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Association of intranasal esketamine, a novel 'standard of care' treatment and outcomes in the management of patients with treatment-resistant depression: protocol of a prospective cohort observational study of naturalistic clinical practice

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ABSTRACT

Introduction Esketamine is the S-enantiomer of racemic ketamine and has been approved by the Food and Drug Administration for the management of treatment resistant depression, demonstrating effective and long-lasting benefits. The objective of this observational study is to elucidate the association of intranasal (IN) esketamine with beneficial and negative outcomes in the management of treatment resistant major depressive disorder.

Methods and analysis This is a multicentre prospective cohort observational study of naturalistic clinical practice. We expect to recruit 10 patients per research centre (6 centres, total 60 subjects). After approval to receive IN esketamine as part of their standard of care management of moderate to severe treatment resistant depression, patients will be invited to participate in this study. Association of esketamine treatment with outcomes in the management of depression will be assessed by measuring the severity of depression symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS), and tolerability by systematically tracking common side effects of ketamine treatment, dissociation using the simplified 6-Item Clinician Administered Dissociative Symptom Scale and potential for abuse using the Likeability and Craving Questionnaire (LCQ). Change in depressive symptoms (MADRS total scores) over time will be evaluated by within-subject repeated measures analysis of variance. We will calculate the relative risk associated with the beneficial (reduction in total scores for depression) outcomes, and the side effect and dropout rates (tolerability) of adding IN esketamine to patients' current pharmacological treatments. Covariate analysis will assess the impact of site and demographic variables on treatment outcomes.

Ethics and dissemination Approval to perform this study was obtained through the Health Sciences Research Ethics Board at Queen's University. Findings will be shared among collaborators, through departmental meetings, presented on different academic venues and publishing our manuscript.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Six research centres across Canada are involved in this study, increasing the power and generalisability of our observations.
⇒ Use of validated scales to assess symptoms of depression and protocols for the safe administration of esketamine.
⇒ Because of the limitations of the ongoing COVID-19 pandemic, we are doing our assessment scales virtually or over the phone, making our ability to interpret body language and other visual cues more difficult.

INTRODUCTION

Major depressive disorder (MDD) is one of the top mental health disorders, being the main culprit for disability related to mental health and second for overall causes of disability,[1–3] causing significant losses in quality of life and productivity.[2 3] Low-dose ketamine treatments have demonstrated significant effectiveness in the management of treatment-resistant depression (TRD) in MDD and bipolar depression.[4–6] Ketamine acts by blocking the NMDA receptor and thus triggering a series of downstream effects that promote neuroplasticity and neurogenesis.[4 7 8]

Esketamine is the S-enantiomer of ketamine and possesses an affinity for the NMDA receptor that is around fourfold stronger than the affinity of the other enantiomer

in the racemic mixture—R-enantiomer (arketamine). Hence, it can be provided at lower dose than R-ketamine or racemic ketamine,[9] which may be an advantage, since higher doses of ketamine are linked with more side effects, including dissociative symptoms.[9] Studies with intranasal (IN) esketamine have shown effectiveness in the treatment of TRD for acute and long-term maintenance use, with a response rate of 63% and a remission rate of 48%.[10] Moreover, while esketamine is available as an IN spray, racemic ketamine is available via several other routes such as oral, IN and intravenous. However, most of the evidence about racemic ketamine focuses on intravenous administration which could deter some patients.[6] Nevertheless, it is important to note that despite the higher affinity of esketamine for the NMDA receptor, some studies have raised concerns about the use of esketamine over racemic ketamine, namely the presence of dissociative symptoms with similar intensities between the two treatments and the cost of the esketamine treatment.[11–13]

The extant clinical research has resulted in the approval of this treatment by the US Food and Drug Administration (FDA) and Health Canada, among other regulatory agencies, for the management of TRD.[5] However, it is important to highlight the lack of studies that have evaluated this novel treatment in naturalistic clinical practice.[14–17] Thus, this research study aims to fill this gap, through this Canada-wide multicentre evaluation of naturalistic clinical practice study.[4 7 8 10 14 18–21]

Thus, in this study we aim to elucidate the association of IN esketamine treatment with a reduction in the severity of depressive symptoms (primary outcome) by assessing response to treatment, remission from depression and improvement in suicidality severity scores using the Montgomery-Åsberg Depression Rating Scale (MADRS[22]). Our secondary outcome involves the evaluation of the tolerability of IN esketamine by systematically assessing the emergence of the most common reported adverse effects. Finally, looking at the recruitment process of patients with TRD MDD, and the primary and secondary outcome of this treatment across our collaborating centres, we will comment on the implementation of IN esketamine as a standard of care treatment as our exploratory outcome objective. Our goal is for this analysis to help guide clinical practice in the use of IN esketamine in the management of TRD.

METHODS

Study design overview

This is a multicentre (Interventional Psychiatry, Providence Care Hospital in Kingston, Canadian Rapid Treatment Center of Excellence (three locations in Toronto, Mississauga, Ottawa), Misericordia Community Hospital/Envision Mindcare in Edmonton, Sunnybrook Hospital in Toronto, Center for Addiction and Mental Health in Toronto and Mood Disorders Centre in Vancouver) prospective cohort observational study of naturalistic clinical practice of patients with moderate to severe TRD[23] receiving IN esketamine as part of their standard of care treatment. The collaborating research centres will adhere to the pharmaceutical's monograph approved by Health Canada[24 25] and standards of care of national clinical guidelines.[26] Patients eligible to receive IN esketamine will be directed to contact their health insurance to determine whether they have appropriate coverage to receive this treatment. On confirmation by their health insurance (if this is not possible, some patients may be able to cover the cost of the treatment out of pocket or ask their affiliated institution to cover the cost), they will be enrolled in IN esketamine treatment and will be invited to participate in this research study. IN esketamine treatment has two phases. This study will focus on the acute phase of the treatment, which consists of eight sessions, at a frequency of two sessions per week for 4 weeks. Then, depending on their clinical response and tolerability, patients can continue to the maintenance phase as per each centre clinical protocols, but they will not be followed as part of this research project. Changes in the severity of depressive symptoms (using the MADRS[22]) and the tracking of side effects (using a checklist of common side effects of ketamine treatment[27] and the simplified 6-Item Clinician Administered Dissociative Symptom Scale (CADSS-6)[28] for dissociation) will be recorded. Since the FDA and Health Canada both list IN esketamine as having potential for misuse and abuse,[25 29] we will include a measure of abuse potential using a Likeability and Craving Questionnaire (LCQ) developed by Dr Jennifer Swainson and Dr Jay Wang (University of Alberta, Edmonton)[30] to better contextualise real world risks. The Queen's University Health Sciences and the Affiliated Teaching Hospitals Research Ethics Board approved this protocol. Figure 1 presents a summary of the experimental design.

Participants

Patients (n=60), aged 18–65 years old with MDD as determined by the Diagnostic and statistical manual of mental disorders (DSM-5) diagnostic criteria and characterised as moderate to severe TRD (baseline MADRS score ≥20 and experienced at least two failed antidepressant trials of adequate dose and duration[23 31]), will be assessed to receive IN esketamine treatment as part of their standard of care treatment. Exclusion criteria include patients reporting any active substance abuse, symptoms of psychosis, diagnosis of bipolar disorder, personality disorder as the primary diagnosis (as defined by the patient's psychiatrist or primary care provider), uncontrolled hypertension, previous negative reaction to racemic ketamine or esketamine, currently pregnant or breastfeeding. As this is a naturalistic observational study of clinical practice, we will not exclude patients taking other psychiatric medications. Thus, we are only exploring the effects of esketamine as an add-on treatment to real-world patients' current medication plans. Patients who are in agreement with the inclusion and exclusion criteria will be recruited for this study. Also, considering previous studies on the antidepressant effects of IN esketamine,[11 32–35] a CI of 95%, and a sample size

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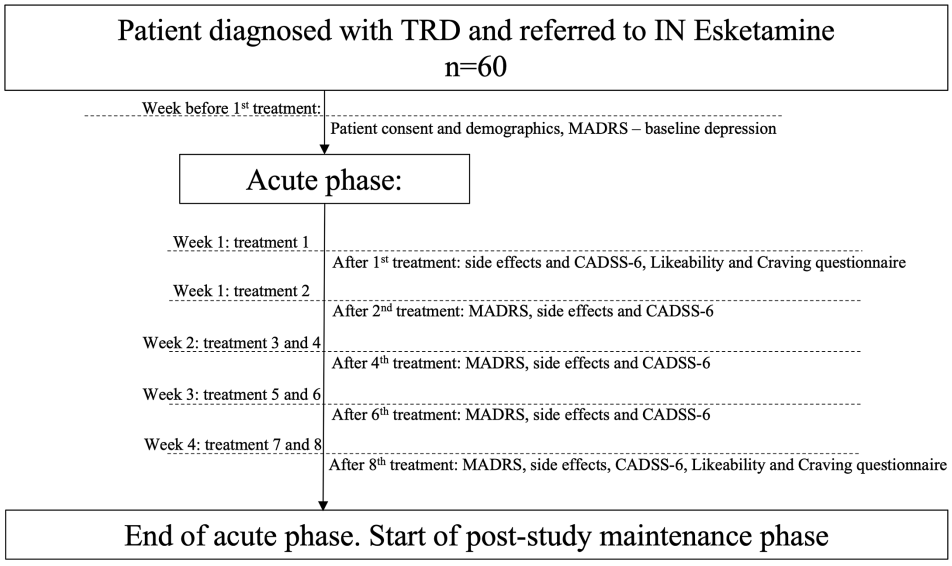

Figure 1 Study design overview. This study involves 4 weeks of acute esketamine treatment. During the acute phase the patients will have up to 2 esketamine sessions per week. Baseline MADRS will be done the week before the first esketamine session. Then, MADRS, side effects and CADSS6 will be done up to 24 hours after the second, fourth, sixth and eighth sessions (side effects and CADSS-6 done up to 24 hours after the first session too). Likeability and Craving Questionnaire will be done up to 24 hours after the first and eighth. CADSS6, 6-Item Clinician Administered Dissociative Symptom Scale; IN, intranasal; MADRS, Montgomery-Åsberg Depression Rating Scale; TRD, treatment resistant depression.

of N=60, we estimated our study power to be at or above 90%.[36]

Demographics

After the consent process, participants will complete a demographics questionnaire to capture the following data: age, gender, marital status, living situation, education, employment, health plan/means of accessing either treatment, drug use, and diagnosed medical and/or psychiatric comorbidities. These are relevant factors that could significantly impact treatment response and the severity of their symptoms.[37 38] For instance, attaining a higher degree in their education could influence treatment response. Thus, these data will be used to stratify our results and determine if they may have a substantial impact on treatment outcomes.

IN esketamine treatment

IN esketamine is administered as a nasal spray. Patients must not have had any solid food or liquids 2 hours prior to treatment. Treatment sessions will occur at each of the six sites as part of their ongoing clinical services. The patient self-administers the spray, which delivers a 14 mg dose per spray per nostril (28 mg total per device) under the supervision of a healthcare provider. Depending on the patients' clinical response and tolerability, the dose can be increased to a maximum of 84 mg of IN esketamine, by using up to three devices, waiting 5 min in between each 28 mg dose, as per the esketamine manufacturer product monograph.[24] Patients are allowed to start activity as tolerated about 1 hour after administration. Nasal cannula oxygen may be administered as needed using side-stream capnometry monitoring. Pulse, blood pressure and pulse oximetry are assessed before the start and every 40 min after the IN spray of esketamine. Physiological monitoring data are recorded on a standard anaesthesia record beginning 5 min before treatment. Then, patients are discharged after a minimum of 2 hours postadministration, provided that the vital signs have returned to baseline and that the patient is calm, alert and oriented.[39]

Outcome evaluation

Assessment scales (MADRS, side effect checklist, CADSS-6 and LCQ) will be used to elucidate the association of IN esketamine treatment with a reduction in depression symptoms (primary outcome) and the tolerability of this treatment by a trained interviewer over the phone, through video conference or in person when possible. Understanding the risks associated with phone or videoconference, we will ask the patients for consent before starting each assessment. Association of esketamine treatment with outcomes in the management of depression (efficacy) will be assessed using the MADRS.[22] We will start by measuring baseline severity of depressive symptoms the week before their first IN esketamine treatment. We will then measure the progression of depressive symptoms through the treatment course once per week, up to 24 hours after the second, fourth, sixth and eighth (study endpoint) sessions. Tolerability will be assessed by tracking the presence of side effects and potential for addiction to IN esketamine. We will use the side effects checklist (online supplemental appendix 1)[27] and the CADSS-6 for symptoms of dissociation (a common side effect of ketamine treatment)[28] up to 24 hours after the first, second, fourth, sixth and eighth sessions. Potential for addiction will be determined using a LCQ (online

supplemental appendix 2)[30] up to 24 hours after the first and eighth sessions. Please refer to figure 1 for an overview of the study design and the application of each of the mentioned scales through the treatment course.

Primary outcome measure

Elucidate the association of IN esketamine treatment with a reduction in the severity of depressive scores from baseline to study endpoint (completion of the treatment course) using the MADRS in patients with an episode of MDD TRD in naturalistic clinical practice. Response to treatment will be defined as ≥50% reduction in their baseline depression score. Remission from depression will be defined as MADRS total score ≤10. Improvement in suicidality will be determined by change in suicidal ideation severity from baseline to study endpoint using the MADRS item 10.[22 40]

Secondary outcome measures

Determine the tolerability of IN esketamine by systematically tracking the presence of adverse events using a checklist of side effects (online supplemental appendix 1)[27] and dissociation will be assessed using the CADSS-6.[28] In addition, since a potential adverse event is the development of craving for this treatment, this will be assessed using a LCQ at baseline and study endpoint (online supplemental appendix 2). We will also track the number of patients who completed the treatment (completed 8 sessions of treatment) versus drop-outs (dropping out of the study prematurely) due to any cause and drop-outs due to adverse events.

Exploratory outcome measures

After completing the treatment course and data collection part of this study, we will share our experiences recruiting and implementing (each researcher is asked to keep a systematic record of their recruitment process and patient retention) IN esketamine among the attending physicians participating in this multicentre study. We will use this expert commentary and the primary and secondary outcome results of this treatment to make a qualitative commentary on the implementation of IN esketamine as a standard of care treatment in naturalistic clinical practice.

Data analysis

The collected data will be analysed by applying descriptive statistics: mean, median, SD, maximum and minimum scores for primary and secondary outcome measures and patient's demographics data. To assess treatment outcomes, changes in depression symptoms as measured by the MADRS will be tracked over time (1 month of acute phase) using within-subjects, repeated measures analysis of variance. Also, we will calculate the response to treatment as the proportion of patients who reached a minimum reduction of 50% from their baseline depression score by study endpoint and the remission from depression as the proportion of patients who reported an MADRS total score equal or less than 10 at study endpoint.[40] We will calculate the relative risk (RR) associated with the beneficial (response to treatment, remission from depression and reduction in suicidality measured by the MADRS) and negative (proportion of patients who completed the study versus the drop-outs; adverse events—side effects checklist and CADSS-6) outcomes of adding IN esketamine treatment.[41] Linear regression will examine the contribution of site, and a socioeconomic variable to changes in mood over time (selection bias). Adverse events will be reported in terms of frequency through the treatment course. Data will be analysed based on intention to treat.

Patient and public involvement

Patients and public were not formally involved in the design of this research paper. However, an important part of our study is determining the overall tolerability and potential for addiction of IN esketamine. To this end, we are systematically recording and reporting all side effects noted by the patients and changes in their likeability or craving for esketamine through their treatment course. This information will present a clear picture of IN esketamine treatment and its application in naturalistic clinical practice and will help patients make an informed decision when deciding to participate in this treatment course.

ETHICS AND DISSEMINATION

This study was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. To protect their privacy, participants will be given an anonymous and unique code, which will be used to identify their data through all the assessment measures, data processing and for all purposes of knowledge dissemination (including but not limited to peer-reviewed publications, scientific presentations, grant proposals and reports). Assessment data will be stored in secured and password protected laptops for 5 years after the study completion date, hard copies of consent forms and participants identifying data will be stored on site in secured lockers and destroyed 5 years after study completion. The research team will safeguard the privacy of the participants to the extent permitted by the applicable laws and duty to report (eg, immediate physical risk to the self or others).

We intend on disseminating our results broadly. Findings will be shared among collaborators, through departmental meetings, presented on different academic (scientific presentation, grant proposals and reports) venues and publishing our manuscript in a high impact peer-reviewed medical journal.

RESULTS

We began offering patients the opportunity to participate in this study in March 2021 at the Mood Disorders Services in Providence Care Hospital, Kingston, Ontario. We expect to finalise data gathering from all the centres involved in August 2022 and analyse the findings by

October 2022 at which point we will begin our process of knowledge dissemination.

DISCUSSION

Ketamine is a relatively old compound that has been used and continues to be used for medical procedures that requires sedation due to its anaesthetic properties in high enough doses. More recently, this drug has found a new application in psychiatry at subanaesthetic doses and has shown significant success as a novel and effective management option for MDD, even in treatment resistant populations.[4–6 18–21] Thus, this has powered more research around this compound, eventually resulting in the synthesis of the S-enantiomer of racemic ketamine, esketamine. Esketamine has been approved for use in patients experiencing TRD (defined as patients who have completed at least two courses of antidepressants[23]) by the FDA and Health Canada.[5 14 24] Also, esketamine may have some potential benefits over the racemic mixture and the R-enantiomer (arketamine), mainly its higher affinity for the NMDA receptor and its mode of administration as an IN spray. Though, despite these putative benefits, IN esketamine remains a costly medication, which can make accessibility much more challenging from a personal and healthcare system perspective.[42–44] However, despite the promising effects of low-dose intravenous ketamine treatment and the beneficial features of IN esketamine, a few studies have focused on the effect of this coadjutant treatment in naturalistic clinical practice.[10 14] Thus, this research study will focus on providing evidence for the application of IN esketamine on patients suffering MDD TRD in the real world, through a multicentre Canada-wide (Providence Care hospital in Kingston, Toronto Western Hospital in Toronto, Sunnybrook Health Sciences Centre in Toronto, Misericordia Community Hospital/Envision Mindcare in Edmonton, Center for Addiction and Mental Health in Toronto and Mood Disorders Centre in Vancouver) prospective cohort observational study of naturalistic clinical practice.

Thus, in this research study of this novel standard of care treatment, we will focus on three main outcomes—the association of IN esketamine treatment with improvements in severity of depressive symptoms (primary outcome), the tolerability of IN esketamine treatment (secondary outcome) and a qualitative commentary on the implementation IN esketamine as a standard of care management for TRD in naturalistic clinical practice (exploratory outcome objective). Association of esketamine treatment with outcomes in the management of depression will be determined by tracking the progression of depression symptoms through the treatment course using the MADRS,[22] and by calculating the treatment response, remission from depression and reduction in suicidal ideation. Tolerability will be determined by tracking the side effects of IN esketamine treatment, using a checklist of common side effects[27] and the CADSS-6[28] for dissociation symptoms. Another potential negative effect of IN esketamine treatment is the potential for abuse/craving, which will be assessed with the LCQ.[30] Finally, our exploratory qualitative outcome will include expert commentary by the attending physicians at each of the collaborating research centres, and the assessment of the primary and secondary outcomes. Though it is important to note that due to the sparsity of healthcare coverage to access IN esketamine, we foresee that this treatment may be less feasible for the average person suffering with TRD.

Based on the results obtained in clinical trials,[4–6 14 18–21] we hypothesise that IN esketamine will be associated with beneficial (reduction in severity of depressive symptoms) outcomes and with a low side effects profile and dropouts (tolerability) in the treatment of patients with MDD TRD in naturalistic clinical practice. If supported, this would have important implications due to the prevalence, morbidity and mortality of MDD as one the top mental health disorders in the USA and Canada.[1–3] The potent effect of IN esketamine has been attributed to the blockade of the NMDA receptor, as well as the activation of a myriad of other reactions, such as the opioid receptors, GABA, non-NMDA glutamate receptors (AMPA), cholinergic neuromodulation and increased release of neuromodulators among others, which result in a neuroplastic and neurogenic response.[4 6–8 14] Thus, with this research study, our aim is to fill some of the gaps in our understanding of IN esketamine with the hope to guide clinical practice in favour of the widespread application of this treatment.

Limitations and future research

This study has several limitations, mainly potential slight variations in the treatment schedule of each of the patients—since we are observing naturalistic clinical practice, we may encounter several unexpected variables such as scheduling conflicts and changes. Furthermore, due to the limitations of the COVID-19 pandemic, we have opted to use phone or video conference for all the assessments scales. This may represent a significant limitation, as talking to a person over the phone or through video conference removes important visual cues about their mental state. This in turn can influence our assessment and interpretation of the severity of their depression symptoms through their treatment course. Also, due to the cost of IN esketamine, most patients will require health insurance coverage to afford the full treatment. At the moment, only certain private insurance companies cover IN esketamine and thus our patient population will be biased in favour of patients with specific types of health insurance or high socioeconomic status.

Future projects will focus on expanding our study to include a comparison with other standard of care treatments for MDD TRD, such as repetitive transcranial magnetic stimulation and electroconvulsive therapy. Another goal will be to follow patients over a period of 6 months and 1 year to study the long-term effects of IN esketamine in naturalistic clinical practice. Here, it will be important to distinguish patients who remained on a

long-term regimen of IN esketamine and patients who decided to discontinue their IN esketamine treatments after the acute phase. Hence, if this drug continues to demonstrate significant benefits in the long term, it can further support its widespread use in clinical practice.

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