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Sublingual ketamine: a pilot study on clinical evaluation of rapid treatment of suicidal ideation in treatment-resistant depression

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Abstract:

Sublingual ketamine is becoming an alternative possible route in the treatment of acute suicidal thoughts, especially those towards patients that are resistant to the regular antidepressants. This was a pilot open label trial to test safety, tolerability, and the quick antidepressant effect of sublingual ketamine administration in patients with treatment resistant depression (TRD), with active suicidal thoughts. Through the evaluation of 10 adult patients with mild-to-severe depression over a two-week period and twice per week, 100 mg of sublingual ketamine was used and the subjects were followed up on day 1, 4, 7 and 14 using the Columbia-Suicide Severity Rating Scale (C-SSRS), MADRS, and CGI scales. Significant improvements were also seen in the suicidal ideation in 70 percent of the patients within 4 hours after taking the drug and persisted through day 14. Side effects were limited (dizziness, nausea) and there were no psychotic symptoms. There was great patient tolerability, and clinician acceptability of the intervention. These initial findings lead to the possibility of sublingual ketamine as a quick and available avenue of therapeutics of psychiatric emergencies and should be followed up with other randomized controlled studies to justify efficacy.

Keywords: ***Sublingual ketamine as a treatment-resistant depression, suicidal thoughts, pilot test, antidepressant, psychiatric emergency, Columbia-Suicide Severity Rating Scale, MADRS, Clinical Global Impression.***

1. Introduction

1.1 Treatment Resistant Depression (TRD) Overview

Treatment-resistant depression (TRD) is one of the major problems within the area of psychiatry that is characterized as a depression, which is not responding to at least two classes of antidepressant drugs in a sufficient amount and a prolonged period of time. Intelligence has a significant prevalence of treatment resistance among patients with major depressive disorder (MDD), and some literature implied that 30-40 percent of the patients with MDD have treatment resistance. Such patients tend to experience extended depressive states, poor quality of life and functional impairment and therefore intervention is of utmost importance. Due to the possibility that conventional antidepressants might not be enough because of TRD, there is an increased need to develop alternative avenues of treatment that could manage the symptoms of depression along with its comorbid diseases like suicidal thought.

1.2 TRD Suicidal Ideation Management Issues

One of the most serious manifestations of depression is suicidal ideation as it is admitted to represent a psychiatric emergency that has to be treated as soon as possible. Suicidal thoughts in the case of TRD are persistent and intense more often, which increases the rates of suicide and self-harming. Conventional antidepressants usually require a number of weeks before they can begin to offer treatment, which makes them inadequate when it comes to acute suicidal thoughts. Further more, the treatment resistance may make establishing the effective therapy difficult since not all the patients with TRD respond to conventional pharmacological treatment. These length of time may emphasize how quick-acting methods of alleviating symptoms are required, especially in the case of people in immediate danger of self-death. Suicidal ideation in TRD is a pressing problem that requires immediate solutions and new treatment opportunities, and any form of relief will be of great necessity to avoid tragic experience.(1)

1.3 Ketamine in acute psychiatric care

A potent drug N-methyl-D-aspartate (NMDA) receptor antagonist and antidepressant, Ketamine, has gained a lot of attention as a prospective treatment of TRD because of its fast onset antidepressant effects. Ketamine, initially applied as an anesthetic, has demonstrated potentiality in reducing the manifestations of depression and suicidal contemplation on the patients who have been unresponsive to the typical medications. Ketamine has been noted

to exhibit fast effectiveness on the depressive symptoms compared to other traditional antidepressants which normally take several weeks before they can be effective. This quick set has been especially useful in the acute treatment of suicidal ideation because immediate action is needed. Moreover, the fact that ketamine has the capacity of acting upon the glutamatergic system gives it a distinct advantage over any other antidepressant, not only in perspective but also in the basis of how the molecule will ultimately work differently than any other medication and thus could become a saving grace to those with TRD.

1.4 Rationale of Sublingual Administration

Owing to fast results of depressive syndrome treatments with ketamine, there are still difficulties in its conventional methods of administering the drug (using intravenous and intramuscular controls), which involve the possibility of requiring the special medical oversight and care. Sublingual administration of Ketamine provides a possible substitute that integrates the ameliorative effects of Ketamine with an easy way more neighborhood and least obnoxious dispensing technique. The sublingual route has the advantage of speed of absorption thereby giving faster onset of action as compared to oral formulations by absorption through mucous membrane present under the tongue. It is also more convenient to the patient and clinicians, and eliminates an intravenous access or monitoring in a medical space. The sublingual route of ketamine is also now in line with the purpose of delivering fast and effective treatment in psychiatric emergencies where fast access to the patient is the key to patient safety.

1.5 Aim and Scope

In this open-label pilot study, the safety, tolerability, and acute anti-depressant effects of sublingual ketamine on patients with TRD and active suicidal ideation will be determined. The article aims at the evaluation of the viability of sublingual ketamine as a future choice of treatment of this group of patients and gives a preliminary report on the possible effectiveness of this medicine in decreasing suicidal ideation and depressive symptoms. With an intervention consisting of 100 mg of sublingual ketamine given twice a week on a two-week regimen, the research explores how quickly the symptoms may be alleviated, especially the depressive symptoms, such as suicidal ideation, with the help of the established psychiatric scales. The results of this pilot research will be used to guide similar research in the future, on a larger scale, and must be added to the body of evidence demonstrating the resulting usefulness and feasibility of ketamine as a readily available, safe intervention to help individuals in a psychiatric emergency.(2)

2. Experimental Background

2.1 Ketamine modulates NMDA receptors in the brain and this process inhibits depression.

The antidepressant effects of ketamine are mainly because it is an N-methyl-D-aspartate (NMDA) receptor antagonist which sets it apart with conventional antidepressants that have been suggested to work by activating the serotonin and norepinephrine systems. This blockade of the NMDA receptor by ketamine increases the activity of glutamate, which causes brain-derived neurotrophic factor (BDNF) to be quick released promoting the process affair, synaptogenesis, which promotes neuronal plasticity. This increment in synaptic connection is believed to be part of the reason why ketamine has rapid antidepressant-like effects, which has been shown to occur hours after administration. However, in addition to the above signaling pathway, it is possible that ketamine can stimulate other signaling mechanisms, such as the mammalian target of rapamycin (mTOR), which is associated with cell growth and survival. The way in which ketamine creates such swift alterations in brain activity has given rise to the theory that they can help to reprogram pathological neural networks that exist through mood illnesses, providing a new method of treating depression most specifically in patients who have not reacted to conventional treatments.

2.2 Previous research on Ketamine and Suicidal Ideation

A number of studies have been conducted to investigate the prospect of ketamine of quickly relieving suicidal ideation that presents a crucial symptom in the treatment of TRD. Remarkably, ketamine showed fast effects on suicidal thoughts when a single intravenous infusion was utilized in patients with TRD (Price et al. 2009). The effects lasted up to one week indicating that ketamine could be a short-term solution to people who are at a risk of committing suicide. These results have been corroborated in more studies and it has been found that within hours of administration, ketamine can reduce the incidence of suicidal thoughts significantly. Notably, these effects were found to occur in patients whose depression and suicidal thoughts had a long history and were otherwise not responsive to other forms of treatments. In addition, other research outfits have also established that the quick action of ketamine, coupled with its ability to confer considerable amounts of relief within a short period makes it

an attractive alternative to be used in the treatment of patients considered to be at a high risk of suicide. Nonetheless, it is unclear how ketamine achieves its immediate effects on suicidal thoughts, with some scientists suggesting that ketamine acts on certain cerebral networks centering on self-referential thinking and emotional regulation.(3)

2.3 Sublingual versus Intravenous Route

The administration route of ketamine is a major factor considering its clinical use because it determines the rate at which the drug will take effect as well as ease of putting one under. Although intravenous (IV) ketamine can prove to be very effective in treating depression and suicidal intentions, its application requires specialized facilities and trained personalities, which may create a barrier to its accessibility in acute psychiatric facilities. Conversely, sublingual ketamine will provide an easier alternative, as it can be administered by yourself, or under a lighter supervised manner. The sublingual administration route is that which applies when the ketamine is placed beneath the tongue, where it may have a quicker onset of action as compared to oral formulation. Earlier reports have suggested that the efficacy of sublingual ketamine can be similar to that of the IV in terms of the rapidness of antidepressant effects. The fact that it does not require intravenous access is a potential advantage as well as the sublingual route is a more accessible means of treatment in acute care conditions. Moreover, it is more convenient to make dose adjustments and be more flexible in the outpatient setting, which is essential in the rapid treatment of suicide-prone patients.

2.4 Rationale Justification of Pilot Design and Dose Selection

The logic of the design of this pilot study is based on the necessity to determine the feasibility of administration, the maintenance of the safety, and the early efficacy of sublingual ketamine concerning patients with treatment-resistant depressive state and active suicidal thoughts. It is also important to establish the dose, frequency, and schedule of ketamine administration as sublingual administration is a new method of medication in the population. One hundred mg of dose was chosen on the basis of the evidence derived earlier, which showed its effectiveness and safety profile of the drug in both intravenous and sublingual form. Although the 100 mg dose is smaller than what is typically reported in IV ketamine studies, it was selected to balance the trade-offs between an effective dose that has a fast onset of action and dose increases needed to avoid adverse effects. The decision to have the dosing frequency of twice weekly over a period of two weeks was done to offer an initial assessment of the both short term and sustained account of the treatment. One of the purposes of selecting this pilot design is that it simultaneously permits the detection of potential side effects or tolerability problems, which can entail great importance in establishing the feasibility of sublingual ketamine as a treatment option of suicidal ideation in TRD. Data on this pilot trial will be used to design future and bigger randomized controlled trials.

3. The enrolment of patients and the study design

3.1 inclusion/exclusion criteria

The inclusion and exclusion criteria of this pilot study were formulated not only to make the participants representative of the persons with treatment-resistant depression (TRD) and active suicidal ideation but also to reduce possible confounders.

Inclusion Criteria:

- Between 18 years old, and 65 years old adults.
- Diagnosis Diagnosis: The major depressive disorder (MDD), which stems as a result of the current episode that is lasting not less than 6 months.
- Treatment-Resistant Depression: The participants must not have responded adequately to at least two classes of antidepressants and must have failed to respond adequately to at least 4 weeks of adequate dose of an antidepressant.
- Active suicidal Ideation: Participants were supposed to be active in their suicidal ideas as it is measured using Columbia-Suicide Severity Rating Scale (C-SSRS).
- Clinical Stability: The participants will be required to be medically stable before taking part in the study, and they are not supposed to have acute medical issues that will be a hindrance to the study.

Exclusion Criteria:

- Psychiatric Comorbidities: Past reliable severe psychiatric records of conditions such as schizophrenia, bipolar or severe personality disorders given because the drug may confuse the effects of the ketamine.

- Substance Abuse: Last 12 months subs. disr. or subs. severe abus. lt 12 mo ago.
- History of Psychosis: Previous history of psychotic episodes or psychotic disorders were also not permitted as it has the risk of bringing up flare-ups during the use of ketamine.
- Severe Medical Conditions: heart disease, liver and kidney disease or brain disorders that may intrude into the safe application of ketamine.
- Pregnancy and Lactation: Women who were pregnant or breastfeeding were not allowed to participate because the safety data as far as the use of ketamine during such phases is not adequately possessed.

The research objectively assessed the effects of ketamine in an objective population of people with high risks of suicidal behavior and who had not responded to conventional antidepressants due to careful selection of participants in terms of these characteristics.

3.2 Study design: the DOSE and labeling: Open, Dose plan:

This pilot study was an open-label type, which implies that the researchers and those receiving the treatment knew about the type of treatments. The open-label design was selected because the study was exploratory since the main objectives of the study were aimed at investigating the safety, tolerability, and preliminary effectiveness of sublingual ketamine in patients with treatment-resistant depression and active suicidal thoughts. The open-label design created more leeway to evaluate adverse events and fast alterations in clinical condition giving a helpful insight about the potential advantages and dangers of ketamine in a clinical condition in real life circumstances.

In two weeks, dose policy was carried out with 100 mg of sublingual ketamine two times every week. The choice of this regimen was founded upon the available literature which showed safety and efficacy in terms of identical doses, aspiring to strike a balance between the therapeutic effects and the patient tolerability. Secondary evaluations were performed on the 1, 4, 7, and 14 days after treatment was done and thus the progress in the reduction of morphine of depressive and suicidal symptoms was continuously monitored. The opportunity to examine how long the effect of ketamine is, in both enhancing suicidal ideation quickly and the long-term effect of desirable improvement was also presented through the study design.(4)

3.3.7 Informed Consent Ethical Approval

The participating medical center had an institutional review board (IRB) that approved its protocol. Each of the studies was ethically approved so that it responds to the ethical considerations mentioned in the Declaration of Helsinki especially regarding the protection of vulnerable groups of the population including suicidal people. All the participants were informed and they gave an informed consent prior to the commencement of the study since they were well aware of the possible risks and benefits of sublingual ketamine treatment. Information pertaining to the study process was given to the participants in detail and their consent was taken without any propulsion. The participants also were guaranteed that they have the right to drop out of the study at any moment and that would not affect their continued treatment and medical support.

3.4 C-SSRS, MADRS, CGI clinical scales

Clinical efficacy of sublingual ketamine was evaluated with the help of a number of psychiatric scales which are well accepted in the field of research and practice. These measurement scales enabled the standardized determination of two variables that were of utmost interest in this study including depression and suicidal ideation.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is another common scale that determines the suicidal ideation and behavior complexity and severity. This study has employed it to measure variations between the baseline and follow-up outcome of suicidal thoughts, thereby giving a firm outcome of the effects of ketamine on suicidal thoughts.

Montgomery- Asberg Depression Rating Scale (MADRS): The MADRS is a Depression scale rated by a clinician or interested party to determine the vulnerability of depressive mood. It was used to assess the variations in the depressive symptoms after a period of the study and assist in the estimation of the general antidepressant outcome of the sublingual ketamine.

Clinical Global Impression (CGI): In this test, the clinician was asked to give an overall impression of how the patient was doing concerning their mind in terms of both level and the improvement of symptoms with CGI scale. The CGI assisted in offering the big picture regarding the situation of the patient which was what was needed in addition to the assessment of the depression and suicidal thoughts.

All these clinical scales were applied at baseline, follow-up measurements on days 1, 4, 7, and 14, making it inclusive assessment of the work of ketamine on both suicidal ideation and depressive symptoms.

4. Dosing Regimen and Safety Observation

4.1 Method and Frequency of Administration

This pilot study gave treatment-resistant depression (TRD) patients with active suicidal ideation sublingual ketamine. The route that was used was sublingual, whereby the ketamine tablet was placed under the tongue of the participant to dissolve and be absorbed by the mucous membranes. The preference of this approach was based on its convenience, the comparatively fast action and the fact that it could be administered outpatients which is essential in the case of psychiatric emergencies.

The dosing regimen consisted of 100 mg of sublingual ketamine two times a week during the period of two weeks. The above dosing regimen was chosen because of the prior research findings that indicated safety and efficacy by using similar amounts of sublingual ketamine in the treatment of depression and suicidal thoughts. This was to have a sufficient therapeutic effect but to alleviate the possible side effects an administration frequency of twice-weekly was instituted. The subjects were dosed under clinical conditions, with proper monitoring of the subjects by skilled medical personnel. The period of two weeks was to check the both immediate and short term outcome of sublingual ketamine in suicidal ideation and depressive symptoms.(5)

4.2 Monitoring Schedule: Day 1, 4, 7 and 14

Safety and efficacy of the trial were tracked in the study through a well-defined follow-up timeline. These patients were evaluated on the 1 st, 4th, 7 th and 14 th days after the administration of Ketamine to monitor the immediate and the long-term effects of ketamine on suicidal thoughts and depression.

Day 1: On first dose, the subjects were observed to experience any immediate effects of ketamine. The day-two observations were to monitor acute effects of suicidal ideations and depressive symptoms as well as the side effects or adverse reactions. Assessment instruments like Columbia-Suicide Severity Rating Scale (C-SSRS) and Montgomery-Asberg Depression Rating Scale (MADRS) were used to determine the intensity of the symptoms.

On day 4, the second dosage was not tested, but the patients were reobserved to determine the persistence of the effects on the first dose. Such a mid-point evaluation gave us an idea of the continuance of ketamine and its impact on suicidal ideas and depression. At this stage, side effects that might have occurred then the initial dose were also followed up.

The assessment on day 7, gave a window to see the effects of having twice weekly dosing that may represent the longer-term benefit, and or reduction of the mentioned improvement. The follow-up also made it possible to reveal all the negative consequences that occurred late or changes in tolerance.

The last follow-up day 14 measured the effect of the treatment in general. Participants were compared on the measures of sustained positive change or relapse on symptoms of depression and suicidal ideation. Any beneficial outcomes of the use of ketamine that may occur after a given period and any side effects that may persist could now be monitored after a considerable time.

In all these analyses, the study team made sure that the participants were taken care of well with check ups on therapeutic and safety consequences.

4.3 Safety assessments and adverse event monitoring

Safety observation was an essential element of this pilot study, especially because the use of sublingual ketamine with active suicidal ideation patients was a new treatment. AEs were monitored closely in the course of the study. Volunteers were requested to report in case of any unusual symptom or discomfort during each treatment session and all the side effects were noted separately.

Dizziness, nausea and dissociation that are common side effects of ketamine like were anticipated and closely observed. The strength of these adverse effects was evaluated according to the standard criteria of differences between mild, moderate and severe ones. Any possible adverse effects which were strong (psychosis, altered cardiovascular dynamics) were indicated as early as possible and approached by the medical team. These checkups were done to make sure that the safety of patients was paramount and in the event of a negative outcome, they could be corrected immediately.

Adverse events and any not anticipated side effects were reported in accordance with the principles of ethics to the institutional review board (IRB) so that safety requirements were addressed in the course of the study. Side effects were also observable in real time because the participants were asked to report them to ensure the side effects were assessed continuously.(6)

4.4 Tolerability and Resistance Metrics by Clinicians

Tolerability constituted a critical part of the study, because the main focus was not just to determine the effectiveness of sublingual use of ketamine, but also to determine whether the treatment could be used safely and in a comfortable environment. Clinician feedback was collated at each follow-up visit where they were asked to rate the ease of administration, amount of supervision needed and any worries with side effects. These measures facilitated the determination of the viability of sublingual ketamine as a practical intervention to the treatment of suicidal ideation.

Clinicians also gave a reaction to how they perceived the participants response to treatment especially in terms of the rate of improvement in these symptoms and the continuity of such advantages. Structured interviews and assessments were used to gather feedback so as to make sure that the professional opinion of the clinicians in regard to the clinical applicability of the treatment was properly documented.

The overall goal of the safety/tolerability measures was to inform future practice and ensure that should sublingual ketamine prove effective, it can safely be used in psychiatric emergency care services, and more specifically with patients who have treatment- resistant depression and who experience active suicidal ideations.

5. Results

5.1 Decreases in Suicidal Ideation in 4 Hours

Assessing the rapid action of sublingual ketamine on suicidal ideation was one of the main aims of the present study. The findings revealed that, after sublingually talking 100 mg of ketamine and its first dose, from 4 hours, 70 of the participants showed a major improvement in the suicidal thoughts. The evaluation of such a prompt impact was done, and it was revealed by using Columbia-Suicide Severity Rating Scale (C-SSRS), which demonstrated a significant reduction in the intense character of suicidal thoughts by the participants, most of whom declared that their thoughts about self-harm were alleviated almost completely. The response is rapid as is the antidepressant effects of ketamine in general via its effects as an NMDA receptor blocker and its effect on synaptic plasticity.

The effect by which suicidal thoughts were reduced so quickly underlines the possibility that sublingual ketamine may be a therapeutic tool in treating acute suicidal ideations in a psychiatric crisis. The observation that there were improvements as soon as several hours after administration is reminiscent of the clinical significance of the rapid-onset effect of ketamine that could potentially save the lives of people who are in imminent risk of suicide.(7)

5.2 Long-term Symptom Reduction Through Day 14

Other than the rapid response, which was the subject of the study, there was also the need to determine the sustainability of ketamine effect throughout the treatment period of two weeks. Subsequent measurements were done after 4, 7 and 14 days that showed that the decrease in suicidal ideation and symptoms of depression were not solely fast, but also their effects were consistent. During the 1-month follow-up period, 60 percent of the participants had a considerable lower score of suicidal thoughts using C-SSRS than the base score. Depressive symptoms, which were measured using the Montgomery-Asberg Depression Rating Scale (MADRS), also demonstrated a sustained improvement wherein the average percent change in the MADRS scores compared with baseline was 40 percent.

Sublingual ketamine can be continuously beneficial beyond its immediate effect according to these results; a long-lasting decreasing of suicidal ideation, and, at the same time, depression indicators, lasting till 14 days after the treatment. This long-term effect helps to justify the prospect of ketamine as a potential intervention in management of acute suicidality in patients of treatment-resistant depression.

5.3 percent of patients that indicated positive response

The response rate to sublingual ketamine appeared excellent in this pilot study as the overall response rate to treatment was 70 percent. The definitions of a positive response were assigned to represent a meaningful decrease in the presence of suicidal ideation and depressive symptoms; in other words, 50-percentage or more improvement on the C-SSRS and MADRS were stated. These findings indicate that sublingual ketamine can be an effective remedy and rapid treatment alternative among depressed patients with active suicidal thoughts who cannot be controlled through conventional ways of treatment.(8)

The percentage of response to the treatment of treatment-resistant depression with ketamine corresponds to the existing literature on the topic and thus it once again exemplifies how this treatment option is promising to those who have not responded to conventional antidepressants.

5.4 Reported Adverse Reactions and the Levels of Severity

Although sublingual ketamine was shown to be effective in the reduction of suicidal ideation and depressive symptoms, the trial had control of the adverse events to evaluate the perceived safety and tolerability of the intervention. Majority of the reported adverse effects were mild and temporary with the most commonly encountered side effects being dizziness and nausea that occurred in 30 percent of the participants. These were self-limiting symptoms and they disappeared without intervention.

There were also other side effects, like headaches or mild dissociation, but these effects were on a low level. Notably, none of the participants displayed any serious or protracted side effects, with all the side effects associated with mild and moderate intensity. These results indicate that sublingual ketamine is well-tolerated in general, and side effects are tolerable and do not last long.

5.5 No Practice of Psychosis or Severe Complications

Of utmost safety concern regarding the use of ketamine is that it may precipitate serious complications, including psychosis or cardiovascular complications. Nonetheless, the study has not found cases of psychosis and severe complications. No participants showed delusions or hallucinations or any other psychotic symptoms, which are sometimes reported with high doses of ketamine in medical practice. In addition, no serious cases of cardiovascular event, including high blood pressure, or high heart rate, that can be associated with the use of ketamine were reported.(9)

Psychosis or severe complications were absent in relation to this pilot study which is a valuable result as it implies that sublingual ketamine might be administered safely in outpatient or emergency clinical context with proper supervision. This adds to the possibility of sublingual ketamine as a valid treatment alternative of people at acute risk of suicide, and a good safety profile with minimal severe adverse events.

6. Conclusion

6.1 Key findings Summary

This pilot was aimed at evaluating the safety and tolerability, as well as the rate of the antidepressant efficacy of sublingual ketamine in patients with treatment-resistant depression (TRD) with active suicidal ideations. These findings showed that sublingual ketamine could be an effective intervention in alleviating suicidal ideations in this high-risk group in a short period. After 4 hours of taking it, pupils experienced a significant decrease in suicidal thoughts 70 percent of the time, which is also a significant finding that highlights the rapidity of ketamine. And, the efficacy of the improvement of depressive symptoms has been maintained till the duration of two weeks of treatment, with 60 percent of the participants reporting the persistence of a decrease in symptoms after two weeks of treatment. The safety of sublingual ketamine was found to be favourable of having only minor adverse experiences of dizziness and nausea with no instances of psychosis or major complications. These results might indicate that the sublingual ketamine would be a good tolerable treatment of acute suicidality in TRD patients.

6.2 Relevance to psychiatric emergency of sublingual ketamine

It is the fast acting characteristic of sublingual ketamine that can have clinical significance in the treatment of emergent events in psychiatry by its ability to alleviate acute suicidal thoughts in a person in a timely manner. In an emergency psychiatric facility where suicidal thoughts may result in an immediate death threat to the individual, the capability of reducing suicidal thoughts within the short run can save someone. Conventional antidepressants have proven to be efficacious in terms of long-term use in the prescription of depression but they take time to take effect which cannot be used in emergent cases. Conversely, the fact that ketamine takes just a few hours can provide early intervention in patients who are at imminent risk. Moreover, the advantage of sublingual ketamine over intravenous (IV) ketamine is its ease of delivery and possibility of using it as an outpatient product when using intravenous form requires special medical supervision and facilities. The high-potential outcomes of this pilot study indicate that sublingual ketamine may be incorporated into the areas of emergency care that would address patients with a treatment-resistant depression condition or with active suicidal thoughts and offer a quickly accessible solution.

6.3 Limitation of the Study and RCTs Necessary

In spite of these positive results, there are also a number of limitations associated with the pilot study that should be addressed in further studies. The sample group of 10 was also small, and therefore, the conclusions made on its result cannot be generalized and definite conclusions about the effectiveness of sublingual ketamine are not possible. As well, the design is open label and although it provides a lot of information, it is not extremely

controlled like a randomized controlled trial (RCT) which is needed to get rid of all the potential biases to know the real therapeutic effect of sublingual ketamine. There is also a lack of a placebo group and as such it makes it difficult to differentiate between the effects of ketamine and the natural progression of the depressed state and the placebo effect. Further, the follow-up of 14 days is too short to give a detail of the long-term consequences and safety of sublingual ketamine. In order to verify results of this pilot study and have a better idea on clinical applicability of sublingual ketamine, it is required to conduct furtherical studies with larger sample size and populations and following them through longer duration of time.

6.4 The Way Forward in respect of Research

Future research is needed to overcome the limitations of this pilot study in terms of the results by searching more significant, well-powered RCTs that will compare sublingual ketamine with a placebo or well-established medications. To achieve a better comprehension of the performance of sublingual ketamine in the various subgroups of patients, this study should have a wider scope of participants, with different degrees of treatment resistance, different comorbid conditions, etc. Also, it should be investigated how to administer doses in the future in order to achieve the best results, and how working with sublingual ketamine would affect the ideation of suicide, depression, and functional outcomes in the long-term perspective. Exploring the mechanisms of the quick effects of ketamine on suicidal ideation can help come up with valuable information on the unique ways in which it can improve treatment outcomes. Additionally, the studies must be conducted to evaluate the practicality of the sublingual administration of ketamine into clinical operations, addressing the ways it can be successfully administered as outpatient drug or emergency care. Last but not least, the cost-effectiveness of sublingual ketamine as compared to other rapid-onset interventions should be evaluated to ascertain its viability in a broader application in clinical practice.

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Conflicts of interest

The authors have no conflicts of interest to declare

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