Spravato™ (esketamine) CIII nasal spray

THE FIRST AND ONLY NMDA RECEPTOR ANTAGONIST APPROVED IN CONJUNCTION WITH AN ORAL ANTIDEPRESSANT FOR TREATMENT-RESISTANT DEPRESSION (TRD) IN ADULTS.[1]

SHE THOUGHT HER DEPRESSION SYMPTOMS WOULD NEVER GET BETTER

A NEW DAY BEGINS WITH SPRAVATO™

Learn more at SPRAVATOHCP.com.

Device as shown does not depict actual position for administration.

Indication

SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

SPRAVATO™ is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO™ as an anesthetic agent have not been established.

Important Safety Information

WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).**
- **Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO™ prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).**
- **SPRAVATO™ is only available through a restricted program called the SPRAVATO™ REMS (5.4).**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO™ is not approved for use in pediatric patients (5.5).**

CONTRAINDICATIONS

SPRAVATO™ is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or any of the excipients

NMDA=N-methyl-D-aspartate.

Reference: 1. SPRAVATO™ [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. May 2019.

WARNINGS AND PRECAUTIONS

Sedation: In clinical trials, 49% to 61% of SPRAVATO™-treated patients developed sedation and 0.3% of SPRAVATO™-treated patients experienced loss of consciousness.

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Closely monitor for sedation with concomitant use of SPRAVATO™ with CNS depressants *[see Drug Interaction (7.1)]*.

SPRAVATO™ is available only through a restricted program under a REMS.

Dissociation: The most common psychological effects of SPRAVATO™ were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 75% of SPRAVATO™-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO™; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

SPRAVATO™ is available only through a restricted program under a REMS.

Abuse and Misuse: SPRAVATO™ contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.

SPRAVATO™ is available only through a restricted program under a REMS.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.

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Important Safety Information (continued)

SPRAVATO™ Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO™ is available only through a restricted program called the SPRAVATO™ REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

Important requirements of the SPRAVATO™ REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO™ is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO™.
- Pharmacies must be certified in the REMS and must only dispense SPRAVATO™ to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies, is available at www.SPRAVATOrems.com or 1-855-382-6022.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults: In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included adult and pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. SPRAVATO™ is not approved in pediatric (<18 years of age) patients.

There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO™ and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure: SPRAVATO™ causes increases in systolic and/or diastolic blood pressure (BP) at all recommended dosages. Increases in BP peak approximately 40 minutes after SPRAVATO™ administration and last approximately 4 hours.

Approximately 8% to 17% of SPRAVATO™-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO™ is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO™ outweigh its risk.

Assess BP prior to administration of SPRAVATO™. In patients whose BP is elevated prior to SPRAVATO™ administration (as a general guide: >140/90 mmHg), a decision to delay SPRAVATO™ therapy should be taken into account to balance the benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO™ administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO™ with psychostimulants or monoamine oxidase inhibitors (MAOIs) *[see Drug Interactions (7.2, 7.3)]*.

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment

Short-Term Cognitive Impairment: In a study in healthy volunteers, a single dose of SPRAVATO™ caused cognitive performance decline 40 minutes post-dose. SPRAVATO™-treated subjects required a greater effort to complete the cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO™ and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment: Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO™ nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO™ have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery: Before SPRAVATO™ administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO™.

Ulcerative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO™ nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO™-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO™ and refer to an appropriate healthcare provider as clinically warranted.

Embryo-fetal Toxicity: SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention.

DRUG INTERACTIONS

CNS depressants (e.g., benzodiazepines, opioids, alcohol): Concomitant use may increase sedation. Closely monitor for sedation with concomitant use of CNS depressants.

Psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of psychostimulants.

Monoamine oxidase inhibitors (MAOIs): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of MAOIs.

USE IN SPECIFIC POPULATIONS

Pregnancy: SPRAVATO™ is not recommended during pregnancy. SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ *in utero*. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO™, treatment with SPRAVATO™ should be discontinued and the patient should be counseled about the potential risk to the fetus.

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO™, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at *https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/*.

Lactation: SPRAVATO™ is present in human milk. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO™.

Females and Males of Reproductive Potential: SPRAVATO™ may cause embryo-fetal harm when administered to a pregnant woman. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO™.

Pediatric Use: The safety and effectiveness of SPRAVATO™ in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO™, 12% were 65 years of age and older, and 2% were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients.

The treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO™ plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥65 years of age. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS).

Hepatic Impairment: SPRAVATO™-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO™ has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: SPRAVATO™ contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

Abuse: Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO™. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO™ may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be "spaced out." Monitoring for signs of abuse and misuse is recommended.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO™ plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

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Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.

Janssen Neuroscience

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SPRAVATO®

(esketamine) nasal spray, CIII

Brief Summary

BEFORE PRESCRIBING SPRAVATO®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

Sedation

- **Patients are at risk for sedation after administration of SPRAVATO *[see Warnings and Precautions]*.**

Dissociation

- **Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO *[see Warnings and Precautions]*.**

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting *[see Warnings and Precautions]*.

Abuse and Misuse

- **SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse *[see Warnings and Precautions]*.**

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS *[see Warnings and Precautions]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

SPRAVATO® is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Limitations of Use:

SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

CONTRAINDICATIONS

SPRAVATO is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation *[see Warnings and Precautions]*
- History of intracerebral hemorrhage *[see Warnings and Precautions]*
- Hypersensitivity to esketamine, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS

Sedation

In clinical trials, 49% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer's Alertness/Sedation scale (MOAA/s) *[see Adverse Reactions]*, and 0.3% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/s score of 0).

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants *[see Drug Interaction]*.

SPRAVATO is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Dissociation

The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 75% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale) *[see Adverse Reactions]*. Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

SPRAVATO is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Abuse and Misuse

SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence. *[see Drug Abuse and Dependence]*.

SPRAVATO is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)

SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse *[see Boxed Warning and Warnings and Precautions]*.

Important requirements of the SPRAVATO REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO *[see Dosage and Administration (2.4) in Full Prescribing Information]*.
- Pharmacies must be certified in the REMS and must only dispense SPRAVATO to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies is available at www.SPRAVATOrems.com or 1-855-382-6022.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients (SPRAVATO is not approved in pediatric patients), the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range (Years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient
≥65	6 fewer patients

* SPRAVATO is not approved in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure

SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO administration and last approximately 4 hours *[see Adverse Reactions]*.

Approximately 8% to 17% of SPRAVATO-treated patients and 1% to 3% of placebo-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage) *[see Contraindications]*. Before prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks.

Assess BP prior to administration of SPRAVATO. In patients whose BP is elevated prior to SPRAVATO administration (as a general guide: >140/90 mmHg) a decision to delay SPRAVATO therapy should take into account the balance of benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO administration *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information]*. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs) *[see Drug Interactions]*.

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment

Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment

Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery

Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive *[see Clinical Studies (14.3) in Full Prescribing Information]*. The effects of SPRAVATO 84 mg were comparable to placebo at 6 hours and 18 hours post-dose. However, two SPRAVATO-treated subjects in one of the studies discontinued the driving test at 8 hours post-dose because of SPRAVATO-related adverse reactions.

Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO.

Ulcerative or Interstitial Cystitis

Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients *[see Adverse Reactions]*. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.

SPRAVATO® (esketamine) nasal spray, CIII

Embryo-fetal Toxicity

Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Sedation *[see Warnings and Precautions]*
- Dissociation *[see Warnings and Precautions]*
- Increase in Blood Pressure *[see Warnings and Precautions]*
- Cognitive Impairment *[see Warnings and Precautions]*
- Impaired Ability to Drive and Operate Machinery *[see Warnings and Precautions]*
- Ulcerative or Interstitial Cystitis *[see Warnings and Precautions]*
- Embryo-fetal Toxicity *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure

SPRAVATO was evaluated for safety in 1709 patients diagnosed with treatment resistant depression (TRD) *[see Clinical Studies (14.1, 14.2) in Full Prescribing Information]* from five Phase 3 studies (3 short-term and 2 long-term studies) and one Phase 2 dose-ranging study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 479 (30%) received at least 6 months of treatment, and 178 (11%) received at least 12 months of treatment.

Adverse Reactions Leading to Discontinuation of Treatment

In short-term studies in adults < 65 years old (Study 1 pooled with another 4-week study), the proportion of patients who discontinued treatment because of an adverse reaction was 4.6% in patients who received SPRAVATO plus oral AD compared to 1.4% for patients who received placebo nasal spray plus oral AD. For adults ≥ 65 years old, the proportions were 5.6% and 3.1%, respectively. In Study 2, a long-term maintenance study, the discontinuation rates because of an adverse reaction were similar for patients receiving SPRAVATO plus oral AD and placebo nasal spray plus oral AD in the maintenance phase, at 2.6% and 2.1%, respectively. Across all Phase 3 studies, adverse reactions leading to SPRAVATO discontinuation in more than 2 patients were (in order of frequency): anxiety (1.2%), depression (0.9%), blood pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in TRD patients treated with SPRAVATO plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. Table 2 shows the incidence of adverse reactions that occurred in TRD patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with placebo nasal spray plus oral AD.

Table 2: Adverse Reactions Occurring in ≥2% of TRD Patients Treated with SPRAVATO + Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

	SPRAVATO + Oral AD (N=346)	Placebo + Oral AD (N=222)
Cardiac disorders		
Tachycardia*	6 (2%)	1 (0.5%)
Ear and labyrinth disorders		
Vertigo*	78 (23%)	6 (3%)
Gastrointestinal disorders		
Constipation	11 (3%)	3 (1%)
Diarrhea	23 (7%)	13 (6%)
Dry mouth	19 (5%)	7 (3%)
Nausea	98 (28%)	19 (9%)
Vomiting	32 (9%)	4 (2%)

Table 2: Adverse Reactions Occurring in ≥2% of TRD Patients Treated with SPRAVATO + Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD (continued)		
	SPRAVATO + Oral AD (N=346)	Placebo + Oral AD (N=222)
General disorders and administration site conditions		
Feeling abnormal	12 (3%)	0 (0%)
Feeling drunk	19 (5%)	1 (0.5%)
Investigations		
Blood pressure increased*	36 (10%)	6 (3%)
Nervous system disorders		
Dizziness*	101 (29%)	17 (8%)
Dysarthria*	15 (4%)	0 (0%)
Dysgeusia*	66 (19%)	30 (14%)
Headache*	70 (20%)	38 (17%)
Hypoesthesia*	63 (18%)	5 (2%)
Lethargy*	37 (11%)	12 (5%)
Mental impairment	11 (3%)	2 (1%)
Sedation*	79 (23%)	21 (9%)
Tremor	12 (3%)	2 (1%)
Psychiatric disorders		
Anxiety*	45 (13%)	14 (6%)
Dissociation*	142 (41%)	21 (9%)
Euphoric mood	15 (4%)	2 (1%)
Insomnia	29 (8%)	16 (7%)
Renal and urinary disorders		
Pollakiuria	11 (3%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort*	23 (7%)	11 (5%)
Oropharyngeal pain	9 (3%)	5 (2%)
Throat irritation	23 (7%)	9 (4%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	14 (4%)	5 (2%)

* The following terms were combined:
Anxiety includes: agitation; anticipatory anxiety; anxiety; fear; feeling jittery; irritability; nervousness; panic attack; tension
Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension
Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; ocular discomfort; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment
Dizziness includes: dizziness; dizziness exertional; dizziness postural; procedural dizziness
Dysarthria includes: dysarthria; slow speech; speech disorder
Dysgeusia includes: dysgeusia; hypogeusia
Headache includes: headache; sinus headache
Hypoesthesia includes: hypoesthesia; hypoesthesia oral, hypoesthesia teeth, pharyngeal hypoesthesia
Lethargy includes: fatigue; lethargy
Nasal discomfort includes: nasal crusting; nasal discomfort; nasal dryness; nasal pruritus
Sedation includes: altered state of consciousness; hypersomnia; sedation; somnolence
Tachycardia includes: extrasystoles; heart rate increased; tachycardia
Vertigo includes: vertigo; vertigo positional

Sedation

Sedation was evaluated by adverse event reports and using the Modified Observer's Alertness/Sedation scale (MOAA/s). In the MOAA/s scale, 5 means "responds readily to name spoken in normal tone" and 0 means "no response after painful trapezius squeeze." Any decrease in MOAA/s from pre-dose is considered to indicate presence of sedation, and such a decrease occurred in a higher number of patients on esketamine than placebo during the short-term trials (Table 3). Dose-related increases in the incidence of sedation were observed in a fixed-dose study *[see Warnings and Precautions]*.

Table 3: Incidence of Sedation (MOAA/s <5) in Double-Blind, Randomized, Placebo-Controlled Fixed-Dose Study with Patients <65 Years of Age and Double-Blind, Randomized, Placebo-Controlled Flexible-Dose Study with Patients ≥65 years					
	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO + Oral AD		Placebo + Oral AD	SPRAVATO + Oral AD
		56 mg	84 mg		28 to 84 mg
Number of patients*	N=112	N=114	N=114	N=63	N=72
Sedation (MOAA/s <5)	11%	50%	61%	19%	49%

*Patients who were evaluated with MOAA/s

Dissociation/Perceptual Changes

SPRAVATO can cause dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the Clinician-Administered Dissociative States Scale (CADSS) questionnaire. A CADSS total score of more than 4 indicates presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on esketamine compared to placebo during the short-term trials (see Table 4). Dose-related increases in the incidence of dissociative symptoms (CADSS total score >4) were observed in a fixed-dose study. Table 4 shows the incidence of dissociation (CADSS total score >4) in a double-blind, randomized, placebo-controlled, fixed-dose study in adults <65 years of age and a double-blind, randomized, placebo-controlled, flexible-dose study with patients ≥ 65 years of age.

Table 4: Incidence of Dissociation (CADSS Total Score >4) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Patients <65 Years and Flexible-Dose Study with Patients ≥65 Years)					
	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO + Oral AD		Placebo + Oral AD	SPRAVATO + Oral AD 28 to 84 mg
		56 mg	84 mg		
Number of patients*	**N=113**	**N=113**	**N=116**	**N=65**	**N=72**
CADSS total score >4 and change >0	5%	61%	69%	12%	75%

* Number of patients who were evaluated with CADSS

Increase in Blood Pressure

The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antidepressants (Table 5).

Table 5: Increases in Blood Pressure in Double-blind, Randomized-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD				
	Patients <65 years		Patients ≥65 years	
	SPRAVATO + Oral AD N=346	Placebo + Oral AD N=222	SPRAVATO + Oral AD N =72	Placebo + Oral AD N=65
Systolic blood pressure				
≥180 mmHg	9 (3%)	---	2 (3%)	1 (2%)
≥40 mmHg increase	29 (8%)	1 (0.5%)	12 (17%)	1 (2%)
Diastolic blood pressure				
≥110 mmHg	13 (4%)	1 (0.5%)	---	---
≥25 mmHg increase	46 (13%)	6 (3%)	10 (14%)	2 (3%)

Nausea and Vomiting

SPRAVATO can cause nausea and vomiting (Table 6). Most of these events occurred on the day of dosing and resolved the same day, with the median duration not exceeding 1 hour in most subjects across dosing sessions. Rates of reported nausea and vomiting decreased over time across dosing sessions from the first week of treatment in the short-term studies, as well as over time with long-term treatment (Table 6).

Table 6: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled, Fixed-dose Study					
Treatment (+ Oral AD)		Nausea		Vomiting	
	N	All	Severe	All	Severe
SPRAVATO 56 mg	115	31 (27%)	0	7 (6%)	0
SPRAVATO 84 mg	116	37 (32%)	4 (3%)	14 (12%)	3 (3%)
Placebo Nasal Spray	113	12 (11%)	0	2 (2%)	0

Sense of Smell

Sense of smell was assessed over time; no difference was observed between patients treated with SPRAVATO plus oral AD and those treated with placebo nasal spray plus oral AD during the double-blind maintenance phase of Study 2 *[see Clinical Studies (14.2) in Full Prescribing Information]*.

DRUG INTERACTIONS

Central Nervous System Depressants

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation *[see Warnings and Precautions]*. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

Psychostimulants

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafanil, armodafinil) may increase blood pressure *[see Warnings and Precautions]*. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure *[see Warnings and Precautions]*. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at *https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/*.

Risk Summary

SPRAVATO is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women *(see Data)*. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. There are risks to the mother associated with untreated depression in pregnancy *(see Clinical Considerations)*. If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

Published studies in pregnant primates demonstrate that the administration of drugs that block N-methyl-D-aspartate (NMDA) receptors during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans *[see Use in Specific Populations]*.

In an embryo-fetal reproduction study in rabbits, skeletal malformations were noted at maternally toxic doses when ketamine was intranasally administered with a No Observed Adverse Effect Level (NOAEL) at estimated esketamine exposures 0.3 times the exposures at the maximum recommended human dose (MRHD) of 84 mg/day. In addition, intranasal administration of esketamine to pregnant rats during pregnancy and lactation at exposures that were similar to those at the MRHD resulted in a delay in sensorimotor development in pups during the preweaning period and a decrease in motor activity in the post-weaning period.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

SPRAVATO® (esketamine) nasal spray, CIII

Data

Animal Data

Based on published data, when female monkeys were treated intravenously with racemic ketamine at anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. This period of brain development translates into the third trimester of human pregnancy. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits.

Racemic ketamine was administered intranasally to pregnant rats during the period of organogenesis at doses of 15, 50, and 150 mg/kg/day. The No Observed Adverse Effect level (NOAEL) for embryo-fetal toxicity in rats was the highest dose of 150 mg/kg/day. Estimating 50% of the exposure to be from esketamine, the NOAEL associated with esketamine plasma exposure (AUC) is 12-times the AUC exposure at the MRHD of 84 mg/day. In pregnant rabbits, racemic ketamine was administered intranasally from gestational day 6 to 18 at doses of 10, 30, and 100 mg/kg/day. The high dose was lowered from 100 to 50 mg/kg after 5 days of dosing due to excessive mortality in the pregnant rabbits. Skeletal malformations were observed at doses ≥ 30mg/kg/day, which were maternally toxic. The NOAEL for skeletal malformations was associated with a plasma esketamine exposure (AUC) that was 0.3 times the AUC exposure at MRHD of 84 mg/day.

Administration of esketamine to pregnant rats during pregnancy and lactation at intranasal doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200-gram rat) produced AUC exposures 0.07, 0.5, and 0.7 times the MRHD of 84 mg/day, respectively. Maternal toxicity was observed at doses ≥ 15 mg/kg/day. In addition, a dose-dependent delay in the age of attainment of Preyer response reflex was observed in pups at all doses during the preweaning period. This sensory/motor developmental measure was tested starting on postnatal day (PND) 9, and the effect normalized by PND 19 in treatment groups as compared with PND 14 for the majority of the control animals. There is no NOAEL for this delay in sensory/motor response observed in pups during the preweaning period. During the postweaning period, a decrease in motor activity was observed at doses ≥ 15 mg/kg which is 0.5-times the human exposure at the MRHD of 84 mg/day. The NOAEL for maternal toxicity and decreased motor activity during the postweaning period was 4.5 mg/kg/day which was associated with a plasma exposure (AUC) that was 0.07-times the AUC exposure at MRHD of 84 mg/day.

Lactation

Risk Summary

Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity *(see Data)*. Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

Data

Published juvenile animal studies demonstrate that the administration of drugs that block NMDA receptors, such as ketamine, during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but this window may extend out to approximately 3 years of age in humans.

Females and Males of Reproductive Potential

Contraception

Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered to a pregnant woman *[see Warnings and Precautions and Use in Specific Populations]*. However, it is not clear how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO.

Pediatric Use

The safety and effectiveness of SPRAVATO in pediatric patients have not been established. Clinical studies of SPRAVATO in pediatric patients have not been conducted.

Geriatric Use

Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO, (N=1601), 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

The efficacy of SPRAVATO for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥ 65 years of age. SPRAVATO was initiated at 28 mg twice weekly

and could be titrated to 56 mg or 84 mg administered twice-weekly. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Asberg Depression Rating Scale (MADRS).

Hepatic Impairment

The mean esketamine AUC and $t_{1/2}$ values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SPRAVATO contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be "spaced out". Monitoring for signs of abuse and misuse is recommended.

Abuse Potential Study

A cross-over, double-blind abuse potential study of SPRAVATO and ketamine was conducted in recreational polydrug users (n=34) who had experience with perception-altering drugs, including ketamine. Ketamine, the racemic mixture of arketamine and esketamine, is a Schedule III controlled substance and has known abuse potential. In this study, the mean "Drug Liking at the Moment" and "Take Drug Again" scores for single doses of intranasal SPRAVATO (84 mg and 112 mg – the maximum recommended dose and 1.3 times the maximum recommended dose, respectively) were similar to these scores in the intravenous ketamine (0.5 mg/kg infused over 40 minutes) control group. However, these scores were greater in the SPRAVATO and ketamine groups compared to the placebo group. The 112 mg dose of intranasal SPRAVATO was associated with significantly higher scores for "Hallucinating," "Floating," "Detached," and "Spaced Out" than the 84 mg dose of intranasal SPRAVATO and the intravenous ketamine dose.

Dependence

Physical dependence has been reported with prolonged use of ketamine. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or significant dosage reduction of a drug. There were no withdrawal symptoms captured up to 4 weeks after cessation of esketamine treatment. Withdrawal symptoms have been reported after the discontinuation of frequently used (more than weekly) large doses of ketamine for long periods of time. Such withdrawal symptoms are likely to occur if esketamine were similarly abused. Reported symptoms of withdrawal associated with daily intake of large doses of ketamine include craving, fatigue, poor appetite, and anxiety. Therefore, monitor SPRAVATO-treated patients for symptoms and signs of physical dependence upon the discontinuation of the drug.

Tolerance has been reported with prolonged use of ketamine. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Similar tolerance would be expected with prolonged use of esketamine.

OVERDOSAGE

Management of Overdosage

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. Contact a Certified Poison Control Center for the most up to date information on the management of overdosage (1-800-222-1222 or www.poison.org).

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Contribution of Intellectual Disability–Related Genes to ADHD Risk and to Locomotor Activity in *Drosophila*

Novel ADHD genes identified by investigating whether genes carrying rare mutations linked to intellectual disability contribute to ADHD risk through common genetic variants.

Alcohol Use Disorder and Risk of Suicide in a Swedish Population-Based Cohort

Alcohol use disorder is strongly associated with suicide risk, even after accounting for psychiatric comorbidity. This relationship is due in part to shared familial factors—both genetic and environmental—in conjunction with a likely causal association. The increased risk of suicide persists for years beyond registration for alcohol use disorder.

AJP CME

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This month's courses appear on pages 469–472.

Each short course is based on one article in this issue and can earn up to 1 *AMA PRA Category 1 Credit™*. CME credit is issued only **online**, and a paid subscription to AJP's CME course program is required.

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AJP Multimedia

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In AJP Audio this month, Executive Editor Michael Roy speaks with Collin M. Reiff, M.D., and William M. McDonald, M.D., about their review of the literature on the clinical application of psychedelic drugs in psychiatric disorders (p. 391).

In this month's video, Deputy Editor Daniel S. Pine, M.D., discusses the articles "Multimodal Abnormalities of Brain Structure and Function in Major Depressive Disorder: A Meta-Analysis of Neuroimaging Studies" (p. 422) and "The Rearing Environment and Risk for Major Depression: A Swedish National High-Risk Home-Reared and Adopted-Away Co-Sibling Control Study" (p. 447).

History of Psychiatry

Revisit the field's rich history through the AJP Archive

75 years ago this month: Prefrontal Lobotomy: The Problem of Schizophrenia

Exactly 8 years after Egas Moniz published his first paper on prefontal leucotomy in *The American Journal of Psychiatry*, his protégé Walter Freeman along with James W. Watts contributed this look at mostly positive outcomes of 50 individuals with schizophrenia who had undergone the procedure 2–7 years earlier. Four years later, Dr. Freeman went on to successfully nominate his mentor for a Nobel Prize: in 1949 Dr. Moniz was awarded the Nobel in physiology and medicine.

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