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Spravato© (Esketamine); An old drug with a new indication for major depressive disorder

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According to the World Health Organization, Major depressive disorder (MDD) is a world-wide illness affecting up to 300 million people every day. Approximately 800,000 people commit suicide each year, making it the second leading cause of death in young adults.[1] There are several known and effective therapies available for treating individuals with MDD including: selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine. Second-line therapies such as tricyclic antidepressants and monoamine oxidase inhibitors are also effective, but less widely used due to their side effect profiles. In treatment naive patients who start a first-line antidepressant, 63% will fail to achieve remission.[2] Remission is defined using clinical depression scales to assess severity of symptoms such as the Montgomery-Åsberg Depression Rating Scale (MADRS), with a score of ≤ 12 being indicative of remission, although some sources have also considered a HAM-D score < 7 to be indicative of remission as well.[3] Alternatively, efficacy may be measured via response criteria which is generally defined by a 50% reduction in clinical depression scale scores, such as the MADRS.[4]

In treatment-experienced patients who have tried one or more antidepressant therapies, 30% will fail to achieve remission.[5] In general, patients who have tried at least two different antidepressant regimens and who failed to achieve a clinical improvement in their depressive symptoms on both attempts are classified with treatment-resistant depression (TRD).[6] The current prevalence of TRD is estimated to be between 7-35%.[7] Additionally, patients classified as treatment-resistant are at a higher risk for anxiety disorders, personality disorders, a poorer quality of life, and suicide compared to responsive patients.[8] Compared to responsive MDD patients, TRD patients have substantially higher healthcare costs and total number of medical visits (about twice that of responsive MDD patients). The total medical costs for a TRD patient are approximated to be almost $19,000 directly after the patients first year on antidepressant therapy, compared to almost $11,000 for a responsive MDD patient.[7]

On March 5th, 2019 the FDA approved Esketamine (SPRAVATO©) with the specific indication of TRD via intranasal (IN) administration. Esketamine separates itself from previous agents in that it is the first FDA approved antidepressant in a novel class. All current antidepressants on the market exert their effects anywhere from one week to a month after therapy initiation. Esketamine, however, demonstrated an onset of action in a matter of hours to days in phase III clinical trials. Thus, esketamine may fill a clinical need for an antidepressant with a more rapid onset of efficacy. This article aims to evaluate current clinical evidences on the efficacy and safety of esketamine in the management of treatment-resistant depression.

Pharmacology

Mechanism of Action

Esketamine is the S-enantiomer of ketamine, a drug that, until recently, is used primarily as a general anesthetic. Esketamine exerts its effects principally through negative allosteric modulation of the ionotropic N-methyl-D-aspartate (NMDA) receptor on glutamatergic neurons.[9] Although the precise mechanism by which esketamine/ketamine generates its antidepressant activity is unknown, clinical research in recent years has unveiled a rapid antidepressant response within as little as two hours and activity that persists for up to two weeks when given intravenously.[10, 11] Since the half-life of esketamine is very short, lasting only a few hours, this would suggest that the long-term antidepressant activity is not mediated directly through NMDA blockade alone.[9] Thus, blockade of NMDA receptors in the short term may induce downstream plastic changes in neuronal structure that contribute to long term antidepressant effects. [12]

Pharmacokinetic properties

Esketamine, when administered nasally, has a mean bioavailability of about 48% with peak plasma concentrations achieved in 20 to 40 minutes after administration. All pharmacokinetic parameters are summarized in **Table 1**.

Esketamine is metabolized mainly via CYP3A4 and CYP2B6, and to a lesser extent CYP2C9 and CYP2C19, to its active metabolite noresketamine. This metabolite has a lower affinity for the NMDA receptor than the parent drug.[9] Noresketamine is then glucoronidated through cytochrome dependent path-

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ways. Esketamine exhibits a biphasic elimination with a rapid initial clearance after the first 2 to 4 hours with an average half-life that ranges from 7 to 12 hours. Noresketamine follows similar elimination kinetics, being metabolized through CYP-dependent pathways and glucuronidation. Noresketamine elimination, likewise, follows a biphasic clearance with a rapid decline in plasma concentration seen in the first 4 hours and a mean terminal half-life of 8 hours. The inactive glucoronidated metabolites of noresketamine are excreted renally (≥78%) with less than 2% excreted in the feces. Esketamine was reported to have induction effects on CYP3A4 and CYP2B6, but does not produce any clinically significant drug-drug interactions when given concomitantly with major CYP3A4 and CYP2B6 substrates such as midazolam and bupropion. In phase I clinical trials, patients with moderate hepatic dysfunction (Child-Pugh score of 7-9) had a higher AUC and mean half-life compared to patients without liver dysfunction.[9, 13] It is for this reason that esketamine is not recommended for use in patients with severe liver dysfunction (Child-Pugh score ≥ 10) due to a lack of data in this patient population.9 No dosage adjustments are needed for individuals with mild to severe renal impairment (creatinine clearance [CrCL] < 80 ml/min), though, in clinical trials, esketamine did exhibit higher plasma concentrations and AUC in this patient population.[9, 14] There were no clinically meaningful variances in esketamine pharmacokinetics between the patient specific factors of age, sex, or weight.[9]

Table 1 | Esketamine Pharmacokinetics[9]

Parameters	Value
Absorption (intranasal)	
T_{max}[a]	20-40 minutes
Bioavailability	48%
Distribution	
V_d[b]	709 L
Protein binding	43-45%
Metabolism	
Liver Cytochrome p450	CYP3A4, CYP2B6, CYP2C9, CYP2C19
Active Metabolite	Noresketamine
Elimination	
Renal Excretion	≥ 78%
Fecal Excretion	2%
Total Body Clearance	89 L/h
$T_{1/2}$[c]	7.1 hours

[a]Time to maximum concentration; [b]Volume of distribution; [c]Half-life

Clinical Trials

Esketamine (SPRAVATO©) was approved by the FDA as a treatment for TRD based on four phase III randomized controlled trials under New Drug Application 211243. Three of the RCTs TRD3001 (TRANSFORM-1), TRD3002 (TRANSFORM-2), and TRD3005 (TRANSFORM-3) were short-term parallel-group RCTs.[15-17] TRD3004 (SUSTAIN-1) studied the long-term efficacy of esketamine for TRD.[18] These four phase III trials evaluated the safety and efficacy of esketamine via intranasal administration for the treatment of TRD compared to an active-placebo group.[15-18] Additionally, two phase II trials were relevant in establishing safety and efficacy of esketamine nasal spray for TRD, Study SUI2001 and Study 2003 (SYNAPSE).[19, 20] The following section will highlight the phase II and III RCTs. A summary of adverse events from these trials will also be discussed in the "Adverse Events and Precautions" section of this article. The results of the primary and secondary endpoints of the phase III clinical trials are summarized in **Table 2** and **Table 3,** respectively.

Phase II Trials:

Daly et al. conducted a fixed-dose randomized, placebo-controlled, sequential parallel comparison design, dose-response trial with the objective to assess dosage regimens of esketamine to be carried forward to phase III clinical trials. (Study 2003 SYNAPSE). Individuals with TRD, defined as inadequate response to two or more antidepressants with at least one inadequate response in the current depression episode, were included. Subjects with moderate to severe symptoms of depression, measured using the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) scoring tool (Score >10 = moderate to severe depression), were randomized to receive intranasal esketamine 28 mg, 56 mg, or 84 mg or placebo twice weekly, in addition to standard of care oral antidepressant therapy, for a two week period. The primary outcome was the mean change in MADRS total score from baseline line vs placebo.[19]

Similarly, Canuso et al. conducted a phase II double-blind, randomized, placebo-controlled, multicenter trial with the objective of establishing efficacy and safety of intranasal esketamine for rapid reduction of MDD symptoms, such as suicidal ideation, for patients at imminent risk of suicide. (Study SUI2001). Subjects were randomized to receive double-blind treatment of intranasal esketamine 84 mg or placebo, with concomitant standard of care oral antidepressant treatment, dosed twice weekly for 4 weeks (25 days total). The SUI2001 trial's primary efficacy endpoint was the mean change in MADRS score from baseline four hours after the dose was administered on day one.[20]

The SYNAPSE trial's results suggested a dose-response relationship in which higher doses of intranasal esketamine may have superior efficacy. This hypothesis influenced the design of the TRANSFORM and SUSTAIN-1 trials, particularly the TRANSFORM-1 trial, in directing the dosages of the esketamine treatment groups in order to investigate efficacy trends at increasing dosages administered twice weekly. The SUI2001 trial presented supportive evidence for esketamine efficacy at proximate post-treatment time points, which directed efficacy data collection time points in the subsequent phase III trials.[19, 20]

Phase III Trials

The four phase III clinical trials used to evaluate esketamine (TRANSFORM trials and SUSTAIN-1 trial), all had similar inclusion and exclusion criteria. The inclusion criteria for the TRANSFORM-1, TRANSFORM-2, and SUSTAIN-1 trials were the following: Age 18 to 64 years, MDD diagnosis in accordance with the Diagnostic and Statistical Manual of Mental Disorders 5 criteria (DSM-5), an Inventory of Depressive Symptomatology-

Clinician rated 30 (IDS-C30) ≥ 34, an inadequate response to antidepressant treatment (inadequate response was measured using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire [MGH-ATRQ]), taking a different oral antidepressant treatment, from previously failed one, for at least the previous 2 weeks, and a MADRS score ≥ 28. Likewise, the exclusion criteria for these three phase 3 trials were: inadequate treatment response to esketamine or ketamine, inadequate treatment response to all of the standard of care oral antidepressants used (duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]), history of vagal nerve stimulation (VNS) or deep brain stimulation (DBS), DSM-5 diagnosis of psychotic disorder or MDD with psychotic features, DSM-5 diagnosis of substance use disorder, history of adequate ECT treatment (adequate treatment defined as at least seven treatments with unilateral/bilateral ECT), DSM-5 diagnosis of intellectual disability, and homicidal or suicidal ideation (defined as intent to act within six months prior to the start of the screening/prospective observational phase). The TRANSFORM-3 trial had the same inclusion/exclusion criteria as the previously mentioned trials with a few exceptions. Differing inclusion criteria included: Age ≥ 65, IDS-C30 score ≥ 31, and a MADRS score ≥ 24. Additional exclusion criteria included: history of hallucinogen-related use disorder, Mini Mental State Examination (MMSE) score < 25 or < 22 if less than high school education, neurodegenerative disorder or evidence of mild cognitive impairment, electrocardiogram abnormalities, and history of uncontrolled hypertension, pulmonary insufficiency, seizures, or cerebral/cardiac vascular disease.

TRANSFORM-1

TRANSFORM-1 was a fixed-dose, randomized, parallel-group, double-blind, active-controlled, multicentered phase III clinical trial with the objective of evaluating the efficacy, safety and tolerability of fixed-doses of intranasal esketamine adjunctive to new oral antidepressant standard of care for patients with TRD. Notable baseline characteristics of subjects included: mean age of 46.3 years, 70.3% female, and 76.5% Caucasian. Subjects were enrolled from the United States (39.5%), Belgium, Brazil, Canada, Estonia, France, Hungary, Mexico and Slovakia. More patients (48%) in the 84 mg esketamine group had a history of failing 3 or more antidepressants vs 30% in the 56 mg esketamine group and 41% in the placebo group.[15]

Subjects were randomized in a 1:1:1 ratio to self-administer intranasal esketamine 56 mg (n=111), esketamine 84 mg (n=97) or placebo (n=107) twice weekly for four weeks during a double-blind induction phase. Any patient that received at least one dose of any drug in the double-blind treatment phase that chose to not participate in, or was otherwise ineligible for, the SUSTAIN-1 trial (discussed in the SUSTAIN-1 section) entered into an additional 24-week posttreatment follow-up phase to monitor for long term adverse event outcomes (see Adverse Events and Precautions). All subjects were provided with an additional two week supply of oral antidepressant therapy during the posttreatment phase to prevent interruption of standard of care. Utilization of this oral antidepressant therapy in the posttreatment phase, including beyond the initial two week supply, was left to the clinical discretion of the investigator or the subject's treating physician. At the start of the double-blind treatment phase, all treatment groups were newly initiated on one of four standard of care oral antidepressant regimens (duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]). The primary efficacy endpoint was change from baseline in mean MADRS score on day 28 of the double-blind induction phase. Secondary efficacy endpoints included: percentage of subjects who achieved ≥ 50% reduction in MADRS score from baseline on day 28, percentage of subjects in remission (defined as MADRS ≤ 12) on day 28, change from baseline in Clinical Global Impression-Severity (CGI-S), Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and EuroQol-5 Dimension-5 Level (EQ-5D-5L) on day 28.[15]

The primary efficacy endpoint, the mean change from baseline in MADRS score vs placebo on day 28 of the double-blind induction phase was statistically significant at –4.1 in the esketamine 56 mg group (95% CI –7.67 to –0.49; p=0.027) and not statistically significant at –3.2 in the esketamine 84 mg group (95% CI –6.88 to 0.45; p=0.088). The percentage of subjects in remission (MADRS ≤ 12) on day 28 was 36%, 38.8% and 30.6% in the esketamine 56 mg, 86 mg and placebo groups respectively. The percentage of subjects that achieved response (MADRS ≥ 50% reduction from baseline) on day 28 was 54.1%, 53.1% and 38.9% in the esketamine 56 mg, 86 mg and placebo groups respectively. Due to the lack of statistical significance vs placebo in the 84 mg esketamine group, all endpoints for the 56 mg esketamine group were evaluated independently of the initially planned fixed-sequence testing protocol, thus all analyses for the esketamine 56 mg arm are considered nominal.[15]

TRANSFORM-2

The TRANSFORM-2 was a randomized, double-blind, active-controlled, multicenter study with the objective to assess the efficacy, safety, and tolerability of flexible doses (as opposed to the fixed-doses in TRANSFORM-1) of intranasal esketamine adjunctive to new standard of care oral antidepressant therapy in subjects with TRD. Notable baseline characteristics across all treatment groups were a mean age of 45.7 years, 62.1% female, and 93.3% Caucasian. Subjects were enrolled from the United States (40.2 %) Czech Republic, Germany, Poland, and Spain.[16]

Subjects were randomized in a 1:1 ratio to receive, under their health care provider's (HCP) discretion, flexibly dosed intranasal esketamine 56 mg to 84 mg (n=98) or intranasal placebo (n=99) twice weekly for four weeks during a double-blind treatment phase. Any patient that received at least one dose of any drug during the double-blind treatment phase that chose to not participate in, or was otherwise ineligible for, the SUSTAIN-1 trial (discussed in the SUSTAIN-1 section) entered into an additional 24-week posttreatment follow-up phase to monitor for long term adverse event outcomes (see Adverse Events and Precautions). All subjects were provided with an additional two week supply of oral antidepressant therapy during the posttreatment phase to prevent interruption of standard of care. Utilization of this oral antidepressant therapy in the follow-up phase, including beyond the initial two week supply, was left to the clinical discretion of the investigator or the subject's treating physician. At the start of the double-blind treatment phase, subjects received newly initiated standard of care antidepressants of either duloxetine, escitalopram, sertraline, or venlafaxine XL. The primary efficacy endpoint was change from baseline in MADRS score on day 28 at the end of the double-blind treatment phase. Secondary efficacy endpoints included: Percentage of patients with clinical response on day 2 and day 28, change from baseline in the Sheehan Disability Scale (SDS), PHQ-9, GAD-7, EQ-5D-5L and CGI-S, percentage of subjects who achieved ≥ 50% reduction in MADRS score from baseline on day 28, percentage of subjects in remission (MADRS

Table 2 | Primary Endpoints from Intranasal Esketamine Phase III Trials[15-18]

Trial	Mean Change in MADRS[a] (Baseline to Day 28)	Difference vs Placebo (95% CI)	p-Value
TRANSFORM-1[15]			
56 mg INE[b] + OAD[c]	-19 ± 13.86	-4.1 (-7.67 to –0.49)	0.027*
84 mg INE + OAD	-18.8 ± 14.12	-3.2 (-6.88 to 0.45)	0.088
INP[d] + OAD	-14.8 ± 15.07	-	-
TRANSFORM-2[16]			
56-84 mg INE + OAD	-21.4 ± 12.32	-4.0 (-7.91 to –0.64)	0.020
INP + OAD	-17 ± 13.88	-	-
TRANSFORM-3[17]			
28-56-84 mg INE + OAD	-10 ± 12.74	-3.6 (-7.20 to 0.07)	0.029
INP + OAD	-6.3 ± 8.86	-	-
Trial	**Median Time to Relapse is Stable Remitters (Days)**	**Hazard Ratio (95% CI)**	
SUSTAIN-1[18]			
56-84 mg INE + OAD	Not estimable†	0.49 (0.29 to 0.84)‡	
INP + OAD	273	-	

[a]Montgomery-Åsberg Depression Rating Scale; [b]Intranasal Esketamine; [c]Oral Antidepressant; [d]Intranasal Placebo

*84 mg was not significant, 56 mg could not be formally evaluated, and the 2-sided p-value for this dose is considered to be nominal
†Not estimable due to not having sufficient events to meet the threshold for 50% on the Kaplan-Meier curve
‡HR and CI for this outcome were calculated as a weighted estimate utilizing gsDesign and mvtnorm package in R

≤ 12) on day 28, and percentage of subjects that achieved a response (defined as SDS ≤12 and Individual item score each ≤ 4) on day 28.[16]

The primary efficacy endpoint, the mean change from baseline in MADRS score on day 28 in the 56-84 mg flexible dose esketamine group compared to placebo was statistically significant at –4.0 (95% CI –7.31 to –0.64). By day four of the double-blind phase 45.8% (n=49) of subjects had escalated to an 84 mg esketamine dose and 66.7% (n=71) of subjects had escalated to 84 mg dose by day 28 at the end of the trial. Notably, in an exploratory analysis, the mean change from baseline in MADRS score at 24 hours post-dose in the esketamine group compared to placebo was statistically significant at –3.3 (95% CI −5.75 to −0.85; p= 0.020). The percentage of subjects in remission on day 28 was 48.2% and 30.3% in the esketamine and placebo groups respectively. The percentage subjects that achieved a response was 57.0% and 39.5% in the esketamine and placebo groups respectively. Comparatively, the percentage of subjects that achieved a MADRS score reduction of ≥ 50% from baseline on day 28 (the criteria for response in all other phase III trials) was 63.4% and 49.5% in the esketamine and placebo groups respectively. It is important to note that compared to the placebo arm, the esketamine arm had a slightly higher number of dropouts, 14% (n=18) in the esketamine group vs 10% (n=12) in the placebo group. The higher number of dropouts in the esketamine group was largely due to a higher adverse event rate, comprising 50% (n=9) of the cited reasons for subject withdrawal vs 8.3% (n=1) in the placebo group. See the Adverse Events and Precautions section for details on adverse events.[16]

TRANSFORM-3

TRANSFORM-3 was a randomized, double-blind, active-controlled, multicenter trial with the objective of assessing the efficacy, safety and tolerability of flexible doses of intranasal esketamine adjunctive to new standard of care antidepressant treatments in elderly subjects with TRD. Notable baseline characteristics across all treatment groups were a mean age of 70 years, 85% female, and 94.9% Caucasian. Participants were enrolled from the United States (51.1%) with the remainder being enrolled across Belgium, Brazil, Bulgaria, Finland, France, Italy, Lithuania, Poland, South Africa, Spain, Sweden, and the United Kingdom.[17]

Subjects were randomized in a 1:1 ratio to receive, under their HCP's discretion, flexibly dosed intranasal esketamine 28 mg, 56 mg and 84 mg (n=62) or intranasal placebo (n=60), twice weekly for four weeks during a double-blind treatment phase. Any patient that received at least one dose of any drug during the double-blind treatment phase entered into an additional two-week posttreatment follow-up phase for the purpose of monitoring for long term adverse event outcomes (see Adverse Events and Precautions). All subjects were provided with an additional two week supply of oral antidepressant therapy during the posttreatment phase to prevent interruption of standard of care. Like the previous trials, duloxetine, escitalopram, sertraline, and venlafaxine XL were used as newly initiated standard of care antidepressants. The primary efficacy endpoint was change from baseline in MADRS score on day 28 at the end of the double-blind treatment phase. Secondary efficacy endpoints included: Change from baseline in the EQ-5D-5L and the CGI-S on day 28, percentage of subjects who achieved ≥ 50% reduction in MADRS score from baseline on day 28, and percentage of subjects in remission (MADRS ≤ 12) on day 28. The primary efficacy endpoint, the mean change from baseline in MADRS score on day 28 in the 28-56-84 mg flexible dose esketamine group compared to placebo was found to be not statistically significant at –3.6 (95% CI –7.20 to 0.07). The percentage of subjects in remission on day 28 was 15.5% and 6.3% in the esketamine and placebo groups respectively. The per-

Table 3 | Secondary Endpoints from Intranasal Esketamine Phase III Trials[15-18]

Trial	Percentage of Responders (%) (Baseline to Day 28)	Percentage of Remitters (%) (On Day 28)
TRANSFORM-1[15]		
56 mg INE[a] + OAD[b]	54.1†	36.0†
84 mg INE + OAD	53.1†	38.8†
INP[c] + OAD	38.9	30.6
TRANSFORM-2[16]		
56-84 mg INE + OAD	57.0†	48.2†
INP + OAD	39.5	30.3
TRANSFORM-3[17]		
28-56-84 mg INE + OAD	23.9†	15.5†
INP + OAD	12.5	6.3
Trial	**Median Time to Relapse is Stable Responders (Days)**	**Hazard Ratio (95% CI)**
SUSTAIN-1[18]		
56-84 mg INE + OAD	635.0	0.30 (0.16 to 0.55)
INP + OAD	88.0	-

[a]Intranasal Esketamine; [b]Oral Antidepressant; [c]Intranasal Placebo

†No statistical analysis vs placebo performed

centage of subjects that achieved a MADRS score reduction of ≥ 50% from baseline on day 28 was 23.9% and 12.5% in the esketamine and placebo groups respectively.[17]

SUSTAIN-1

The SUSTAIN-1 trial was a randomized, double-blind, active-controlled, multicenter trial with the objective of evaluating the efficacy of intranasal esketamine adjunctive to new standard of care oral antidepressant in delaying relapse of depressive symptoms in subjects with TRD. It is the only long-term phase III trial conducted (92 weeks) for intranasal esketamine. Patient were eligible for the SUSTAIN-1 trial if they had completed the double-blind treatment phases of either TRANSFORM-1 or TRANSFORM-2 and demonstrated response criteria (≥50% reduction in the MADRS score or an SDS total score <= 12 and individual item scores each <= 4 from baseline on day 28). Alternatively, subjects could be enrolled through direct-entry if they completed a separate four-week open-label intranasal induction phase and achieved response criteria (defined as a MADRS score reduction ≥ 50% from baseline on day 28 of the trial). Baseline characteristics across all treatment arms were a mean age of 46.1 years, 64.8% female, and 79.7% Caucasian. The majority of subjects were enrolled in centers within the United States (27%), Poland (18.7%), the Czech Republic (14%), and Brazil (9.1%), with the rest enrolled in various other countries such as Belgium, Canada, Estonia, France, Germany, Hungary, Italy, Mexico, Slovakia, Spain, Sweden, and Turkey.[18]

The SUSTAIN-1 trial consisted of four phases: the previously mentioned four-week open-label induction phase for those that did not participate in the TRANSFORM 1 or 2 trials, a 12-week open-label dose optimization phase, a double-blind maintenance phase (of variable duration), and a two-week follow-up phase. All esketamine treatments were adjunctive to new standard of care oral antidepressant therapy (duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) throughout all phases of this study.[18]

Once the induction phase was completed, the subjects entered the 12-week dose optimization phase were subjects received either 56 mg or 84 mg of intranasal esketamine once weekly for four weeks. Starting on week five, subjects received esketamine once weekly or bi-weekly, based on severity of depressive symptoms, for the remaining eight weeks. At the end of the dose optimization phase, in order to be randomized to the maintenance phase, subjects need to be classified as either stable remitters (defined as having a MADRS ≤12 for three of the last four weeks of the dose optimization phase) or stable responders (defined as MADRS score reduction ≥50% from baseline in the last two weeks of the dose optimization phase). At the beginning of maintenance phase, those that met the previously mentioned criteria were randomized in a 1:1:1 ratio to receive intranasal esketamine 56 mg or 84 mg once weekly or bi-weekly (n=139 total; 90 remitters, 62 responders) or intranasal placebo (n=177 total, 86 remitters, 59 responders), based on depressive symptoms. The subject continued in the maintenance phase for 92 weeks or until they relapsed (defined as a MADRS score ≥ 22 for two consecutive assessments or a hospitalization/serious clinical event occurred). The primary efficacy endpoint was time to first relapse in stable remitters during the maintenance phase. Secondary efficacy endpoints included: time to first relapse in stable responders during the maintenance phase, and change from baseline in stable remitter/responder clinical assessment scores during the maintenance phase (MADRS, PHQ-9, CGI-S, GAD-7, EQ-ED-5L, and SDS). The primary efficacy endpoint, the median time to relapse in stable remitters who were treated with 56-84 mg esketamine during the maintenance phase vs placebo had a statistically significant hazard ratio of 0.49 (95% CI 0.29 to 0.84). In subjects who achieved stable remission in the 56-84 mg esketamine treatment group, 44% (n=40) were dosed at 56 mg of esketamine at the start

of the maintenance phase, while 55.6% (n=50) were dosed at 84 mg of esketamine. Median time to relapse in the stable responder esketamine group vs placebo was statistically significant with a hazard ratio of 0.30 (95% CI 0.16 to 0.55).[18]

Adverse Events and Precautions

From both the phase II and phase III clinical trials, the most common adverse events of esketamine were gastrointestinal and neurological in the form of nausea, dizziness, somnolence, and vertigo. More serious adverse events took the form of transient blood pressure increases and dissociative disorders. All adverse effects discussed in this section had their incidence pooled from all phase III clinical trials. When reported, incidences of nausea, dizziness, somnolence, vertigo, and dissociation occurred in ≥ 10% of the esketamine treated patients and at least twice the rate of placebo in each respective phase III study. In phase III clinical trials, 49-61% of esketamine treated subjects developed altered consciousness, hypersomnia, or somnolence. Overall, approximately 93% of subjects treated with intranasal esketamine, across all phase III clinical trials, experienced at least one adverse effect of sedation, dizziness and/or dissociation. A summary of adverse events in each phase III clinical trial is presented in **Table 4**.[9, 15-18]

Dissociative symptoms were among the most frequent of the adverse effects reported in phase III clinical trials. Symptoms of delusional perception, depersonalization, derealization, diplopia, dysesthesia, feeling cold or hot, hallucination (auditory or visual), hyperacusis, photophobia, altered sense of time or space, and visual impairment were reported at 61% to 75% in esketamine treated patients.[9]

Additionally, the esketamine treated subjects (8-17%) reported significant increases the systolic and diastolic blood pressure, compared to placebo. Systolic BP increased by up to 40-mmHg in the esketamine group and appeared to be transient, peaking around 40 minutes after administration and returning to baseline after 1.5-4 hours. In general, blood pressure increases did not attenuate with repeated administrations. Thus, patients may still exhibit a blood pressure increase even if they have not with previous administrations. Intranasal esketamine is contraindicated in patients where an increase in blood pressure or intracranial pressure presents a serious risk such as: aneurysmal vascular disease, arterial malformation, or history of intracranial hemorrhage. Caution should be used in initiating intranasal esketamine in patients with blood pressure > 140/90 mmHg prior to administration and blood pressure should be continually assessed. In patients with a history of hypertensive encephalopathy, even small doses of esketamine increases the risk of recurrent encephalopathy, thus more intensive monitoring should be utilized.[9]

Off-label use/abuse of ketamine has also been associated with ulcerative or interstitial cystitis. While there were no reported cases of interstitial/ulcerative cystitis in any clinical trial, esketamine treated patients had a relative 6-fold higher incidence of pollakiuria associated with urinary tract infections (3% in esketamine treated patient's vs 0.5% in placebo). It is thus advised to monitor for urinary tract infections over the course of therapy with intranasal esketamine and refer patients to the appropriate provider when clinically appropriate.[9]

A small number of participants dropped out of the DRiVESaFe trial (phase I clinical trial, that evaluated the effects of intranasal esketamine treatment on driving performance) due to serious adverse events. Therefore patients should be instructed to not engage in activities that require mental alertness such as driving or operating machinery until one full day after administration.[9, 21] Because of increased risk of prolonged sedation patients who take esketamine should be monitored for at least 2-hours post-administration and be assessed by their health care provider for clinical stability before leaving the care of the provider. Additionally, patients should be monitored more closely if they are prescribed concomitant drug therapy known to cause CNS depression.[9]

Pregnancy and Lactation

Although there is currently no published research on the safety of esketamine in pregnancy in human clinical trials, results of other non-clinical animal studies investigating NMDA antagonists in pregnancy suggest esketamine may pose a risk of fetal harm. Brambrink et al demonstrated that when female perinatal rhesus monkeys were given intravenous ketamine in their third trimester, there was an increase in fetal neuroapoptosis.[22] Paule et al correlated this phenomenon with long-lasting cognitive deficits.[23]

Thus, due to insufficient human data and published data on animal studies, esketamine is not recommended in pregnancy or breastfeeding women. Potential candidates for intranasal esketamine should always be screened for pregnancy and advised against use if pregnant. If a woman becomes pregnant, esketamine should be discontinued immediately to reduce potential harm to the fetus.[9]

Abuse Potential and REMS

Esketamine is a schedule III-controlled substance and the S-isomer of ketamine, a drug known for its off-label recreational use as a dissociative agent, which many users associate with a high. Esketamine exhibits the same dissociative properties and thus may increase the risk of abuse or diversion in patients with a history of recreational drug use or those diagnosed with substance use disorder. In order to assess the abuse potential of intranasal esketamine administration, a cross-over, double-blind clinical trial

was conducted using intranasal esketamine (84 mg and 112 mg) as the intervention vs intravenous ketamine (0.5 mg/kg infused over 40 minutes) as the active control vs placebo in polydrug users (n=34). The efficacy endpoints were the mean "Drug Liking at the Moment" score and the mean "Take Drug Again" score. The endpoints for both the intranasal esketamine group and the intravenous ketamine group showed similar scores that were significantly higher vs placebo. If taken frequently and for long periods of time, ketamine will produce withdrawal symptoms such as craving, fatigue, poor appetite, and anxiety. Thus, it is likely that similar withdrawal symptoms would occur if esketamine was abused in a similar fashion. However, no withdrawal symptoms were recorded up to four weeks after stopping esketamine treatment.[9]

In order to mitigate the potential risk of sedation, dissociation and abuse, intranasal esketamine (SPRAVATO©) is only available through a restricted REMS program. In order for SPRAVATO© to be administered, the healthcare setting must be certified to only dispense and administer to patients enrolled in the program. Additionally, patients must be under direct observation and monitoring of an HCP for at least two hours during and after each administration. Lastly, pharmacies that dispense SPRAVATO© must be certified to only dispense to healthcare settings also certified.[24]

Dosing and Administration

The SPRAVATO© nasal spray applicator administers two sprays, one spray in each nostril, for a total of 28 mg of esketamine per device. (E.g. For a 56 mg dose, two devices are required). A five-minute period should elapse between device use. The recommended dosing schedule is the following: For weeks one to four administer 56 mg or 84 mg twice per week, except the max starting dose (Day 1) must be 56 mg. For weeks five to eight, administer 56 mg or 84 mg once weekly. For week nine onward, administer 56 mg or 84 mg once weekly or bi-weekly. If a dose is missed or depression worsens, consider escalating in frequency if schedule permits.[9]

Due to concerns with transient blood pressure increases in clinical trials, the patient's blood pressure should be measured prior to administration. If blood pressure is > 140/90 mmHg, the provider should weigh the risks and benefits of administration. Patients should be advised to avoid food for two hours and fluids 30 minutes prior to administration due to the risk of nausea and vomiting. Patients that require intranasal corticosteroids should administer these medications one hour prior to administration.

Table 4 | Adverse Effects[9,15-18]

Adverse Event	INE[a] + OAD[b]	INP[c] + OAD
TRANSFORM Trials		
Headache	13-21%	3-17%
Nausea	18-32%	5-11%
Vertigo	11-26%	2-3%
Dizziness	21-28%	5-9%
Dissociation	13-28%	2-4%
Somnolence	13-21%	6-12%
SUSTAIN-1		
Headache	18%	10%
Nausea	16%	<1%
Vertigo	25%	6%
Dizziness	20%	5%
Dissociation	35%	0%
Somnolence	21%	3%

[a]Intranasal esketamine; [b]Oral antidepressant; [c]Intranasal placebo

Clinical Implications

Intranasal esketamine presents a novel avenue for the treatment of TRD in patients who have exhausted traditional therapy options. The TRANSFORM-2 trial of flexibly dosed esketamine distinguished itself by showing superiority at improving MADRS scores at all time points throughout the four weeks, including within 24 hours after first administration. The rapid onset of action at 24 hours post-administration is particularly notable considering there is a lack of approved therapies for TRD that demonstrate a comparable effect. This evidence is encouraging, however, the active control group also demonstrated a similar onset of action with a mean MADRS score change of -5.0 (vs -8.3 in the esketamine group) at the post-dose 24 hour time point. Thus it is questionable, with such a small effect size, whether the rapid onset of effect seen in the esketamine treatment group is attributed solely to esketamine, rather than it producing an additive effect in addition to the effect of the oral antidepressant. TRANSFORM-2 was the only trial of three very similar four-week trials (TRANSFORM-1 and 3) to show a non-nominal significant reduction in the primary endpoint vs the active-control group (MADRS change from baseline vs placebo on day 28).[15-17] Additionally, while the esketamine arm in TRANSFORM-2 showed superiority at the early time point of day two, it maintained about the same effect size at all other time points, failing to show further differential beyond the initial. When this evidence is put into con-

text with esketamine's abuse potential and the barriers to adherence the REMS program presents, it seems questionable whether or not the current label-recommended dosing schedule of twice weekly administrations is practical compared to a single dose at the initiation of normal oral antidepressant therapy.[16]

The SUSTAIN-1 trial was the only other phase III trial that showed superiority to placebo for its primary endpoint. However, this trial is unorthodox in that it was a withdrawal study to assess relapse rates over a period of over 600 days. By the second week the esketamine arm had distinguished itself by having a statistically significant reduction in cumulative probability of relapse rate compared to the placebo. For comparison, according to an FDA meta-analysis in clinical studies that investigate maintenance-of-effect and relapse rates in MDD subjects treated with conventional antidepressant regimens vs placebo, significance differences in relapse rates are generally achieved approximately one month into the maintenance phase.[25] The speed at which the esketamine arm separated itself from control may be the main benefit of this new therapy. However, there are several factors that may have biased this apparent rapid separation. Many of the subjects in the SUSTAIN-1 trial were exposed to an open-label phase of esketamine treatment prior to the maintenance phase. Considering esketamine has very notable side effects, such as sedation, dizziness and dissociation, that occur at very high frequencies (with 93% of subjects experiencing at least one of these per administration across all phase III trials), and do not attenuate with repeated dosing, it is probable that subjects may notice a change in ADE when switching among treatment groups. Ergo, subjects randomized to placebo plus oral antidepressant arms would be able to discern that they had been switched, thus increasing the relapse rate compared to the treatment group.[18]

Additionally, esketamine is approved for TRD only as an augmentation agent to conventional antidepressants. Currently, there are several other atypical drug therapies available for TRD through augmentation. These therapies include: lithium, thyroid hormone, buspirone, and/or atypical antipsychotics (i.e. aripiprazole, olanzapine, quetiapine, risperidone). The practice of augmenting antidepressant regimens with atypical therapies has been widely used, albeit with varying degrees of success outside of well controlled studies. In general, augmentation tends to increase the complexity of regimens and introduces additional side effects.[26] A recent meta-analysis demonstrated that patients who took augmented antidepressant regimens were more likely to discontinue than patients taking antidepressant regiments with placebo.[27] Thus, it is probable esketamine may present patients with similar difficulties, especially with the REMS program. Conversely, because esketamine targets depression from a novel mechanism, its side effect profile differs vastly from current augmentation regimens, creating a possible new avenue for treatment when other regimens fail due to a patient intolerance.

The only other augmentation therapy approved for TRD is Symbyax©, a combination product of Fluoxetine and Olanzapine, and while it's onset of efficacy in TRD is faster compared to conventional antidepressant monotherapy, it is slower than the onset of esketamine when looking at the trials for each of them.[28] No head to head studies have been completed to compare these two therapies. Based on the phase III clinical evidence, esketamine may be a faster working antidepressant compared to current therapy on the market, with limited data to support an onset of action that takes effect within hours.[9]

Conclusion

Intranasal esketamine, recently FDA approved offers a new class of medication for the indication of TRD. Clinical trials showed that intranasal esketamine 56 mg to 84 mg may be an alternative or additional therapy option for patients with TRD. Though the trials show mixed results they are consistent with showing that esketamine has a potentially faster rate of onset to relieve depressive symptoms. Esketamine may also decrease relapse rates compared to conventional oral antidepressant therapy alone. With mixed efficacy results, potential abuse risk, and a varied side effect profile, esketamine, for now, will likely be reserved for those TRD patients with no other options.

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