Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

COMMENTARY

Early Clinical Experiences of Esketamine Nasal Spray in the UK in Adults with Treatment-Resistant Major Depressive Disorder: Advisory Panel Recommendations

Allan H Young[1], Mohamed Abdelghani[2], Mario F Juruena[1,3], Viktoriya L Nikolova[1], Ramin Nilforooshan[4,5]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]Camden and Islington NHS Foundation Trust, London, UK; [3]Maudsley Advanced Treatment Service (MATS), South London and Maudsley NHS Foundation Trust, London, UK; [4]Surrey and Borders Partnership NHS Foundation Trust, Leatherhead, UK; [5]Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

Correspondence: Allan H Young, Institute of Psychiatry, Psychology and Neuroscience, King's College London, PO72, 16 De Crespigny Park, Denmark Hill, London, SE5 8AF, UK, Tel +44 207 848 0088, Email allan.young@kcl.ac.uk

Purpose: Treatment-resistant depression (TRD) is associated with profound morbidity for patients, placing a significant burden on those affected, the health service and wider society. Despite this, TRD remains chronically underserved in terms of viable treatment options. To address this gap, an advisory panel of psychiatrists and clinical researchers with experience in managing TRD convened to develop best practice statements on the use of esketamine nasal spray, one of the first TRD treatments to be licensed in 30 years.

Methods: During a virtual meeting held on 12th November 2020, the advisory panel shared their experiences of using esketamine nasal spray in their clinical practice. The meeting focused on developing and refining recommendations for setting up and running an efficient esketamine nasal spray clinic for patients living with TRD. At the conclusion of the meeting, agreement was reached on all recommendation statements.

Results: In setting up an esketamine nasal spray clinic, it is important to consider the logistical requirements involved and put measures in place to ensure it runs as efficiently as possible. Educating patients about the treatment and maintaining their well-being is paramount for preventing discontinuation. Putting in place checklists can be a useful strategy for ensuring treatment appointments run smoothly and safely.

Conclusion: Providing additional treatment options for the management of TRD, such as esketamine nasal spray, is likely to be key to improving the long-term outcomes of this underserved patient population.

Keywords: depression, TRD, MDD, antidepressant, glutamate

Introduction

Depression is a leading cause of disability worldwide and contributes significantly to the global burden of disease. According to the World Health Organization, approximately 280 million people are believed to suffer from depression, equating to 3.8% of the world's total population and 5.0% of all adults.[1] Depression is also a major contributor to suicide, which is thought to be responsible for more than 700,000 deaths every year and is the fourth leading cause of death in 15–29-year-olds worldwide.[1]

It is believed that treatment-resistant depression (TRD) affects around 2.7 million people in the UK, accounting for around 30% of patients living with depression.[2] According to the European Medicines Agency (EMA), TRD is defined as a poor or unsatisfactory response to two different antidepressant (AD) treatments of adequate dose and duration in a current moderate-to-severe depressive episode.[3] Treatment-resistant depression is estimated to cost the UK £3.9 billion per year.[4]

Received: 1 September 2022
Accepted: 26 January 2023
Published: 24 February 2023

Despite the scale of the problem, there have been very few treatment advances for managing TRD. Esketamine offers a long-awaited breakthrough in TRD treatment that, in contrast to traditional oral ADs, works via the glutaminergic system rather than the monoaminergic system to achieve its therapeutic effect.[5–11] Research suggests that nasal esketamine produces a transient increase in glutamate release through *N*-methyl-D-aspartate (NMDA) blockade, leading to an increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor stimulation.[12] Further downstream effects may contribute to restoring synaptic function in brain regions involved in mood regulation and emotional behaviour.[6]

Esketamine nasal spray is indicated in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) for adult patients with treatment-resistant major depressive disorder who have not responded to at least two different AD treatments in the current moderate-to-severe depressive episode.[5] This is supported by an extensive, robust clinical development program, demonstrating both short- and long-term efficacy and safety in adult patients with TRD.[13–17] Esketamine nasal spray is self-administered by patients under the supervision of a healthcare professional. Each device delivers a dose of 28 mg in two sprays (one per nostril), and up to three devices may be used at each appointment depending on the dose required.[5] Intranasal dosing of esketamine has been shown to produce plasma levels equivalent to the pharmacokinetic range achieved by intravenous esketamine administration.[14]

Esketamine nasal spray was approved for use by the US Food and Drug Administration in March 2019, with the EMA granting it marketing authorization in December 2019, and Health Canada announcing its approval in May 2020.[5,18,19] It was accepted for use within NHS Scotland, in line with its indication, by the Scottish Medicines Consortium in September 2020.[20] However, the UK/NHS are still considering its approval and are awaiting NICE recommendation. To date, there are no clinical practical guidelines recommending the use of esketamine in depression.[21]

Materials and Methods

The advisory panel for this project consisted of five psychiatrists and clinical researchers who were already using esketamine nasal spray as part of their clinical practice, either through clinical trials (7+ years), pre-approval access programs, or early treatment adoption soon after its launch (over 6 months). The panel was chaired by Allan H Young and included Mario F Juruena, Viktoriya L Nikolova, Mohamed Abdelghani and Ramin Nilforooshan. Ethical approval and informed consent were not applicable.

The virtual advisory panel meeting was held on November 12th, 2020. The discussions were centered around five key topics to serve as a foundation for generating the best practice recommendations for using esketamine nasal spray. These topics were identified by Allan H Young in collaboration with Janssen and included 1) Setting up an esketamine clinic; 2) Preparing for appointments; 3) Managing the appointment process; 4) Post-administration observations; and 5) Developing a business case.

The recommendations were discussed and revised at the end of the meeting, until a general agreement was reached on all statements. It should be noted that some logistic recommendations are related to UK regulation and UK health care settings and therefore may not apply to other countries or regions. Following the meeting, all five panel members participated in the development and review of this report, which offers the final best practice recommendations in context with the evidence that helped inform their reasoning behind each statement.

Results

Setting Up an Esketamine Clinic

Recommendation #1: When setting up an esketamine clinic, a hospital should consider the logistical implications involved. The size of the care team required will depend on the number of patients who are expected to attend the clinic. A doctor should be present for a patient's first self-administration to ensure they are comfortable with the process and are happy to proceed with the treatment. At subsequent appointments, another healthcare professional can directly supervise the patient's self-administration, provided a doctor is available for any emergencies. In addition, the presence of a nurse or healthcare assistant is necessary to help monitor patients' vital signs and provide reassurance and support as needed. Once patients have completed their initial appointments and are more comfortable with the treatment, simultaneous dosing of up to four patients is feasible (facilities permitting) without the need for additional staff. For psychiatrists working in the private sector, the panel recommends they should contact the Care Quality Commission to ensure they meet any regulatory requirements before setting up an esketamine clinic.

Box 1 Controlled Drug Register requirements

- Date supplied
- Name and address of person supplied
- Quantity, form, and strength supplied
- Details of authority to possess prescriber or license holder details
- The name of the healthcare professional who collected the drug

Note: Data from Pharmaceutical Services Negotiating Committee.[22]

As a Schedule 2 Controlled Drug, there are specific requirements for storage, record-keeping, handling, and disposal of the esketamine nasal spray.[22] It is subject to the complete Controlled Drug requirements relating to prescriptions, safe custody, and the need to keep a Controlled Drug register.[22] When dispensed from the pharmacy, the Controlled Drug register must include all information relating to the supply of the esketamine nasal spray (Box 1). As well as risk–benefit assessment systems and prescription drug monitoring programs, there may also be the need to go beyond the quality standards of setting up esketamine clinics with the implementation of registry-based surveillance systems for monitoring the patterns of use, clinical efficacy, safety and tolerability of esketamine and related compounds in TRD.[23]

Before setting up an esketamine nasal spray clinic, the pharmacy should be consulted to ensure suitable storage, dispensing and disposal arrangements are put in place. The pharmacy will receive the esketamine nasal spray and be responsible for overseeing the Controlled Drug register. Establishing a provisional dispensing and disposal schedule with the pharmacy team for use on clinic days may be useful to avoid any treatment delays. In the private setting, centers are generally required to nominate a "chosen pharmacy" who will supply the drug. This pharmacy should be made aware of any standard operating procedures for esketamine nasal spray followed by the clinic, including the duties and responsibilities of the staff.

The panel agreed that it was important always to consider the room in which the esketamine nasal spray self-administration takes place. A quiet, comfortable environment should be chosen, in which patients can feel safe and relaxed. Preferably the temperature and brightness of the room should be adjustable and include as little visual stimulation as possible. A comfortable chair or medical couch is necessary, ideally one that reclines at a 45° angle to aid the patient with the self-administration.

If several patients are going to be treated simultaneously, they should each be appropriately counselled and asked to sign a section in their consent form agreeing to be treated in a clinical setting with other patients. While curtains or screens are recommended to maintain privacy where necessary, patients should still be made aware that they might experience side effects during the post-observation period that other patients could witness. However, it is also important to recognize that some patients may like the opportunity to meet others undergoing the same esketamine nasal spray treatment program as themselves. Although it may be possible for some patients to undergo other treatments immediately following the observation period (such as talk therapies, etc), they will often feel drowsy or uncommunicative, so it may be better to schedule these on another day.

Preparing for Appointments

Recommendation #2: A checklist can be a valuable tool to confirm that a patient is a suitable candidate for treatment with esketamine nasal spray. Janssen has developed one that covers pre-appointment checks, pre-administration checks, post-administration checks and readiness for discharge. Having such a tool can also help with paperwork and communication between team members.

As the *S*-enantiomer of ketamine, patients may have concerns about potential adverse events and addictive potential of esketamine nasal spray. Therefore, dissociation and other side effects should be discussed with patients before they agree to esketamine nasal spray treatment. Side effects should be described in lay-person's language, indicating their likelihood, as this will generally help patients better cope with them if they do arise. The most common symptoms of dissociation should be described, however, it should be emphasized that they are generally transient, usually lasting for

Box 2 Pre-Appointment Criteria for Patients

Advise your patient:
1. Not to engage in potentially hazardous activities following their treatment with esketamine nasal spray, such as driving or operating machinery, until the day after following a restful night's sleep
2. To plan suitable travel arrangements following each of their appointments, ideally booking a taxi or arranging for a friend/family member to collect them, as driving is not recommended
3. Not to eat for at least 2 hours before administration to avoid potential nausea and vomiting
4. Not to drink liquids for at least 30 minutes before administration to avoid potential nausea and vomiting
5. Not to use any nasally administered corticosteroids or decongestants for at least 1 hour before administration
6. To arrange for a carer or chaperone to accompany them if considered necessary

Note: Data from Spravato® (esketamine hydrochloride).[5]

a maximum of ~90 min.[5] It may be useful to provide patients with written information on esketamine nasal spray and its potential side effects, so they can refer to the information in their own time. In addition, patients should be advised to follow some pre-appointment criteria before attending the hospital for their treatment (Box 2).

Blood pressure monitoring equipment should also be available during each self-administration appointment to allow for regular monitoring – transient hypertension is a common adverse event observed with esketamine nasal spray.[5] It should be checked at the start of each appointment and, if not initially within the normal range, checked again 10–15 minutes later. If blood pressure remains consistently elevated, the patient should be referred to a healthcare professional experienced in blood pressure management. As a general guide: elevated blood pressure is >140/90 mmHg for patients <65 years of age and >150/90 mmHg for patients ≥65 years of age.[5] If a patient's blood pressure changes significantly beyond these parameters, a robust protocol should be in place in all hospitals and clinics so that staff are aware of how to manage the situation and when to refer for specialist advice. As described in its summary of product characteristics (SmPC), patients with clinically significant or unstable cardiovascular or respiratory conditions should only receive esketamine nasal spray if the benefit outweighs the risk. Treatment in these circumstances must be in a setting where appropriate resuscitation equipment is available and by healthcare professionals who have cardiopulmonary resuscitation training.[5]

The panel felt that most healthcare professionals would feel comfortable carrying out the clinical assessments required for esketamine nasal spray, as they would already be familiar with them in their day-to-day clinical practice. However, they advised that all staff should be encouraged to seek the necessary training if they were unsure about any of the requirements.

Managing the Appointment Process

Recommendation #3: During each patient's appointment, the following aspects of using esketamine nasal spray should be considered, to ensure appointments run as efficiently as possible and to maintain patients' engagement with the treatment.

Dosing

Esketamine nasal spray should be dosed according to its SmPC: starting dose of 56 mg (two devices) in patients <65 years and 28 mg (one device) in patients >65 years.[5] A "low and slow" approach may be advisable, starting with the lowest dose for a particular patient's age, then titrating up according to efficacy and tolerability. This may be especially appropriate with patients in whom the potential for adverse reactions is a particular concern.

As recommended in the SmPC, response should be assessed following 4 and 8 weeks of treatment.[5] It should then be continued for at least 6 months if effective. Although not in the SmPC, the panel felt that 6 months was a good timepoint to consider treatment discontinuation. They recommended this should be done gradually, increasing the intervals between treatment doses and carefully monitoring response throughout the process. Psychiatrists should use their clinical judgment to decide whether a patient is in remission and ready to discontinue treatment gently.

Dissociation

Some patients experience a degree of dissociation and/or sedation with their first dose, while others may not feel back to their normal self until they have had a restful night's sleep. However, the presence of dissociation is not necessary to show that the treatment is working. The effects of dissociation can vary not just between individual patients, but between appointments for the same patient, with some patients experiencing dissociation and/or sedation following every dose to varying degrees.

Dissociative adverse events are generally transient, resolving typically in 90 minutes. In clinical trials, their intensity (as measured by Clinician-Administered Dissociative States Scale [CADSS] scores) usually decreased with subsequent doses of esketamine nasal spray.[5,6] The panel highlighted the importance of maintaining open communication with patients, highlighting a case where one of their patients did not identify their symptoms as dissociation until their third treatment session. They noted that their patients' most typically reported symptoms were sedation, disorientation, hypersensitivity to sounds and light, time distortion and visual distortions, and altered sense of self and reality.

Determining whether dissociation is mild/moderate or severe plays an important role in determining the suitability of esketamine nasal spray for a patient. In the clinical experience of the panel, patients generally reported mild dissociation as feeling a bit "spaced out", whereas severe dissociation was usually associated with some degree of hallucination. Severe dissociation is also often reported in combination with greater and longer-lasting sedation, with more pronounced increases in blood pressure. Whereas with milder cases of dissociation, patients reported being more able to keep their eyes open and engage with the outside world (eg, use their phones or chat to clinical staff). The panel also found that their patients did not necessarily report dissociation as particularly unpleasant, with the majority finding it short-lived and not a reason to discontinue treatment.

In two pivotal Phase III esketamine nasal spray trials, TRANSFORM-2 (patients aged 18–64) and TRANSFORM-3 (patients aged ≥65), 26.1% (n=30/114) and 12.5% (n=9/72) of patients respectively reported dissociative effects.[13,16] In the SUSTAIN-2 trial (patients aged ≥18, N=806), which examined the long-term safety of esketamine nasal spray, less than 4% of dissociative/perceptual changes were reported as severe in intensity.[15] Across the registrational trials as a whole, the onset of dissociative symptoms and perceptual changes (as measured by the CADSS total score) typically peaked at around 40 minutes following esketamine nasal spray dosing and were completely resolved by 90 minutes.[13–15,17]

Changes in Blood Pressure

Transient increases in blood pressure may occur in some patients after administration.[5] Increases in blood pressure typically peak 40 minutes after the first spray is administered and generally return to or near baseline levels within 1–2 hours.[5] In the long-term SUSTAIN-2 trial, less than 1% of patients discontinued nasal esketamine due to blood pressure increases.[5] Across the clinical trials for esketamine nasal spray, blood pressure increases resulting in clinically acute hypertension (defined as systolic ≥180 mm/Hg or diastolic ≥110 mm/Hg) were reported in 3–4% of patients.[5] In the clinical experience of the panel, increases in blood pressure occurred after almost every administration, but decreased to acceptable levels without further treatment within 1.5–2 hours. One of the panel commented that higher elevations in blood pressure were often related to what their patient described as "heavier" treatment sessions; ie, those that resulted in more sedation and dissociation. These sessions were difficult to predict but were easily resolved by keeping the patient calm. Instances of acute hypertension were typically very rare.

Blood pressure should be measured at 40 minutes post-dose, during the appointment as clinically warranted, and before the patient leaves the clinic. It is important to keep the patient comfortable and relaxed. If blood pressure remains elevated, the patient should be monitored until it returns to normal. If there is clinical concern that the blood pressure increase is not resolving, further advice should be sought from a healthcare professional experienced in blood pressure management.

Sedation

Across the clinical trials, sedation and somnolence were primarily mild or moderate in severity following esketamine nasal spray, generally only occurring on the day of the self-administration. No symptoms of respiratory distress were observed, and hemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges.[5] The panel felt that sedation was generally only reported as an issue when patients first began treatment with esketamine nasal spray and waned with subsequent doses.

Box 3 Pre-Discharge Criteria for Patients

Before discharging the patient, ensure:
• The next treatment session appointment has been scheduled and the patient supplied with a written record as a reminder
• Blood pressure has returned to acceptable levels[a]
• Symptoms from any treatment-related adverse reactions have resolved to a point where the patient is considered clinically stable and ready to leave the healthcare setting
• The patient has been reminded not to engage in potentially hazardous activities, such as driving or operating machinery, until the next day after a restful night's sleep

Notes: [a]As a general guide: ≤140/90 mmHg for patients <65 years of age and ≤150/90 mmHg for patients ≥65 years of age.[5]

Post-Administration Observations

Recommendation #4: Patients should be observed by a healthcare professional during and after each esketamine nasal spray administration. To help provide support throughout the observation period, patients should be advised to bring items from home to make the experience more comfortable for them. This could include headphones with music they find relaxing, an eye mask and a warm blanket. Using a checklist can be helpful to ensure all patient measures are completed during the observation period (Box 3). Clinical judgement should be used to determine when the patient is ready to leave the healthcare setting, but symptoms from any treatment-related adverse events should have resolved to the point where the patient is considered clinically stable. In the phase III TRANSFORM-2 trial, 44.3% of patients were ready to leave at 60 minutes post-treatment, rising to 93.2% of patients at 90 minutes.[13] Although the panel generally allocated 2 hours of post-administration observation time, it is considered clinically acceptable to shorten this to 60–90 minutes if the patient is ready to leave sooner. In total, each treatment session for esketamine nasal spray usually lasts between 1.5 and 2 hours.

Before discharging a patient, it is important to ensure that suitable transport home has been arranged and they will not be driving themselves. Booking a taxi or arranging for a friend or a family member to drive them home is preferable. In addition, many patients reported a dislike of being in crowded, public places immediately after their appointment or anywhere else that could trigger nausea, so these should be avoided.

A concern the panel had was how and when to stop using the drug. Further research is needed to provide the optimal duration for esketamine. Overall, the panel had no other concerns about esketamine's long-term use.

Assessing the Financial Impact and Sustainability of Esketamine Nasal Spray

Recommendation #5: The panel agreed on four key steps to assessing the financial impact and sustainability of esketamine nasal spray use:

Identify and Outline the Problem (or Business Opportunity in the Private Care Sector)

Can you identify the costs associated with TRD to your hospital or clinical commissioning group? Can you determine the number of patients who have TRD within your catchment area? A SWOT (strength, weakness, opportunity, and threat) analysis may be a useful tool here.

Present Evidence to Support Your Solution

To present esketamine nasal spray as a strategy for alleviating the burden of TRD, a thorough literature search and presentation of key efficacy and safety data is recommended. In addition, outcomes demonstrating the proportion of patients achieving remission and individual case studies can be helpful.

Set Out a Strategy for Achieving the Desired Outcome

Identify a suitable location of your clinic and investigate the financial implications: How many patients could you treat simultaneously? How many clinic sessions per week would be required? What would staffing the clinic entail? Identify key staff members and build a team to help develop the protocols required for each clinic.

Identify Key Success Criteria

How will you measure the success of your clinic, and within what timeframe? For example, would you run a pilot of 6–12 months and assess at the end of that period?

Conclusion

The recommendations presented here are intended to provide agreed best practice for setting up and running an efficient esketamine nasal spray clinic for patients living with TRD. In addition, providing additional treatment options for the management of TRD should help improve the long-term outcomes of these patients and lessen the wider impact of the disease on the health service and society as a whole.

At the Time of Going to Press

In the UK, the Spravato® Register and Alert System has come into place. Once the prescribing decision has been made and recorded according to standard clinical practice, the patient must be enrolled onto the Spravato® Register and Alert System. To minimize the risk of abuse, the Register and Alert system is an active part of the controlled access program in the UK approved by the MHRA: https://spravatoregister.clinpal.com

Abbreviations

AD, antidepressant; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CADSS, Clinician-Administered Dissociative States Scale; EMA, European Medicines Agency; NMDA, N-methyl-D-aspartate; SmPC, summary of product characteristics; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression.

Acknowledgments

Janssen provided financial support to the advisory panel and was also in attendance. Janssen also provided financial support to Brandcast Health to help facilitate the meeting and for editorial assistance in the preparation of this report. Janssen contributed minimally in terms of prompting clarifications from the advisory panel for development of the report but did not directly contribute to the advisory process or the preparation of the manuscript. Professor Young's independent research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr Juruena's independent research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Author Contributions

All authors made substantial contributions to conception, design, and interpretation; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

The preparation of this manuscript was financed by Janssen. They were not involved in developing the best practice recommendations or in the development of this manuscript.

Disclosure

Mohamed Abdelghani: Vice president/President Elect of the Clinical TMS Society. Founder and Medical Director of Dyad Medical, London TMS Centre and London Esketamine Clinic. Honoraria and consultancy fees from Janssen and Takeda. Mario F Juruena: Honorary Consultant, South London and Maudsley NHS Foundation Trust (SLaM-NHS UK) supported by National Institute for Health Research (NIHR); Biomedical Research Centre (BRC) and Clinical Senior

Lecturer at King's College London. Honoraria and consultancy fees from Janssen, Lundbeck, Libbs, EMS, and Daiichi Sankyo. Viktoriya L Nikolova: Honorarium and consultancy fee from Janssen. Ramin Nilforooshan: Professor in Psychiatry at University of Surrey and consultant psychiatrist at Surrey and Borders Partnership NHS Foundation Trust. Honorarium and consultancy fee from Janssen. Personal fees from Roche and Biogen. Allan H Young: Employed by King's College London; Honorary Consultant for SLaM (NHS UK); Deputy Editor of BJPsych Open; Consultant to Johnson & Johnson and Livanova. Paid lectures and advisory boards for AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS Pathways, Sage, Novartis. Principal Investigator on: RESTORE-LIFE VNS registry study (funded by LivaNova, NCT03320304; An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression (funded by Janssen, NCT02497287); The Effects of Psilocybin on Cognitive Function in Healthy Participants (funded by COMPASS Pathways, EudraC No: 2018-000978-30); The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD) (funded by COMPASS Pathways, NCT03775200). UK Chief Investigator for Novartis MDD study MIJ821A12201. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK). No shareholdings in pharmaceutical companies. The authors report no other potential conflicts of interest in this work.

References

1. World Health Organization. Depression fact sheet. Available from: https://www.who.int/news-room/fact-sheets/detail/depression. Accessed December 16, 2021.
2. McLachlan G. Treatment resistant depression: what are the options? *BMJ*. 2018;363:k5354. doi:10.1136/bmj.k5354
3. European Medicines Agency. Clinical investigation of medicinal products in the treatment of depression. Available from: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-depression. Accessed December 16, 2021.
4. McCrone P, Rost F, Keeser L, et al. The economic cost of treatment-resistant depression in patients referred to a specialist service. *J Ment Health*. 2018;27(6):567–573. doi:10.1080/09638237.2017.1417562
5. Spravato® (esketamine hydrochloride). Summary of product characteristics. High Wycombe, UK: Janssen-Cilag Ltd; 2021.
6. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016;22(3):238–249. doi:10.1038/nm.4050
7. Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry*. 2017;4(5):409–418. doi:10.1016/S2215-0366(17)30015-9
8. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol*. 2015;23(1):1–21. doi:10.1037/a0038550
9. Whiting D, Cowen PJ. Drug information update: agomelatine. *Psychiatrist*. 2013;37(11):356–358. doi:10.1192/pb.bp.113.043505
10. Valdoxan® (agomelatine). Summary of product characteristics. Suresnes, France: Servier Laboratories Ltd; 2021.
11. Mirtazapine 15mg tablets. Summary of product characteristics. Ruislip, UK: Milpharm Ltd; 2021.
12. Duman RS. Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin Neurosci*. 2014;16(1):11–27. doi:10.31887/DCNS.2014.16.1/rduman
13. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibility dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active controlled study. *Am J Psychiatry*. 2019;176(6):428–438. doi:10.1176/appi.ajp.2019.19020172
14. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(9):893–903. doi:10.1001/jamapsychiatry.2019.1189
15. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a Phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry*. 2020;81(3):19m12891. doi:10.4088/JCP.19m12891
16. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression. *Am J Geriatr Psychiatry*. 2020;28(2):121–141. doi:10.1016/j.jagp.2019.10.008
17. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol*. 2019;22(10):616–630. doi:10.1093/ijnp/pyz039
18. FDA. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. Available from: www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified. Accessed December 16, 2021.
19. Health Canada. Product information: Spravato. Available from: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=98903. Accessed December 16, 2021.
20. Esketamine (Spravato). Scottish Medicines Consortium. Available from: https://www.scottishmedicines.org.uk/medicines-advice/esketamine-spravato-full-smc2258. Accessed December 16, 2021.

21. López-Díaz Á, Murillo-Izquierdo M, Moreno-Mellado E. Off-label use of ketamine for treatment-resistant depression in clinical practice: European perspective. *Br J Psychiatry*. 2019;215(2):447–448. doi:10.1192/bjp.2019.102
22. Pharmaceutical Services Negotiating Committee. Controlled Drug regulations. Available from: https://psnc.org.uk/contract-it/pharmacy-regulation/controlled-drug-regulations. Accessed December 16, 2021.
23. López-Díaz Á, Rendón de Lope L, De la Vega Sánchez D. Patterns of use, clinical efficacy, safety and tolerability of Ketamine and Esketamine in treatment-resistant depression: towards registry-based surveillance systems. *J Affect Disord*. 2022;297:145–147. doi:10.1016/j.jad.2021.10.036