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.

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.

cp-79821v1

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

Janssen Neuroscience

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

 September 2019 cp-108113v1

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
		56 mg	84 mg		28 to 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 health care 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).

Manufactured by:
Renaissance Lakewood LLC
Lakewood, NJ 08701

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

cp-79820v2

Go Online

Visit **ajp.psychiatryonline.org** for these features!

AJP in Advance

Discover the latest research advances before they appear in print

Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder

Carmi and colleagues evaluate the efficacy of deep transcranial magnetic stimulation in patients with treatment-refractory obsessive-compulsive disorder, using a multi-site, randomized controlled trial. They report important new findings suggesting that this form of stimulation to prefrontal areas may outperform a credible control condition.

Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder

In a randomized controlled trial among 50 currently drug-free individuals with a history of a heroin use disorder, Hurd and colleagues examined the effects of acute cannabidiol administration on drug craving and anxiety. The data provide important preliminary evidence on the potential therapeutic utility of this phytocannabinoid for the treatment of substance use disorders.

AJP CME

Earn CME credit: 3 courses per issue

This month's courses appear on pages 881–884.

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.

Visit psychiatryonline.org/cme and click on the "American Journal of Psychiatry" tab.

AJP Multimedia

Access Audio or Video for highlights of each issue

In AJP Audio this month, Executive Editor Michael Roy speaks with Abraham Reichenberg, Ph.D., about research on cognitive decline after the first episode of schizophrenia and other psychoses (p. 811).

In this month's video, Deputy Editor Daniel S. Pine, M.D., discusses the articles "White Matter in Schizophrenia Treatment Resistance" (p. 829) and "Baseline Frontoparietal Task-Related BOLD Activity as a Predictor of Improvement in Clinical Symptoms at 1-Year Follow-Up in Recent-Onset Psychosis" (p. 839).

History of Psychiatry

Revisit the field's rich history through the AJP Archive

175 Years Ago this Month: Definition of Insanity—Nature of the Disease

In the second-ever issue of what was then called *The American Journal of Insanity*, the Editors accompanied the definition of the condition they were endeavoring to cover with contemporary (at the time) examples.

Psychiatry Online
@AmJPsychiatry

AMERICAN PSYCHIATRIC ASSOCIATION PUBLISHING

www.appi.org
1-800-368-5777
appi@psych.org

A novel, once-daily treatment option for patients with ADHD 6 years and older

JORNAY PM™

methylphenidate HCl CII extended-release capsules

20mg 40mg 60mg 80mg 100mg

Now Available

The first and only ADHD stimulant dosed in the evening

Help your patients wake up ready for the day

When dosed in the evening, the delayed-release and extended-release technology of JORNAY PM enables the drug to be delivered in the early morning—and it lasts throughout the day

Mornings matter. Learn more at JORNAYpm.com and prescribe today.

Indication and Important Safety Information

INDICATION

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE
CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products.
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Reactions:* Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulants at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, coronary artery disease, and other serious cardiac problems.
- *Blood Pressure and Heart Rate Increases:* CNS stimulants may cause an increase in blood pressure and heart rate. Monitor all patients for hypertension and tachycardia.
- *Psychiatric Adverse Reactions:* CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychiatric disorder and may induce a manic or mixed episode in patients with bipolar disorder. In patients with no prior history of psychotic illness or mania, CNS stimulants, at recommended doses, may cause psychotic or manic symptoms.
- *Priapism:* Prolonged and painful erections, sometimes requiring intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism has also appeared during a period of drug withdrawal. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed.
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.
- *Long-Term Suppression of Growth:* CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Monitor height and weight at appropriate intervals in pediatric patients.

ADVERSE REACTIONS

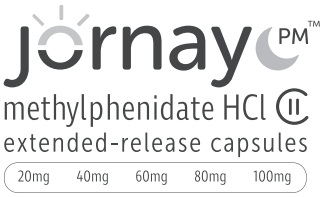
- Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.
- Additional adverse reactions (≥5% and twice the rate of placebo) in pediatric patients 6 to 12 years treated with JORNAY PM: headache, psychomotor hyperactivity, and mood swings.

PREGNANCY AND LACTATION

- CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion.
- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition. Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Please see additional safety information in the Brief Summary of Prescribing Information for JORNAY PM on adjacent pages.

IRONSHORE PHARMACEUTICALS



JORNAY PM™ (methylphenidate hydrochloride) extended-release capsules, for oral use, CII Rx only

BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

INDICATIONS AND USAGE

JORNAY PM is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

DOSAGE AND ADMINISTRATION

JORNAY PM should be taken only in the evening. Adjust the timing of administration between 6:30 pm and 9:30 pm to optimize the tolerability and efficacy the next morning and throughout the day.

The recommended starting dose for patients 6 years and above is 20 mg daily in the evening. Dosage may be increased weekly in increments of 20 mg per day up to a maximum daily dose of 100 mg.

Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce.

Do not substitute for other methylphenidate products on a milligram-per-milligram basis.

CONTRAINDICATIONS

Hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products.

Concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of a monoamine oxidase inhibitor, because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines have a high potential for abuse and dependence. Assess the risk for abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

Serious Cardiovascular Reactions Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulants at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, and other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with JORNAY PM.

Blood Pressure and Heart Rate Increases CNS stimulants may cause an increase in blood pressure (mean increase 2 to 4 mmHg) and heart rate (mean increase 3 to 6 bpm). Individuals may have larger increases. Monitor for hypertension and tachycardia.

Psychiatric Adverse Reactions Exacerbation of Pre-existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). New Psychotic or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history. If such occur, consider discontinuing JORNAY PM. In a pooled analysis of studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared with 0 in placebo-treated patients.

Priapism Prolonged, painful erections, sometimes requiring surgery, have been reported with methylphenidate in both pediatric patients and adults. Priapism was not reported with drug initiation but developed after time on the drug, often after an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent, painful erections should seek immediate medical attention.

Peripheral Vasculopathy, including Raynaud's Phenomenon CNS stimulants, including JORNAY PM, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Long-term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth in pediatric patients. Careful follow-up of weight and height in patients ages 7 to 10 years who were randomized to either methylphenidate or placebo over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and placebo-treated patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth (on average, 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period. Closely monitor growth (weight and height) in children treated with CNS stimulants, including JORNAY PM. Patients not growing or gaining height or weight as expected may need their treatment interrupted.

ADVERSE REACTIONS

Clinical Trial 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. Clinical Trials Experience with JORNAY PM in Pediatric Patients (6 to 12 years) with ADHD The safety of JORNAY PM was evaluated in 280 patients (6 to 12 years of age) who participated in two controlled clinical studies of patients with ADHD. Study 1, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose-optimization phase in which all patients received JORNAY PM (n=125; mean dose 50 mg), followed by a 1-week, double-blind controlled phase in which patients were randomized to continue JORNAY PM (n=65) or switch to placebo (n=54). During the open-label JORNAY PM treatment phase, adverse reactions reported in >5% of patients included: any insomnia (41%), decreased appetite (27%), affect lability (22%), headache (19%), upper respiratory tract infection (17%), upper abdominal pain (9%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%). Three patients discontinued treatment because of affect lability, panic attacks, and agitation and aggression. Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected in clinical practice. No difference occurred in the incidence of adverse reactions between JORNAY PM and placebo during the 1-week, double-blind, placebo-controlled phase. Study 2 was a 3-week, placebo-controlled study of JORNAY PM (n=81; mean dose 52 mg) in pediatric patients 6 to 12 years. *Most Common Adverse Reactions* (incidence of ≥ 5% and at a rate at least twice placebo): any insomnia, decreased appetite, headache, vomiting, nausea, psychomotor hyperactivity, and affect lability or mood swings. One patient in the JORNAY PM group discontinued from the study due to mood swings. Table 1 provides the incidence of adverse reactions reported in Study 2 (incidence of 2% or more and at least twice placebo) among pediatric patients 6 to 12 years in a 3-week clinical trial.

Table 1: Adverse Reactions Occurring in ≥2% of JORNAY PM-treated Pediatric Patients and Greater than Placebo in a 3-Week ADHD Study (Study 2)

Body Organ System	Adverse Reaction	JORNAY PM (N=81)	Placebo (N=80)
Psychiatric disorders	Any insomnia	33%	9%
	Initial insomnia	14%	5%
	Middle insomnia	11%	4%
	Terminal insomnia	11%	1%
	Insomnia, not specified	4%	1%
	Affect lability/Mood swings	6%	1%
Metabolism and nutrition disorders	Decreased appetite	19%	4%
Nervous system disorders	Headache	10%	5%
	Psychomotor hyperactivity	5%	1%
Cardiovascular	Blood pressure diastolic increased	7%	4%
Gastrointestinal disorders	Vomiting	9%	0%
	Nausea	6%	0%
Infections and infestations	Nasopharyngitis	3%	1%
	Pharyngitis streptococcal	3%	0%
Injury, poisioning and procedural complications	Contusion	3%	0%
Musculoskeletal and procedural complications	Back pain	3%	0%
Skin and subcutaneous tissue disorders	Rash	2%	0%

Postmarketing Experience The following adverse reactions have been identified during postapproval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Hyperpyrexia

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus, Rashes, Eruptions, and Exanthemas

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, Severe hepatic injury

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania

Urogenital System: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

DRUG INTERACTIONS

MAO Inhibitors Do not administer JORNAY PM concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary Published studies and postmarketing reports on methylphenidate use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 2 and 9 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis, respectively. However, spina bifida was observed in rabbits at a dose 31 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 3.5 times the MRHD given to adolescents. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations *Fetal/Neonatal Adverse Reactions* CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Data *Human Data* A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing methylphenidate use during pregnancy. Due to the small number of methylphenidate-exposed pregnancies with known outcomes, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. *Animal Data* In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis.Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 31 times the MRHD of 100 mg/day given to adolescents on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (9 times the MRHD given to adolescents on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (6 times the MRHD given to adolescents on a mg/m^2 basis, which is also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD given to adolescents on a mg/m^2 basis).

Lactation Risk Summary Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown.The devlopmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition. Clinical Considerations Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Pediatric Use The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established. The safety and effectiveness of JORNAY PM have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical studies in pediatric patients 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Long-Term Suppression of Growth Growth should be monitored during treatment with stimulants, including JORNAY PM. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted. Juvenile Animal Toxicity Data Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis. In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal Day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with ≥ 50 mg/kg/day (approximately ≥ 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis), and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (0.25 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

Geriatric Use JORNAY PM has not been studied in patients older than 65 years of age.

DRUG ABUSE AND DEPENDENCE

Controlled Substance JORNAY PM contains methylphenidate, a Schedule II controlled substance.

Abuse CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration, which can result in overdose and death. To reduce the abuse of CNS stimulants including JORNAY PM, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for JORNAY PM use.

Dependence Tolerance Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including JORNAY PM. Dependence Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants, including JORNAY PM. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include: dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

OVERDOSAGE

Signs and Symptoms Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

Management of Overdose Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosages. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

IRONSHORE
PHARMACEUTICALS

THE AMERICAN PSYCHIATRIC ASSOCIATION

800 Maine Avenue, S.W., Suite 900, Washington, D.C. 20024
(888) 357-7924 (toll-free inside the U.S. and Canada)
web site: www.psychiatry.org • e-mail: apa@psych.org

Chairpersons of Councils, Committees, and Task Forces

Standing Committees

Bylaws	Esperanza Diaz, M.D.
Elections	Josepha A. Cheong, M.D.
Ethics	Rebecca W. Brendel, M.D., J.D.
Finance and Budget	Ann Marie T. Sullivan, M.D.
Audit	Gregory W. Dalack, M.D.
Investment Oversight	David Fassler, M.D.
Joint Reference	Jeffrey L. Geller, M.D., M.P.H.
Membership	Eric R. Williams, M.D.
Nominating	Altha J. Stewart, M.D.
Tellers	Jose P. Vito, M.D.

Non-Standing Committee

Conflict of Interest — Sandra M. DeJong, M.D., M.Sc.

Councils

Council on Addiction Psychiatry
Jill Williams, M.D.

Council on Advocacy and Government Relations
Patrick S. Runnels, M.D.
Advocacy and Litigation Funding
Bhasker J. Dave, M.D.

Council on Children, Adolescents, and Their Families
Gabrielle Shapiro, M.D.

Council on Communications
Carol A. Bernstein, M.D.

Council on Consultation-Liaison Psychiatry
Jon A. Levenson, M.D.

Council on Geriatric Psychiatry
Robert P. Roca, M.D.

Council on Healthcare Systems and Financing
Ronald M. Burd, M.D.
Integrated Care
Henry Chung, M.D.
RBRVS, Codes and Reimbursement
Gregory G. Harris, M.D.
Reimbursement for Psychiatric Care
Laurence H. Miller, M.D.
Telepsychiatry
James H. Shore, M.D.

Council on International Psychiatry
Bernardo Ng, M.D.
Chester Pierce Human Rights Award Committee
James L. Griffith, M.D.

Council on Medical Education and Lifelong Learning
Mark H. Rapaport, M.D.
Innovation
Nina Vasan, M.D.
Scientific Program
Philip R. Muskin, M.D., M.A.
Scientific Program–IPS (Oct. to Oct. tenure)
Eric Yarbrough, M.D.
Vestermark Award Committee
Lowell D. Tong, M.D.
Well-being and Burnout
Richard F. Summers, M.D.

Council on Minority Mental Health and Health Disparities
Eric Yarbrough, M.D.

Council on Psychiatry and Law
Debra A. Pinals, M.D.
Judicial Action
Marvin S. Swartz, M.D.

Council on Quality Care
Grayson S. Norquist, M.D.
Mental Health Information Technology
John Torous, M.D.
Quality and Performance Measurement
Carol Alter, M.D.
Practice Guidelines
Daniel J. Anzia, M.D.

Council on Research
Jonathan E. Alpert, M.D., Ph.D.
Psychiatric Dimensions of Disasters
Joshua C. Morganstein, M.D.

The American Journal of
Psychiatry
Residents' Journal

ajp.psychiatryonline.org/loi/ajp-rj

September 2019: Editorial Board Commentary

Special Theme: Neuropsychiatry

The *Residents' Journal* is an e-publication that serves as a forum for sharing ideas and experiences in training, clinical practice, research, and careers.

The *Residents' Journal* considers manuscripts authored by medical students, resident physicians, and fellows. For information about submitting manuscripts, visit the **Author Resources** page online: https://ajp.psychiatryonline.org/residents_journal/rj_ifora.

2019–2020 Editorial Board

Facebook.com/AJPResidentsJournal
@AJP_ResJournal

AMERICAN PSYCHIATRIC ASSOCIATION PUBLISHING
www.appi.org

ACCORDING TO ONE SURVEY,[a]

~97%

OF ADULTS WHO MET DIAGNOSTIC CRITERIA FOR BINGE EATING DISORDER (BED)

DID NOT RECEIVE A FORMAL DIAGNOSIS[1]

WHY?

Because **deep shame and guilt** causes them to hide their symptoms[2]—even from their psychiatrists. They need your help to open up about their binge eating and the impact it's having on their lives.

Learn more at BurdenofBED.com
Start the BED conversation

[a]From participants in the 2012 and 2013 National Health and Wellness Survey, 3% of respondents (11/344) who reported symptoms within the last 12 months that were consistent with *DSM-5*® criteria for BED had ever received a formal diagnosis.[1]

References: 1. Cossrow N, Pawaskar M, Witt EA, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing *DSM-IV-TR* and *DSM-5* criteria. *J Clin Psychiatry*. 2016;77(8):e968-e974. **2.** American Psychiatric Association. Binge eating disorder. In: *Diagnostic and Statistical Manual of Mental Disorders, 5th ed*. Arlington, VA: American Psychiatric Association; 2013:350-353.

sunovion