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Utilizing Esketamine Short-Term with New Oral Antidepressants in Patients with Treatment Resistant Depression and Suicidal Ideation to Minimize Post-Discharge Suicide Attempts: A Systematic Review

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Esketamine to Minimize Post-Discharge Suicide Attempts

INTRODUCTION

Major depressive disorder (MDD) is the most prevalent psychiatric diagnosis, and at its highest severity, depression can lead to suicide.[1] There are over 700,000 suicide-related deaths annually.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), MDD is diagnosed if five or more of the following symptoms are present for a two-week period with at least one symptom being depressed mood or anhedonia: sleep changes, anhedonia, feelings of guilt or worthlessness, low energy, poor concentration, appetite changes, psychomotor agitation or retardation, and suicidal thoughts.[2]

The current standard of care in treating MDD includes initiating and optimizing oral antidepressants such as selective serotonin reuptake inhibitors (SSRI) which are considered first-line options.[3-5] Although effective for depression, antidepressants can take weeks or months to reach their full effective level[6]; therefore, it can leave patients with severe depression and suicidal thoughts at higher risks while waiting on medications to become therapeutic. Severe depression with suicidal ideation (SI) is considered a psychiatric emergency and warrants urgent hospitalization. The time interval between SI and a suicide attempt is short.[7] This further emphasizes the need for rapid de-escalation of SI not only during a hospitalization but for the weeks following a hospitalization as patients are waiting for medications to achieve optimal effect. Global suicide rates are 200 times more during the first three months after a psychiatric hospitalization.[8]

In patients with SI and treatment resistant depression (TRD), who do not respond to the initial trials of antidepressants prescribed at adequate doses with a sufficient length of time, the need for a rapid-acting agent becomes more crucial.[9] Currently, there is no universal definition for TRD, but poor response to even one adequate trial indicates a poor prognostic factor.[10]

Esketamine to Minimize Post-Discharge Suicide Attempts

Ketamine, a racemic mixture consisting of an R-enantiomer and an S-enantiomer, also known as esketamine, was approved by the Food and Drug Administration (FDA) for TRD; however, there are limited studies with mixed results. Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that is generally administered intravenously due to poor oral bioavailability.[11,12] In comparison, esketamine, an NMDA receptor antagonist that modulates glutamatergic transmission, has a higher affinity for the NMDA receptor and is the most potent of the two enantiomers.[11,13,14] Esketamine can be administered intranasally (IN). Not only is IN esketamine more effective, but it is also more practical for inpatient and outpatient clinical use. Inpatient settings and outpatient clinical areas are not often supplied with the proper equipment or trained staff to administer intravenous medications like ketamine. There are also safety concerns with subjecting already suicidal patients to equipment that could be used to harm themselves or others. Spravato®, a schedule III-controlled substance, is the FDA-approved IN esketamine available on the market.[15] According to the available prescribing information, Spravato® is approved for use in adults with MDD and acute SI or suicidal behavior.[15] However, one limitation of use listed on the prescribing information reveals that suicide prevention, reducing SI, or minimizing suicidal behavior has not been demonstrated.[15]

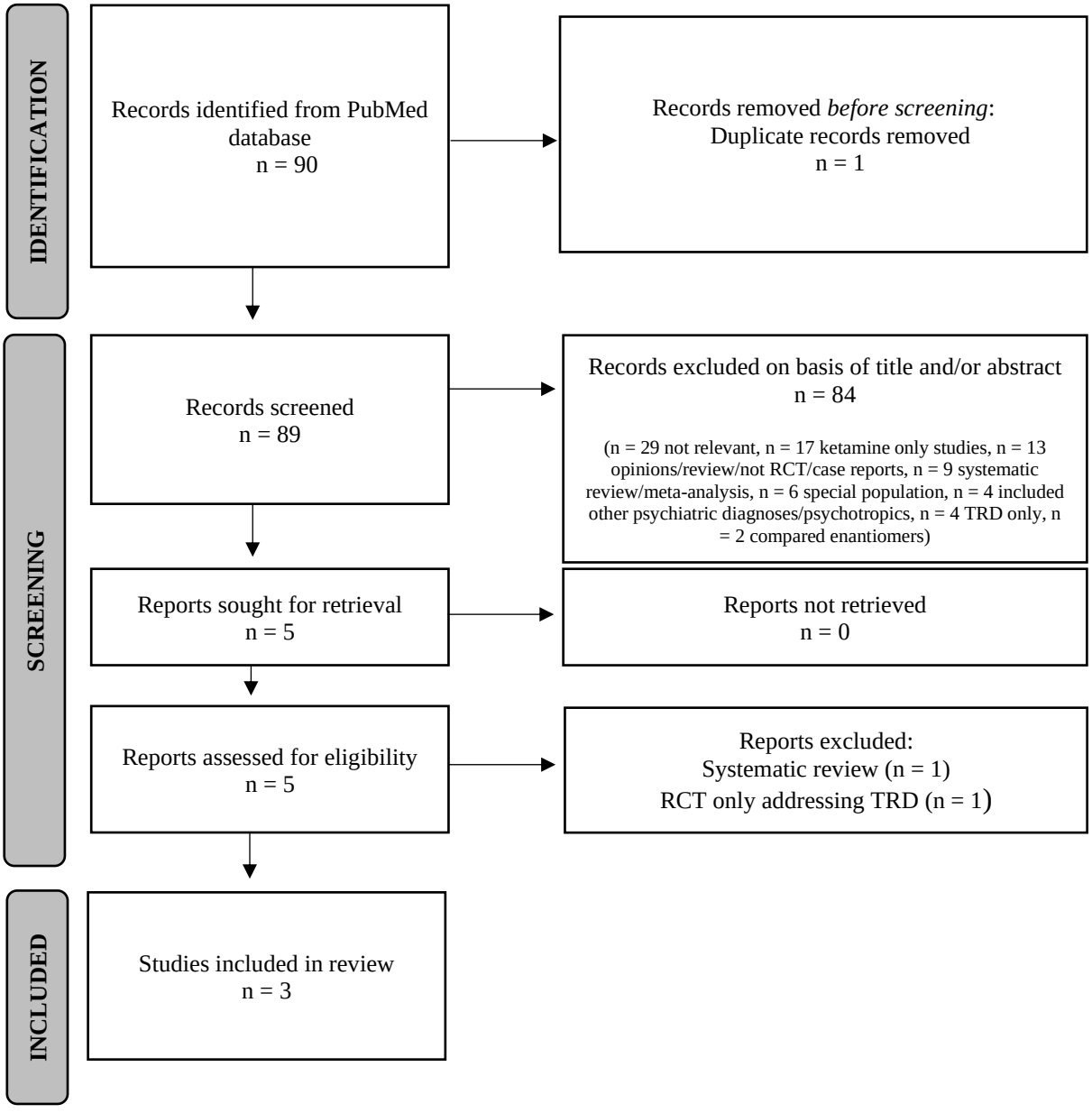
There are many studies regarding the antisuicidal and antidepressant benefits of ketamine but very limited completed trials regarding esketamine's antisuicidal and antidepressant effects. In this review, we will evaluate the most current esketamine randomized controlled trials (RCT) in patients with TRD and SI and its potential to decrease suicide attempts post-discharge while awaiting antidepressants to reach therapeutic levels.

METHOD

Esketamine to Minimize Post-Discharge Suicide Attempts

On December 9th, 2021, a PubMed search was conducted using the advanced search builder, and the terms "esketamine" and "suicide" were entered. Under additional filters, "5 years" was selected to limit the search to the most recent studies. This resulted in 90 articles. Of these, only three articles were RCTs that addressed the comparison of IN esketamine to placebo in patients with depression and active SI as depicted in Figure 1.

Figure 1. Flow chart of literature searching and screening for articles concerning esketamine and suicide as per PRISMA guidelines



One duplicate was noted in the initial search. The primary aim was to review pertinent RCTs regarding esketamine's antisuicidal effects in the TRD population, and there were 84 articles that were excluded based on the title, abstract, or both. These excluded articles include not relevant articles, ketamine only studies, opinions, reviews, not RCTs, case reports, systematic reviews, meta-analyses, studies only examining special populations, articles that included other psychiatric diagnoses or psychotropics, examined TRD only, and those that compared the ketamine enantiomers head-to-head. Five full-text articles were read, and two additional articles were excluded as one was a systematic review and the other was an RCT only addressing esketamine's effect on TRD.

As per Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, we utilized the patient group, intervention, comparison, and outcome (PICO) method.[16] Patient group included TRD adults presenting with acute SI. Intervention and comparison consist of short-term esketamine IN spray plus a new oral antidepressant and placebo IN spray with a new oral antidepressant, respectively. The PICO outcome is decreasing suicide attempts in the time following psychiatric hospitalizations.

RESULTS

As noted in Figure 1, the search resulted in three pertinent RCT articles being selected for review. All three studies are double-blind, randomized, and placebo-controlled trials that included only middle-aged adults and were completed at multiple study sites. Table 1 and Table 2 summarize the study population and the study characteristics, respectively.

Table 1. Summary of study population

	CANUSO ET AL. (2018)	**FU ET AL. (2020)**	**IONESCU ET AL. (2021)**
Age	19-64	18-64	18-64
Diagnostic criteria	DSM-IV-TR, MINI	DSM-5, MINI	DSM-5, MINI
MADRS score	≥22	>28	>28

Excluded psychiatric comorbidities	Bipolar disorder, antisocial personality disorder, borderline personality disorder, moderate-to-severe substance disorder, psychotic disorder, intellectual disability	Bipolar disorder, obsessive-compulsive disorder, antisocial personality disorder, borderline personality disorder, moderate-to-severe substance or alcohol use disorder within 6 months, psychotic disorder, positive urine test[a]	Bipolar disorder, obsessive-compulsive disorder, antisocial personality disorder, borderline personality disorder, moderate-to-severe substance or alcohol use disorder within 6 months (12 months in some countries), psychotic disorder, positive urine test[b]

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; MINI, Mini International Neuropsychiatric Interview

[a]Phencyclidine, cocaine, or amphetamines

[b]Phencyclidine, cocaine, or amphetamines unless patients were on prescribed psychostimulants treatment

Table 2. Summary of study characteristics

	CANUSO ET AL. (2018)	**FU ET AL. (2020)**	**IONESCU ET AL. (2021)**
Study design	Double-blind, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled
Sample size	Total (n = 68) Placebo (n = 32) Esketamine (n =36)	Total (n = 226) Placebo (n = 112) Esketamine (n =114)	Total (n = 230) Placebo (n = 115) Esketamine (n =115)
Location	Multicenter, 11 sites in United States	Multicenter, 51 sites in Asia, Europe, South Africa, United States	Multicenter, 47 sites in Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, France, Lithuania, Poland, Spain, Turkey, United States
Time of study completion	June 2014-Februrary 2016	June 2017-December 2018	June 2017-April 2019
Randomization	Computer-generated, 1:1; randomization balanced by randomly permuted blocks and stratified by study centers and standard of care antidepressant type	Computer-generated, 1:1; randomization balanced by randomly permuted blocks and stratified by study centers and standard of care antidepressant type	Computer-generated, 1:1; randomization balanced by randomly permuted 4 patients per block and stratified by study centers and standard of care antidepressant type
Length of study	24- to 48-hour screening period, followed by 25-day double-blind treatment, then 8-week post-treatment follow-up	24- to 48-hour screening period, followed by 25-day double-blind treatment, then 9-week post-treatment follow-up	48-hour screening period, followed by 25-day double-blind treatment, then 9-week post-treatment follow-up
Study drug	600 µL of esketamine (84 mg); dose can be reduced to 400 µL for intolerance (56 mg)	600 µL of esketamine (84 mg); dose can be reduced to 400 µL for intolerance (56 mg) after day 1 and continued thereafter	600 µL of esketamine (84 mg); dose can be reduced to 400 µL for intolerance (56 mg) after day 1 and continued thereafter
Placebo	600 µL of bittering agent; dose can be reduced to 400 µL for intolerance	600 µL of bittering agent; dose can be reduced to 400 µL for intolerance after day 1	600 µL of bittering agent; dose can be reduced to 400 µL for intolerance after day 1

Standard of care provided	Hospitalization and 1 or more non-investigational antidepressant initiated or optimized on day 1	Hospitalization and 1 or more non-investigational antidepressant initiated or optimized on day 1	Hospitalization and 1 or more non-investigational antidepressant initiated or optimized on day 1
Standard of care oral antidepressant	Monotherapy or antidepressant plus augmentation therapy (type not specified); dose adjustments permitted within first 2 weeks then maintained thereafter	Monotherapy or antidepressant plus augmentation therapy[a] (second antidepressant, atypical antipsychotic, or mood stabilizer); dose adjustments permitted within first 2 weeks then maintained thereafter	Monotherapy or antidepressant plus augmentation therapy[b] (second antidepressant, atypical antipsychotic, or mood stabilizer); dose adjustments permitted within first 2 weeks then maintained thereafter
[a]Benzodiazepines permitted; 75% received ≥ 1concomitant benzodiazepines [b]Benzodiazepines permitted within 8 hours before each drug dose administration, none within 4 hours of first dose and within 8 hours of day 2 assessments; an equivalent dosage to lorazepam ≤ 6 mg/d			

The earliest study of the three was a proof-of-concept phase II study conducted by Canuso et al at 11 United States sites from June 2014 to February 2016.[17] It included 68 adults (19-64 years of age) that were assigned in a 1:1 ratio via computer-generated randomization balanced by randomly permuted blocks and stratified by study centers and standard of care antidepressant type (placebo n=32, esketamine n=36).[17] Participants met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) MDD criteria, were required to have a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 22 which necessitated acute hospitalization due to imminent risk, and suicidality was confirmed using the Mini International Neuropsychiatric Interview (MINI).[17] The study drug consisted of 600 µL of esketamine (84 mg) that could be reduced to 400 µL for intolerance (56 mg), and the placebo was a 600 µL formulation with a bittering agent that could be reduced to 400 µL for intolerance.[17] The study consisted of a 24- to 48-hour screening period, followed by 25-day double-blind treatment, then 8-week post-treatment follow-up.[17] Hospitalization and one or more non-investigational antidepressants were initiated or optimized on the first day.[17] The standard of care oral antidepressant options include monotherapy or an antidepressant plus augmentation therapy (type not specified).[17] Dose adjustments were permitted within the first two weeks and

then maintained thereafter.[17] Refer to Table 1 for more exclusion criteria. The most frequently reported adverse reactions are listed in Table 3. The primary efficacy endpoint in this study includes the MADRS score change from baseline to four hours post-dose on day one as summarized in Table 4.[17]

P-values <0.05 were considered significant.[17] The MADRS score from baseline to four hours after the first dose was p=0.015 and approximately 24 hours after the first dose was p=0.015.[17] On day three and day 11, p=0.015 and p=0.029, respectively.[17] After day 11, the p-values were no longer considered significant with p=0.159 on day 25 and p=0.211 on day 81.[17] MADRS suicidal thoughts item at four hours after the first dose was p=0.002, and approximately 24 hours later, p=0.129 when compared to placebo.[17] On day 81, p=0.143 and was not considered significant.[17] Analysis of the clinician global judgement of suicide risk rating showed a p-value of 0.112 at four hours following the first dose and p=0.150 at 24 hours after the first dose.[17] On day 25, the p-value was 0.922, and p=0.271 during follow-up phase.[17]

The second RCT reviewed was one of the two identically designed phase III programs to examine the antidepressant and antisuicidal efficacy of esketamine.[18] The study identified as ASPIRE I by Fu et al was conducted at 51 sites in Asia, Europe, South Africa, and United States from June 2017 to December 2018 and consisted of 226 adult patients ages 18-64 years old (placebo n=112, esketamine n=114).[18] Computer-generated 1:1 randomization balanced by randomly permuted blocks and stratified by study centers and standard of care antidepressant type was completed.[18] Participants met DSM-5 MDD criteria, had MADRS score > 28 which indicated acute hospitalization due to imminent risk and suicidality was confirmed using MINI.[18] Refer to Table 1 for additional exclusion criteria.[18] The study drug consisted of 600 µL of esketamine (84 mg) that could be reduced to 400 µL for intolerance (56 mg), and the placebo

was a 600 µL formulation with a bittering agent that could be reduced to 400 µL for intolerance.[18] The study consisted of a 24- to 48-hour screening period, followed by 25-day double-blind treatment, then 9-week post-treatment follow-up.[18] Hospitalization and one or more antidepressants were initiated or optimized on the first day.[18] The standard of care oral antidepressant options include monotherapy or antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic, or mood stabilizer).[18] Benzodiazepines were permitted, and three-fourths of the patients received greater than or equal to one concomitant benzodiazepine during the double-blind phase.[18] Within the first two weeks, doses could be adjusted but were maintained thereafter.[18] The primary efficacy endpoint was MADRS score change from baseline to four hours post-dose on day one; a secondary efficacy endpoint was added after rejecting the null hypothesis of the primary endpoint.[18] The secondary endpoint was the change in Clinical Global Impression of Severity of Suicidality Revised version (CGI-SS-r) from baseline to 24 hours following the first dose as summarized in Table 4.[18] The most frequently reported adverse reactions are summarized in Table 3.

The percentage of patients who achieved remission with a MADRS score ≤ 12 with 95% confidence interval (CI) was 9.8% approximately 24 hours following the first dose and 16.1% on day 25.[18] MADRS scores decreased significantly from baseline to 24 hours in both treatment groups with 95% CI, -6.56 to -1.09, and 2-sided P=0.006.[18] CGI-SS-r improved in both groups at the 24-hour endpoint but were not considered statistically significant with 2-sided P=0.107.[18]

The last RCT to be reviewed is the second of the two identically designed phase III programs conducted by Ionescu et al and is identified as ASPIRE II.[19] ASPIRE II was completed at 47 sites in Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, France, Lithuania, Poland, Spain, Turkey, and United States from June 2017 to April 2019.[19] Like the first two

studies reviewed, it utilized computer-generated 1:1 randomization; however, unlike the other two RCTs, the randomization was balanced by randomly permuting four patients per block and stratified by study centers and standard of care antidepressant type.[19] It included 230 adults (placebo n=112, esketamine n=114) ages 18-64 years old that met the following criteria: MDD diagnosis per DSM-5 and confirmed with MINI, and MADRS score >28.[19] Psychiatric comorbidities noted in Table 1 were excluded from the study.[19] The study consisted of a 48-hour screening period, followed by 25-day double-blind treatment, then 9-week post-treatment follow-up.[19] The study drug is 600 µL of esketamine (84 mg) that could be reduced to 400 µL for intolerance (56 mg), and the placebo drug was a 600 µL formulation with a bittering agent that could be reduced to 400 µL for intolerance.[19] Similar to ASPIRE I, hospitalization was required with the initiation or optimization of an antidepressant on day one.[19] The standard of care antidepressant could include monotherapy or antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic, or mood stabilizer) that could be adjusted within the first two weeks and maintained thereafter.[19] A significant difference to note is that benzodiazepines (equivalent dosage to lorazepam ≤ 6 mg per day) were permitted within eight hours before each drug dose administration, none within four hours of the first dose, and within eight hours of day two assessments.[19] The primary efficacy endpoint was MADRS score change from baseline to four hours post-dose on day one.[19] A secondary efficacy endpoint was added after rejecting the null hypothesis of the primary endpoint and was established as the change in CGI-SS-r from baseline to 24 hours following the first dose as summarized in Table 4.[19]

The MADRS score decreased from baseline to 24 hours following the first dose in both treatment groups with a 95% CI: -6.60, -1.11 and a 2-sided p-value of 0.006.[19] The treatment difference with 95% CI in remission (MADRS ≤ 12) between the groups were 11.3% at 24 hours

and 10.2% on day 25.[19] There was a reduction in score with CGI-SS-r but were not statistically significant with 2-sided P=0.379.[19]

Table 3. Summary of most frequently reported treatment-emergent adverse events during double-blind phase[a]

	CANUSO ET AL. (2018)[b]		**FU ET AL. (2020)[c]**		**IONESCU ET AL. (2021)[d]**	
Adverse event	Placebo (n=31)	Esketamine (n=35)	Placebo (n=112)	Esketamine (n=113)	Placebo (n=113)	Esketamine (n=114)
Anxiety	1 (3.2)	6 (17.1)	10 (8.9)	6 (5.3)	7 (6.2)	17 (14.9)
Constipation	0 (0.0)	0 (0.0)	5 (4.5)	15 (13.3)	10 (8.8)	16 (14.0)
Depersonalization or derealization disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (7.9)
Dissociation	4 (12.9)	11 (31.4)	4 (3.6)	33 (29.2)	9 (8.0)	44 (38.6)
Diplopia					0 (0.0)	6 (5.3)
Dizziness	4 (12.9)	12 (34.3)	10 (8.9)	40 (35.4)	21 (18.6)	47 (41.2)
Dry mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.4)	8 (7.0)
Dysgeusia	5 (16.1)	11 (31.4)	11 (9.8)	16 (14.2)	18 (15.9)	29 (25.4)
Euphoric mood	2 (6.5)	4 (11.4)	0 (0.0)	0 (0.0)	1 (0.9)	13 (11.4)
Feeling drunk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	6 (5.3)
Headache	8 (25.8)	11 (31.4)	20 (17.9)	21 (18.6)	26 (23.0)	25 (21.9)
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	6 (5.3)
Hypoesthesia	0 (0.0)	0 (0.0)	2 (1.8)	8 (7.1)	1 (0.9)	12 (10.5)
Hypoesthesia oral					2 (1.8)	7 (6.1)
Increased blood pressure	0 (0.0)	0 (0.0)	6 (5.4)	19 (16.8)	3 (2.7)	7 (6.1)
Insomnia	0 (0.0)	0 (0.0)	7 (6.3)	7 (6.2)	11 (9.7)	9 (7.9)
Nasal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (8.0)	10 (8.8)
Nausea	1 (3.2)	13 (37.1)	15 (13.4)	23 (20.4)	16 (14.2)	38 (33.3)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	6 (5.3)
Paresthesia	1 (3.2)	6 (17.1)	0 (0.0)	0 (0.0)	7(6.2)	23 (20.2)
Paresthesia oral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	14 (12.3)
Postural dizziness	0 (0.0)	0 (0.0)	2 (1.8)	6 (5.3)	0 (0.0)	0 (0.0)
Sedation	2 (6.5)	6 (17.1)	2 (1.8)	7 (6.2)	3 (2.7)	16 (14.0)
Somnolence	2 (6.5)	4 (11.4)	11 (9.8)	21 (18.6)	12 (10.6)	26 (22.8)
Suicidal ideation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.3)	5 (4.4)
Throat irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.5)	6 (5.3)
Vertigo	0 (0.0)	4 (11.4)	1 (0.9)	7 (6.2)	0 (0.0)	7 (6.1)
Vision blurred	0 (0.0)	0 (0.0)	5 (4.5)	10 (8.8)	6 (5.3)	17 (14.9)
Vomiting	0 (0.0)	7 (20.0)	7 (6.3)	8 (7.1)	5 (4.4)	18 (15.8)

[a]Values shown as n (%)
[b]Most frequently reported is defined as ≥ 10% of patients in either treatment group[17]
[c]Most frequently reported is defined as ≥ 5% of patients in either treatment group[18]
[d]Most frequently reported is defined as ≥ 5% of patients in either treatment group[19]

The authors concluded in the phase II study that IN esketamine may result in significantly rapid improvement of depressive symptoms including SI; however, its results showed that depression evaluated with the MADRS score demonstrated no significant improvement past day 25. There was no significant improvement in SI per the MADRS suicidal thoughts item

approximately 24 hours after the first dose and no significant improvement with SI per the clinician global judgement of suicide risk rating.[17] In ASPIRE I and ASPIRE II, the authors concluded MADRS scores decreased significantly from baseline to 24 hours in both treatment groups, but the CGI-SS-r scores used for SI were not considered statistically significant at the 24-hour endpoint.[18,19]

Table 4. Summary of efficacy endpoints

	CANUSO ET AL. (2018)	**FU ET AL. (2020)**	**IONESCU ET AL. (2021)**
Primary efficacy endpoint	MADRS change from baseline to 4 hours post-dose on day 1	MADRS change from baseline to 24 hours post-first dose	MADRS change from baseline to 24 hours post-first dose
Secondary efficacy endpoint	None identified	CGI-SS-r change from baseline to 24 hours post-first dose	CGI-SS-r change from baseline to 24 hours post-first dose

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-SS-r, Clinical Global Impression of Severity of Suicidality Revised version

DISCUSSION

Considering all three RCTs, it can be concluded that IN esketamine was effective for the rapid reduction of depressive symptoms and SI. Although it continued to be effective for depression past the 24-hour endpoint, the data does not indicate significant improvement with SI past the same 24-hour endpoint.[17-19] The findings did not support the PICO question proposed as the effects of IN esketamine in comparison to placebo do not provide SI relief for the weeks necessary for standard of care oral antidepressants to reach therapeutic levels.

There are many studies examining esketamine for depression, but few include patients with active thoughts of suicide due to safety concerns. For ethical reasons, standard of care treatment cannot be withheld in this high-risk patient population. Standard of care treatment for acutely suicidal patients with severe depression is typically hospitalization and the initiation or optimization of oral antidepressants. By not withholding standard of care treatment, it may be difficult to evaluate if the benefits from esketamine trials reflect the benefits of the study drug versus the initiation and optimization of a new oral antidepressant regimen.

Another limitation to consider with the standard of care treatment is the variety of antidepressants that were utilized in the three RCTs. In Canuso et al, sertraline was the most used antidepressant in both treatment groups with 32.3% of use in the placebo group and 22.9% in the esketamine group.[17] ASPIRE I lists the following antidepressant therapies: venlafaxine (24.9%), escitalopram (16.0%), duloxetine (15.6%), mirtazapine (15.6%), quetiapine (14.2%), and approximately 75% of patients received concomitant benzodiazepines.[18] ASPIRE II notes the use of the following medications: quetiapine (28.2%), venlafaxine (28.2%), escitalopram (17.2%), duloxetine (14.5%), sertraline (13.7%), and 67.4% of patients received concomitant benzodiazepines.[19] The lengths of the hospitalization also varied from patient to patient dependent on the need which could in turn skew the data due to increased intensity of therapeutic contact and additional support that could have played a role in minimizing SI.

Esketamine poses several challenges itself. It is difficult to formulate a placebo that could accurately represent the side effects of esketamine i.e., dissociative symptoms.[19] Even with an added bittering agent, functional unblinding could have created some bias affecting clinical decisions.[19] The long-term use of esketamine may also pose possible threats due to its potential to be abused and the potential safety concerns.[20]

Highlighting the number of suicide attempts following the double-blind is necessary as it could impact how future studies are conducted. There were no suicide attempts during the double-blind phase in Canuso et al; however, three suicide attempts in the previously treated placebo group were noted in the follow-up phase and none in the esketamine group.[17] During the ASPIRE I trial, there was one suicide attempt in each group during the double-blind phase.[18] In the follow-up phase, two suicide attempts were documented in the placebo group, and three suicide attempts and one completed suicide were noted in the previously treated esketamine

group.[18] In the ASPIRE II trial, three suicide attempts from each group occurred during the double-blind phase.[19] There were four suicide attempts in the esketamine group during the follow-up phase and one suicide attempt in the placebo group.[19]

CONCLUSION

Even though the three RCTs reviewed support that IN esketamine could fulfill unmet needs of rapid depression and SI de-escalation,[17-19] additional studies need to be completed before it can be concluded that IN esketamine is effective in minimizing SI during the weeks required for standard of care oral antidepressants to become optimal. This author recommends that additional high-quality studies with larger sample sizes be completed before esketamine can be determined to be ineffective or effective for rapid treatment of patients admitted for TRD with SI while waiting for oral antidepressants to reach therapeutic levels.

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