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LEADERS IN PSYCHIATRIC MEDICAL LIABILITY INSURANCE

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Important Safety Information (continued)

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.

WARNINGS AND PRECAUTIONS

Sedation: In clinical trials, 48% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% to 0.4% 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 (e.g., benzodiazepines, opioids, alcohol).

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 84% 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.

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® 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 and administered in healthcare settings.
  - Patients treated in outpatient settings (e.g., medical offices and clinics) must be 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 doses. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours.

Approximately 8% to 19% 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 SPRAVATO®, 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 take into account the balance of 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 (e.g., amphetamines, methylphenidate, modafinil, armodafinil) or monoamine oxidase inhibitors (MAOIs).

In patients with a 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.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for SPRAVATO® on next and previous pages.

Spravato® (esketamine) CIII
28 mg nasal spray

When depressive symptoms escalate, relief can't come soon enough.

SPRAVATO® is the first and only esketamine nasal spray approved in conjunction with an oral antidepressant for treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior (MDSI).[1]

- SPRAVATO® demonstrated rapid reduction of depressive symptoms with superior improvement at 24 hours[1,2]*
  - *At 24 hours, 15.9-point reduction with* SPRAVATO® *+ SOC (n=111) vs 12.0 with placebo + SOC (n=112) in Study 3 (P=0.006)*
- The benefit of SPRAVATO® appeared as early as 4 hours[1,2]

Find a treatment center in your area today.
spravatohcp.com/find-a-center

Spravato® (esketamine) CIII
28 mg nasal spray

Indications:
SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitations of Use:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.
- SPRAVATO® is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO® as an anesthetic agent have not been established.

*As measured by the least-square mean change from baseline MADRS total score vs placebo in Study 3, a Phase 3, short-term (4-week), randomized, double-blind, multicenter, placebo-controlled study.[1,2]

MDD=major depressive disorder.
MADRS=Montgomery-Åsberg Depression Rating Scale.
SOC=standard of care (initial hospitalization and a newly initiated or optimized oral antidepressant).

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for SPRAVATO® on previous pages.

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).**

References: 1. SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. July 2020. **2.** Fu D-J, Ionescu DF, Li X, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). *J Clin Psychiatry*. 2020;81(3):19m13191.

Subscription and Business Information

The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association.

Periodicals postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *The American Journal of Psychiatry*, Circulation Department, American Psychiatric Association, 800 Maine Avenue, S.W., Suite 900, Washington, D.C. 20024.

Editorial Office
American Journal of Psychiatry
American Psychiatric Association
800 Maine Avenue, S.W., Suite 900
Washington, D.C. 20024
E-mail: ajp@psych.org

Customer Service
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Pages are produced by KnowledgeWorks Global (Waterbury, VT) and printed by Sheridan NH (Hanover, NH) on acid-free paper effective with Volume 169, Number 1, January 2012.

AMERICAN PSYCHIATRIC ASSOCIATION

The American Journal of Psychiatry

Official Journal of the American Psychiatric Association

Please visit the Journal's website at ajp.psychiatryonline.org

The American Journal of
Psychiatry

VOLUME 178 | NUMBER 12 | DECEMBER 2021

PERSPECTIVES

EDITOR'S NOTE

EDITORIALS

REVIEWS AND OVERVIEWS

This overview begins with a discussion of ECT, one of the first attempts to directly affect neural function via stimulation, followed by a discussion of surgical approaches to neuromodulation. "Noninvasive" neuromodulation approaches, which have become possible as a result of technological advances over the past 20-30 years, offer a neuromodulation strategy with fewer side effects and risks compared with ECT and surgical procedures and are therefore more scalable and disseminable. The overview ends with a discussion of potential future directions for neuromodulation for depression and other neuropsychiatric disorders.

NEW RESEARCH

ARTICLES

Older individuals with psychiatric disorders are at significant risk of mortality and suicide. This carefully controlled observation design study examines the association between ECT and all-cause mortality and suicide in over 40,000 individuals. ECT was associated with a substantial (39%) reduction in mortality risk for up to 1 year and a significant but short-term reduction in suicide risk (44% reduction up to 3 months following discharge from a hospital). The findings support greater consideration of ECT for inpatients with mood disorders at short-term risk of suicide.

Lumateperone is a mechanistically novel antipsychotic that is FDA-approved for the treatment of schizophrenia. A recent phase 3, randomized, double-blind, placebo-controlled study showed that lumateperone, 42 mg, significantly improved symptoms of depression in individuals experiencing major depressive episodes associated with either bipolar I or bipolar II disorder. Treatment was generally well tolerated with low risk of extrapyramidal symptoms and minimal prolactin, weight, or metabolic changes.

Cover: This issue of the *Journal* presents new research findings related to the treatment and understanding of major depression and bipolar depression, as well as an overview of neuromodulation strategies currently in use, and in development, for the treatment of depression. (Image by Ekaterina Chernenko, istockphoto.com.)

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800 Maine Avenue, S.W., Suite 900, Washington, D.C. 20024
(888) 357-7924 (toll-free inside the U.S. and Canada)
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AJP in Advance

Discover the latest research advances before they appear in print

Prevalence and Correlates of Cannabis Use and Cannabis Use Disorder Among U.S. Veterans: Results From the NESARC-III

A clear risk for cannabis use disorder was evident among veterans reporting nonmedical cannabis use, with up to 37% meeting criteria for a cannabis use disorder in their lifetime. The odds of cannabis use and use disorder were higher among those of lower socioeconomic status and those with psychiatric and substance use disorders. Odds of use, daily or near daily use, and use disorder were even higher among veterans in states with medical marijuana laws.

AJP Multimedia

AJP Audio is back!

Our popular podcast returns with two new episodes. From an article in AJP's November issue, Dr. Jennifer S. Stevens, Ph.D., discusses a technique to classify trauma victims into discrete biotypes in the immediate aftermath of trauma, with the hope of providing insight into the groups that could guide treatment. From an article in our December issue, Dr. Samuel T. Wilkinson, M.D., discusses the effects of ECT on all-cause mortality and suicide in older patients.

AJP CME

Earn CME credit: 3 courses per issue

You can earn CME credits by reading articles in *The American Journal of Psychiatry*. Three articles in this issue form a short course that consists of reading the article and answering three multiple-choice questions with a single correct answer for up to 1 *AMA PRA Category 1 Credit*™ each. Credit is issued only to subscribers of the online AJP CME Course Program.

See the table below for the articles in this month's issue that are the subject of a CME quiz.

In this issue
Association of ECT With Risks of All-Cause Mortality and Suicide in Older Medicare Patients (p. 1089)
Association Between Systemic Inflammation and Individual Symptoms of Depression (p. 1107)
Coordinate-Based Network Mapping of Brain Structure in Major Depressive Disorder in Younger and Older Adults (p. 1119)

History of Psychiatry

Revisit the field's rich history through the AJP Archive

50 years ago this month: The Psychiatrist, the APA, and Social Issues: A Symposium

With a membership complaining that the Association was both too involved and not involved enough, leaders discussed the need for an operational definition of social issues, whether APA has a special competence for action in social movements, and whether psychiatrists, through the organization, can be effective in matters related to issues of primary prevention.

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