

[a] When administering esketamine nasal spray in patients with clinically significant or unstable cardiovascular or respiratory conditions (Table 1)

Acute hypertension

Treatment of acute hypertension with an antihypertensive can be considered, in consultation with a specialist on a case-by-case basis (e.g., if blood pressure remains elevated for over 1.5 h) [11, 42]. In short-term (TRANSFORM-1, -2 and -3) and long-term (SUSTAIN-2), Phase 3 clinical trials of esketamine nasal spray plus an SSRI/SNRI, ~ 2% of patients who experienced elevated blood pressure were treated with an antihypertensive [45]. Patients with signs of hypertensive crisis (e.g., headache, chest pain, shortness of breath, vertigo or nausea) should be referred for immediate emergency care [27, 42].

In addition to management options for acute hypertension, several preventative measures can be employed to mitigate increases in blood pressure. In Phase 3 clinical trials, elevations in blood pressure that were considered markedly abnormal (systolic blood pressure [SBP] ≥ 180 mmHg and/or diastolic blood pressure [DBP] ≥ 110 mmHg) were more frequent in patients ≥ 65 years old and in those with a history of hypertension, reinforcing the importance of ensuring hypertension is adequately controlled before initiating treatment with esketamine nasal spray [11, 36, 39, 45]. Additionally, advising patients to take their SSRI/SNRI several hours after esketamine nasal spray treatment sessions may help alleviate potential increases in blood pressure associated with some antidepressants, e.g., venlafaxine [45]. Moreover, concomitant administration of medications known to increase blood pressure (e.g., psychostimulants such as amphetamines, methylphenidate or modafinil; ergometrine; xanthine derivatives; vasopressin; thyroid hormones; and monoamine oxidase inhibitors such as selegiline, phenelzine and tranylcypromine,) [22, 42] should be carefully reviewed before administering esketamine nasal spray.

In Phase 2 and 3 clinical trials of esketamine nasal spray plus an SSRI/SNRI, blood pressure elevations following initial administration of esketamine nasal spray did not predict blood pressure elevations following subsequent administrations, and there was no evidence of a dose–response effect [45], highlighting the importance of blood pressure monitoring during each esketamine nasal spray treatment session. In total, < 1% (13/1708) of patients discontinued esketamine nasal spray due to increased blood pressure [45], demonstrating that blood pressure elevations can be successfully managed in most cases.

An example patient case of hypertension associated with esketamine nasal spray administration and its management is shown in Table 5.

Sedation

In Phase 3 clinical trials of esketamine nasal spray plus an SSRI/SNRI, ~ 7–12% of patients experienced clinically relevant sedation (Modified Observer's Assessment of Alertness/Sedation [MOAA/S] score ≤ 3) [36, 38, 39]. However, no cases of sedation were associated with respiratory depression or required ventilation or resuscitation, and all patients woke up spontaneously [22, 24, 36, 38, 39], suggesting that sedation in patients is unlikely to require medical intervention. If a patient loses consciousness following administration of esketamine nasal spray, the patient should be closely monitored for respiratory depression and changes in haemodynamic parameters [11, 42].

To help mitigate AEs of sedation, review concomitant medications such as benzodiazepines and opioids that may increase sedation with esketamine nasal spray administration [22, 42]. Additionally, patients should be advised to avoid alcohol the day before and following esketamine nasal spray treatment [42].

Dissociation

Patient education is a vital mitigation strategy for dissociation [11, 42]. Before administration of esketamine nasal spray, patients should be advised that they may experience dissociation and that it can be either a positive or

Table 5 Patient case of hypertension associated with esketamine nasal spray and its management

- Twenty-three-year-old, morbidly obese male with a history of depression and essential tremors
- Received prior SSRI/SNRI treatment and adjunct therapy with atypical antipsychotics
- Mild-to-moderate response to treatment over a 5-year period, with recurrent relapses and frequent suicidal ideations
- Esketamine nasal spray was initiated while he was receiving sertraline (200 mg), lithium (400 mg) and quetiapine (400 mg at bedtime)
- Prior to the initiation of esketamine nasal spray, the patient had shown mild improvement but no psychosocial progress
- When esketamine nasal spray treatment was initiated, the patient's SBP increased to 140–150 mmHg
- A beta blocker was prescribed to control blood pressure during and after esketamine administration
- By Week 5, the patient had shown significant improvements in affect and mood
- Over time, the patient had started exercising regularly and lost considerable weight
- The patient showed good tolerance to the maintenance phase; lithium was withdrawn as the suicidal ideations ceased
- The patient was maintained on sertraline (150 mg), quetiapine (100 mg at bedtime) and esketamine nasal spray (once a month)

SBP systolic blood pressure, *SNRI* serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

negative experience [42]. Reassure patients that, in clinical trials, dissociative symptoms alleviated relatively quickly (within 1.5 h after administration) and that most cases of dissociation did not require medical intervention [11, 42]. It can be helpful to suggest to patients that they focus on positive thoughts or listen to music during administration of esketamine nasal spray to help reduce the risk of experiencing a negative dissociative event [11, 42].

If a patient experiences dissociation, it is important to offer the necessary support and assistance. If they are concerned, reassure them that their symptoms are likely to subside relatively quickly [11, 42]. It can be helpful to advise patients not to close their eyes if they experience visual dissociative symptoms [42].

Additional mitigation measures for dissociation that clinicians should employ include assessment of patient dissociation risk prior to esketamine nasal spray administration and administration in a calm environment, without bright lights, too much noise or other distracting stimuli [11, 42]. Identified risk factors for dissociation include eating disorders, post-traumatic stress disorder, anxiety and mood disorders, substance abuse, alexithymia, childhood maltreatment or traumatic events, and suicide ideation [46, 47].

In the long-term, Phase 3 SUSTAIN-2 trial of esketamine nasal spray 28/56/84 mg plus an SSRI/SNRI, < 1% (5/802) of patients discontinued esketamine nasal spray treatment due to AEs of dissociation [36], demonstrating that dissociation can be successfully mitigated and/or managed in most cases.

Short-acting anxiolytics to relieve anxiety or agitation associated with dissociation can be considered on a case-by-case basis using clinical judgment [11, 42]. Across Phase 3 clinical trials of esketamine nasal spray plus an SSRI/SNRI, < 4% of patients experienced severe dissociative symptoms [22]. No medications specific for management of dissociation were utilised in clinical trials, but anxiety or agitation associated with dissociation could be treated with short-acting benzodiazepines [11, 42]; in total, < 1% (10/1601) of patients treated with esketamine nasal spray plus an SSRI/SNRI in Phase 3 clinical trials received such treatments for dissociation [11].

An example patient case of transient dissociation associated with esketamine nasal spray administration is shown in Table 6.

Communicating the efficacy and safety of esketamine nasal spray to patients

What instructions and guidance should patients receive before they consent to esketamine nasal spray treatment?

Some patients may experience nausea or vomiting after administration of esketamine nasal spray [22, 42]; therefore, patients should be advised not to eat for 2 h before administration of esketamine nasal spray and not to drink liquids for at least 30 min before administration [22, 42]. Additionally, patients should be advised to avoid administration of nasal corticosteroids or decongestants in the hour prior to administration of esketamine nasal spray [22, 42]. Avoidance of alcohol on the days immediately before and after esketamine nasal spray treatment should also be advised to mitigate any sedative effects the patient may experience with esketamine nasal spray administration [42].

As esketamine nasal spray can cause sedation, somnolence and dissociation, it is vital that patients are instructed to organise their journey home via public transport or arrange for someone to take them home after esketamine nasal spray treatment sessions [42]. Furthermore, patients should be instructed not to drive or perform activities that require complete mental alertness, such as operating machinery, until the day after esketamine nasal spray administration [22, 42].

How soon can patients start experiencing improvements on esketamine nasal spray treatment?

In the short-term, Phase 3 TRANSFORM-1 and -2 trials of esketamine nasal spray 56/84 mg versus placebo (both in combination with an SSRI/SNRI) in patients with TRD aged 18–64 years, those in the esketamine nasal spray arm experienced rapid and clinically meaningful improvements in depressive symptoms (> 2-point difference in LSM MADRS score) [26, 40]. This improvement started 24 h after the first dose and was maintained or increased over time with repeated treatment sessions, reaching statistical significance at 4 weeks (TRANSFORM-2 study Day 28 difference in LSM MADRS score –4.0; 95% CI –7.31, –0.64; $p = 0.020$) [24, 38]. A clinically meaningful improvement in depressive symptoms was also observed with esketamine nasal spray 28/56/84 mg versus placebo (both in combination with an SSRI/SNRI) at 4 weeks in patients with TRD aged ≥ 65 years in the Phase 3 TRANSFORM-3 trial (Day 28 difference in LSM MADRS score –3.6; 95% CI –7.20, 0.07; $p = 0.059$), but this did not reach statistical significance [39]. MADRS scores at 24 h after the first dose were not reported in this trial; however, patients who continued esketamine nasal spray plus SSRI/SNRI treatment in an open-label, roll-over study experienced a sustained reduction in mean MADRS score, suggesting longer treatment durations may be required in older patients to see optimal treatment effects [39]. An age-associated difference in treatment effect at 4 weeks was also demonstrated by regression analyses of symptom improvement (change in MADRS score from baseline) by age, which showed

Table 6 Patient case of dissociation associated with esketamine nasal spray

Initial presentation

- Thirty-two-year-old male healthcare worker with a history of MDD and IBS referred by primary care physician for psychiatric evaluation
- Patient had been symptomatic for 13 years and had been on various medications with little/no effects
- The patient was being treated in a private clinic with fluoxetine (60 mg), clonazepam (2 mg), desvenlafaxine (100 mg), sulpiride (400 mg) and melatonin (6 mg)
- Upon presentation, the patient had severe anhedonia, passive suicidal ideations, intermittent self-injurious behavior, low appetite and poor sleep, all of which had worsened over the previous year. A recent change in job had triggered panic attacks and more intense suicidal ideations

Treatment

- Esketamine nasal spray was initiated at 56 mg, and the patient's previous medications were changed by gradual tapering to olanzapine (2.5 mg) and venlafaxine (225 mg)

Follow-up

- During administration of the initial dose at Week 1, the patient experienced a transient episode of dissociation; esketamine was otherwise well tolerated, with no further AEs. The patient was monitored in the clinic for 90 min, then discharged
- Esketamine was increased to 84 mg for the second dose of Week 1 and there were no reports of dissociation or any other AEs

Outcome

- The patient tolerated the rest of the induction phase without any AEs and showed significant improvements in suicidal ideations, self-injurious behavior, mood and appetite
- PHQ-9 and GAD-7 scores at the time of initial presentation were 26 and 24, respectively, and dropped to 10 and 8, respectively, by the end of the induction period
- Blood pressure remained within reference range pre- and post-dosing session during each visit, with no significant increase after treatment
- The patient stated: *"I am looking forward to life with positivity each day when I wake up. Suicidal thoughts seem to be a distant nightmare that I can no longer relate to."*

AE Adverse event, *GAD-7* Generalized Anxiety Disorder 7, *IBS* irritable bowel syndrome, *MDD* major depressive disorder, *PHQ-9* Patient Health Questionnaire 9

greater treatment effects in younger patients as well as those with an earlier age of MDD onset [39]. These findings are consistent with the literature, which supports increased treatment resistance in people with late-onset depression [48].

Proportions of patients who achieved response and remission while on esketamine nasal spray 56/84 mg plus SSRI/SNRI treatment increased over time in the TRANSFORM-2 trial, reaching 69.3% and 52.5%, respectively [24]. In the TRANSFORM-3 trial of esketamine nasal spray 28/56/84 mg plus an SSRI/SNRI in patients with TRD aged ≥ 65 years, response and remission rates after 4 weeks were 27.0% and 17.5%, respectively [39]. The numbers needed to treat (NNTs; the average number of patients needed to produce one more responder/remitter in the esketamine plus antidepressant group than in the placebo plus antidepressant group) were 6 and 5 for response and remission, respectively, after 4 weeks' treatment in the TRANSFORM-2 study, while the respective NNTs in the TRANSFORM-3 study of adults ≥ 65 years old were 8 and 10 [24, 39].

What are the most common and serious AEs associated with esketamine nasal spray?

The most commonly reported AEs in patients with TRD treated with esketamine nasal spray plus an SNRI/SSRI in Phase 3 clinical trials were dizziness (31%), dissociation (27%), nausea (23%), somnolence (18%), dysgeusia (18%), vertigo (16%), hypoesthesia (11%), vomiting (11%) and elevated blood pressure (10%) [22]. Rates of AEs in patients with TRD aged ≥ 65 years, including those with comorbid conditions such as cardiovascular or thyroid disease, and/or receiving concomitant medications, were similar to those in younger patients [39].

Most reported AEs were mild-to-moderate in intensity, occurred shortly after administration of esketamine nasal spray and resolved within 1.5 h [22, 24, 35, 36, 38, 39]. The transient nature of reported AEs is consistent with the rapid plasma clearance of esketamine, short half-life and low frequency of dosing [36]. The nature and rates of reported AEs in a real-world French cohort study of esketamine nasal spray plus an SSRI/SNRI in TRD were similar to those from Phase 3 clinical trials [37].

Elevations in blood pressure, sedation/somnolence and dissociative symptoms require special consideration before administration of esketamine nasal spray and must be monitored during the post-administration observation period (see questions above on patient clinical criteria and clinical supervision requirements for more information) [11, 22, 42].

Acute hypertension

Among patients with acute hypertension, blood pressure elevations peaked at 40 min post-administration and, in most cases, returned to, or approached, pre-dose

levels within 1.5–2 h after administration of esketamine nasal spray [24, 35, 38, 39]. Increases in SBP and DBP at 40 min post-dose were ~ 7–9 mmHg and ~ 4–6 mmHg, respectively [22]. Elevations in blood pressure that were considered markedly abnormal (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg) occurred in a higher proportion of patients with TRD aged ≥ 65 years (11.1%) versus those aged 18–64 years (2.0–4.9%) [45]. There was no evidence of elevation of mean pre-dose blood pressure with repeated administrations over time in the long-term, Phase 3 SUSTAIN-2 trial [36].

Sedation

For patients who experienced sedation, symptoms started ~ 15 min post-dose and peaked at ~ 30–45 min post-dose before spontaneously resolving by 1–1.5 h after administration [24, 36, 38]. Notwithstanding that 7–12% of patients experienced clinically relevant sedation (MOAA/S score ≤ 3) [36, 38, 39]; no cases of sedation were associated with respiratory depression or required ventilation or resuscitation [22, 24, 36, 38, 39].

Dissociation

Reported dissociative symptoms included perceptual changes (e.g., sounds appearing louder or colours appearing brighter) and feelings of being disconnected from oneself or one's thoughts or feelings (depersonalisation) as well as from space (derealisation) or time (amnesia) [36]. Dissociative symptoms began shortly after esketamine nasal spray administration, peaked at 40 min post-dose and generally resolved by 1.5 h after administration [24, 35, 36, 38, 39]. Dissociative symptoms tended to decrease with repeated esketamine nasal spray administration over time [24, 35, 36], and no symptoms or AEs of psychosis were reported [24, 35, 36, 38]. A dissociative state can be anxiety-provoking, distressing and even prevent further treatment for some patients [49]. To mitigate this, the environment should be considered as there is evidence that listening to music during treatment sessions can help manage dissociative symptoms [49–51]. This could be culturally adapted to the use of esketamine in the GCC region.

What are the common reasons for patient disengagement from treatment with esketamine nasal spray?

Rates of esketamine nasal spray treatment discontinuation due to AEs were low in both short-term (~ 4–7%) [24, 38, 39] and long-term (9.5%) [36], Phase 3 clinical trials, suggesting that most patients tolerate treatment with esketamine nasal spray plus an SSRI/SNRI. In the long-term, Phase 3 SUSTAIN-2 trial, anxiety was the most common AE that led to treatment discontinuation (1.1% [9/802]) [36]. In the authors' experiences, anxiety around dissociative AEs and logistical issues around twice-weekly clinic visits during the induction phase of esketamine nasal spray can lead to patient disengagement from treatment and should be proactively discussed with patients (see below for more information).

What measures can be employed to support patient adherence?

Education on possible AEs that may occur with esketamine nasal spray treatment is crucial to help manage patient expectations, mitigate the impact of any AEs and support patient adherence [11]. Advise patients that the most common AEs associated with esketamine nasal spray are mostly mild-to-moderate in intensity, transient, self-limiting and resolve within 1.5 h [22, 24, 35–39, 42].

Some patients may raise concerns around treatment with a medication that is a derivative of ketamine, a drug with known potential for recreational abuse [11]. It may be helpful to reassure patients that there were no reports of drug seeking, dependence or abuse of esketamine nasal spray in Phase 3 clinical trials or in a real-world study of esketamine nasal spray in everyday clinical practice [24, 35–37, 39].

To help enhance patient adherence, clinicians should discuss with patients the time commitment and logistical considerations required for clinic visits, especially during the induction phase of esketamine nasal spray dosing, which requires twice-weekly clinic visits.

A patient guide to esketamine nasal spray treatment for TRD approved by the Saudi Food and Drug Authority is available [52] and may help with patient adherence to pre-treatment recommendations and improve patients' understanding of esketamine nasal spray treatment.

Treatment duration and switch

How long should patients be treated with esketamine nasal spray?

Once an improvement in MDD symptoms is observed on esketamine nasal spray plus SSRI/SNRI treatment, a minimum of 6 months of additional treatment is recommended [22, 27]. In the long-term, Phase 3 SUSTAIN-2 trial of esketamine nasal spray 28/56/84 mg plus an SSRI/SNRI, improvement in mean MADRS total score from baseline at the end of the induction phase (–16.4) was sustained in patients who were responders (≥ 50% reduction in MADRS total score) and continued maintenance treatment for up to 1 year (mean change in MADRS total score from start of maintenance to end of study: 0.3) [36]. Additionally, the percentage of patients who were responders and remitters (MADRS total score ≤ 12) remained stable between the end of the induction phase (78.4% [593/756] and 47.2% [357/756], respectively) and the end of the maintenance phase (76.5% [461/603]and

58.2% [351/603], respectively) [36]. Moreover, in the long-term, Phase 3 SUSTAIN-1 withdrawal study, treatment with esketamine nasal spray plus an SSRI/SNRI significantly reduced the risk of relapse (MADRS total score ≥ 22 for two consecutive assessments separated by 5–15 days; hospitalization for worsening depression; suicide, suicide attempt or prevention; or other clinical event suggestive of relapse) by 51% (hazard ratio [HR] 0.49; 95% CI 0.29–0.84; $p = 0.003$) in remitters and 70% (HR 0.30; 95% CI 0.16–0.55; $p < 0.001$) in responders, compared with placebo plus an SSRI/SNRI [35].

The long-term safety of esketamine nasal spray plus SSRI/SNRI treatment was assessed in SUSTAIN-2 and was shown to be consistent with the known safety profile of esketamine nasal spray plus an SSRI/SNRI reported in short-term, Phase 3 studies [36]. Long-term, frequent, recreational use of ketamine is associated with potential safety concerns, including dependence, neurocognitive deficits and interstitial/ulcerative cystitis [53]. There was no evidence of any of these safety issues in patients receiving long-term esketamine nasal spray treatment [36].

What factors should be considered in the decision to change treatment?

Several factors should be consideredbefore recommending a switch in MDD treatment, including treatment response, tolerability and patient preference [11]. If a patient is no longer responding to esketamine nasal spray plus SSRI/SNRI treatment, adherence, dose and dosing frequency should be reviewed for both esketamine nasal spray and the prescribed SSRI/SNRI. In the authors' clinical experience, emerging non-response to an SSRI/SNRI can be effectively addressed by switching to an antidepressant of a different class. New comorbidities and concomitant medications should be considered in the event of emerging tolerability issues.

What are the practical considerations around stopping treatment with esketamine nasal spray?

Patients should be closely monitored for relapse in the first month after stopping treatment with esketamine nasal spray. In the long-term, Phase 3 SUSTAIN-1 withdrawal study, for patients experiencing stable remission who were transitioned to a placebo, almost half of relapses (19/39) occurred in the month following the cessation of esketamine nasal spray [35]. Furthermore, ~ 58% (11/19) of patients who relapsed early required weekly esketamine nasal spray dosing to sustain remission, suggesting this subgroup of patients is particularly vulnerable to relapse after stopping esketamine nasal spray [35]. No evidence of a distinct esketamine withdrawal syndrome was observed in patients who discontinued treatment in long-term, Phase 3 studies, with withdrawal symptoms being infrequent, mild and generally indistinguishable from recurrent MDD symptoms [35, 36].

Summary

Esketamine nasal spray represents a new treatment paradigm for TRD. This article serves as a practical tool to help mental health practitioners implement esketamine nasal spray in everyday clinical practice by answering pertinent clinical questions on the management of TRD with esketamine nasal spray in GCC countries. We provide clinical guidance based on the latest published evidence and clinical experience.

Esketamine nasal spray plus an SSRI/SNRI in TRD is supported by a clinical development programme consisting of both short-term [24, 38, 39] and long-term [35, 36], Phase 3 trials in patients with TRD aged > 18 years, including elderly patients aged ≥ 65 years who are known to be more treatment resistant [48]. Short-term trials demonstrated rapid, clinically meaningful improvements in MDD symptoms within 24 h of the first dose of esketamine nasal spray [24, 38] and showed that most common treatment-related AEs were self-resolving, short-lived and mild-to-moderate in intensity [24, 35, 36, 38, 39]. Long-term trials demonstrated sustained response and remission rates with long-term esketamine plus SSRI/SNRI treatment and a tolerability profile consistent with short-term trials [35, 36].

Emerging real-world evidence supports findings from the esketamine nasal spray clinical development programme [37]. As more real-world evidence becomes available, we may be able to answer additional clinical questions of interest for which we do not yet have enough data, including whether treatment outcomes can be optimized by administering a particular SSRI/SNRI in combination with esketamine nasal spray and whether antidepressants from other treatment classes can be administered in combination with esketamine nasal spray.

Conclusion

In conclusion, esketamine nasal spray, an (NMDA) receptor antagonist, combined with an SSRI/SNRI, presents a promising treatment option for patients with TRD. The clinical development program, including short- and long-term Phase 3 trials, demonstrated clinically meaningful improvements in MDD symptoms within 24 h of the first dose. The treatment was well-tolerated, with the majority of adverse events being transient and mild-to-moderate in intensity. Long-term trials also showed sustained response and remission rates, confirming its potential as a durable treatment. Real-world evidence further supports the clinical trial findings, reinforcing the practicality of esketamine nasal spray in everyday clinical practice.

This clinical article serves as a practical tool for mental health practitioners, offering guidance on implementing esketamine nasal spray in everyday clinical practice. The article also highlights important clinical questions addressed, indicating the potential for further optimization of treatment outcomes through ongoing research and real-world evidence. Overall, this article contributes to addressing the high unmet need for effective TRD treatments and offers hope for improved patient outcomes.

Abbreviations

AE	Adverse event
AMPA-R	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ATHF	Antidepressant Treatment History Form
ATRQ	Antidepressant Treatment Response Questionnaire
COVID-19	Coronavirus 2019
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA	US Food and Drug Administration
GABA	γ-Aminobutyric acid
GCC	Gulf Cooperation Council
HDRS17	17-Item Hamilton Depression Rating Scale
IDS-C_{30}	30-Item Inventory of Depressive Symptomatology-Clinician Rating
LSM	Least square mean
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major depressive disorder
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MTI	Maudsley Treatment Inventory
NMDA	*N*-methyl-D-aspartate
QIDS-C	Quick Inventory of Depressive Symptomatology-Clinician Rating
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TRD	Treatment-resistant depression

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