A Role for Psychiatry in Understanding and Overcoming Vaccine Hesitancy

I hope to inspire you to apply your understanding of the human psyche to the curious matter of people who are contracting a life-threatening infection because they are reluctant to heed the advice of their physicians and the public health community. An exuberance of irrationality, not mental illness, seems to be at play here. Can our training and experience as psychiatrists shed light on a flawed decision-making process that leads some people to throw caution to the wind? Commonplace self-defeating behaviors may be understood from the perspective of those hypothetical constructs known as immature defense mechanisms. However, since the 1990s, the so-called Decade of the Brain, such psychodynamic concepts have been receding.
Introducing an associated comorbidity of adult ADHD—amotivational features and chronic fatigue

ADHD is typically seen as a disorder of attention and hyperactivity, but recent evidence suggests it also involves deficits in motivation. Attention deficits in individuals with ADHD seem to be most evident during tasks perceived as boring or repetitive in academic and work situations (ie, where intrinsic motivation is low). Amotivational features seen in patients with ADHD include:

- Avoiding more work than what is strictly necessary
- Avoiding very demanding projects
- Giving up when success does not seem likely
- Not being ambitious

It’s also important to recognize the potential contributions of chronic fatigue syndrome (CFS) when assessing patients with ADHD who have amotivational symptoms.

Find out more at TEAM-ADHD.com/adult/comorbidities/mood-disorders

Hippocrates is quoted as saying, “As to diseases, make a habit of 2 things—to help, or at least to do no harm.” This issue of Psychiatric Times™, we aim to help you do just that. Our coverage of the Annual Psychiatric Times™ World CME Conference™ brings you the highlights and clinical pearls to help you better understand psychiatric illnesses and develop effective treatments for your patients. From the psychopharmacological wisdom of Sheldon H. Preskorn, MD, our Educator of the Year, to guidance in caring for members of special populations—and even yourself—the esteemed faculty shared their tips for providing top quality care.

That theme resonates in this issue, as experts share cautions and concerns to prevent negative outcomes. For example, Steve Adelman, MD, shares his thoughts on prescribing caution in the case of benzodiazepines. According to the Centers for Disease Control and Prevention, there were almost 70,000 deaths attributable to opioids in 2020. Adelman further notes that concurrent use of benzodiazepine and opioids may occur in as many as 50% of opioid overdose deaths. In exploring the relationship between benzodiazepines and opioid use, he shares his concern and cautions for prescribing this class of medication.

Similarly, caution may be warranted in some cases when prescribing other psychotropic medications. Because some agents may trigger torsades de pointes, Margo C. Funk, MD, MA, and John J. Miller, MD, offer a large selection of back issues. Contact Customer Service at mmhinfo@mjhlifesciences.com for back issues. Contact Customer Service at

Care, concern, and cautions are also discussed throughout our Geriatric Psychiatry Special Report. Chaired by Rajesh Tampi, MD, MS, DFAAP, the section discusses issues in sleep, posttraumatic stress disorder, and issues surrounding COVID-19. As the US population ages, it becomes more important to be aware of the unique concerns impacting older adults, and this Special Report aims to support those endeavors.

From cover to cover, we hope this issue of Psychiatric Times™ provides you with the tools, tips, and insights to follow in Hippocrates’ footsteps and help you help patients.

Mike Hennessy
Chairman and Founder, MJH Life Sciences
When reflecting on deeply held and widely divergent belief systems and individual preferences that feel foreign and unusual to me, I am reminded of one of my favorite metaphors for our different experiences of the world. Imagine a mansion with 100 rooms, each decorated in a unique style, setting it distinctly apart from the other 99. The north side of the mansion faces an established and mature forest, the east faces a rocky and turbulent ocean shore, the west overlooks a rugged and endless mountain range, and the south stretches over a grassy expanse with wildflowers and low growing brush. Imagine a mansion with 100 rooms, different experiences of the world.

Our minds are like roommates in this mansion, each decorated in a unique style, setting it distinctly apart from the rest of the mansion. Our understanding about all the secrets and mysteries that lie below the surface. My room is very comfortable, although friends tell me I really should replace some of my overly worn and dated furniture. I try to have an open mind when speaking to a friend, neighbor, or colleague whose views are in opposition to mine, realizing our room and window are based on their unique experiences. Sometimes it is hard when the truth seems so obvious to me. However, despite the potential for unlimited experiences and discoveries, our human tendency is to gravitate to a single room that feels safe and familiar and to forget about the rest of the mansion. Our understanding of the world and reality is determined by whatever we make sense of its place in the physical universe. That brain is thus shaped—through the gifts of neuroplasticity and synaptogenesis—by exploring different rooms and looking out their windows at different times of the day. Through these experiences, combined with inherited genetics and life events that impose themselves into our development, our unique characteristics that define our unique relationship to each other and the world around us.

However, despite the potential for unlimited experiences and discoveries, our human tendency is to gravitate to a single room that feels safe and familiar and to forget about the rest of the mansion. Our understanding of the world and reality is determined by whatever we make sense of its place in the physical universe. That brain is thus shaped—through the gifts of neuroplasticity and synaptogenesis—by exploring different rooms and looking out their windows at different times of the day. Through these experiences, combined with inherited genetics and life events that impose themselves into our development, each of us continues to evolve as a mind with beliefs, opinions, and characteristics that define our unique relationship to each other and the world around us.

At 62 years old, my window could use some repair. Small cracks and random smudges have obscured my view, but I still love looking at the open ocean and wonder about all the secrets and mysteries that lie below the surface. My room is very comfortable, although friends tell me I really should replace some of my overly worn and dated furniture. I try to have an open mind when speaking to a friend, neighbor, or colleague whose views are in opposition to mine, realizing our room and window are based on their unique experiences. Sometimes it is hard when the truth seems so obvious to me. Casual conversations about politics, religion, vaccines, evolution, and kindly to all, and understand that the very beauty of the human experience is our diversity and unique wisdom.

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Introducing an associated comorbidity of adult ADHD—the need to quiet a hyperactive mind

There is a significant overlap between adult ADHD and substance use disorder (SUD)^1,2

SUD is prevalent in adults with ADHD, and may relate to the core symptoms of the disorder. In fact, risk for SUD has been found to be double for individuals with ADHD vs those without^3:

Approximately 50% of adolescents and adults with SUD also have ADHD, which generally develops first.\(^4\)

39% of adults newly diagnosed with ADHD were found to have SUD in a multicenter survey.

- Alcohol use has been found to be nearly 10 times more common in adults with ADHD\(^3\)
- Adolescents and young adults with ADHD are up to 3 times as likely than those without to smoke and 4 to 5 times more likely to progress to heavy use of nicotine and marijuana after trying these substances once\(^2\).

Of the core ADHD symptoms, hyperactivity/impulsivity have shown a more robust relationship with the abuse of alcohol and tobacco.\(^1\)

Find out more at TEAM-ADHD.com/adult/comorbidities/sud

References:

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break and ground myself in the next in-breath and out-breath, which are always patiently awaiting my return. Ah yes, in-breath and out-breath...how simple...and how this exercise reminds me of the large mansion, with all the windows and all the differences that enrich us.

Recently our *Psychiatric Times* editorial team met with our Advisory Board, which consists of early-career psychiatrists and psychiatric mental health nurse practitioners. During our engaging and fruitful meeting, I felt that visceral call to recenter myself with an in-breath and out-breath. Board members were sharing their opinions about the type and format of media that they believed would most effectively connect with our readership. Short videos (2 or 3 minutes), tweets (with the most important content written in the first 2 sentences), and other social media posts were high on the list of recommendations. I felt aversion settle in, as I do not take any of these 3 approaches, nor do I find them helpful for my own style of learning. But through my in-breath and out-breath, I glimpsed those 2 challenging roommates who often impede my learning and exploration of the mansion: I and my. Once again, that neutral and impersonal breath had opened a door to a new room, and I realized that our Advisory Board members were sharing a gift with me, helping me understand how to best connect with the social media generation. In the spirit of this process, I invite you, our readers, to share with me and *Psychiatric Times* what type of content you find most interesting, educational, and inspiring. Help me explore some rooms in the mansion that I have not visited before.

**Mental Health Minute**

*Psychiatric Times* shares insights, commentaries, practice tips, and research reviews from leaders in psychiatry and clinicians like yourself.

The Importance of Sports for Patients With ADHD

BIRGIT AMANN, MD
Child & Adolescent Specialist and Psychiatrist
Medical Director, Crisis Services, Milwaukee County, Wisconsin

Tackling Reentry Anxiety: Strategies for Coping

SUSAN J. NOONAN, MD, MPH
Physician Consultant and Certified Peer Specialist
Author of 4 books and a blog

How Can Digital Tools Improve Medication Adherence?

ALEXIS SKOUFALOS, EdD
Associate Dean and Director of the Doctor of Health Science in Population Health at Thomas Jefferson University

Watch these Mental Health Minute videos on psychiatrictimes.com
NEW ONCE-DAILY DOSING OPTION FOR THE TREATMENT OF ANXIETY DISORDERS IN ADULTS WHO ARE RECEIVING STABLE, EVENLY DIVIDED, THREE TIMES DAILY DOSING WITH LORAZEPAM TABLETS.¹

LOREEV XR™ (lorazepam) Important Safety Information

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; AND DEPENDENCE AND WITHDRAWAL REACTIONS

• Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant use for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

• Use of LOREEV XR exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction.

• Abrupt discontinuation or rapid dosage reduction of LOREEV XR after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce this risk, use a gradual taper to discontinue or reduce the dosage.

CONTRAINDICATIONS
LOREEV XR is contraindicated in patients with:

• hypersensitivity to benzodiazepines or any ingredients in LOREEV XR
• acute narrow-angle glaucoma

WARNINGS AND PRECAUTIONS
Central Nervous System (CNS) Depression

• LOREEV XR may produce CNS depression. Caution against engaging in hazardous occupations or activities requiring complete mental alertness.
• Use alone and with other CNS depressants may lead to potentially fatal respiratory depression. Alcohol should be avoided, and other CNS depressants used with caution.

Patients with Depression or Psychosis

• LOREEV XR is not recommended in patients with a primary depressive disorder or psychosis. Preexisting depression may emerge or worsen.
• A possibility for suicide should be kept in mind in patients with depression. Benzodiazepines should not be used without adequate antidepressant therapy.

Risk of Paradoxical Reactions

• Paradoxical reactions have occasionally been reported during benzodiazepine use and are more likely to occur in the elderly. If this occurs, discontinue LOREEV XR.

Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

• LOREEV XR 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain individuals and is seen frequently in patients who also have aspirin hypersensitivity.

Neonatal Sedation and Withdrawal Syndrome

• LOREEV XR use during later stages of pregnancy can result in sedation and/or withdrawal symptoms in the neonate. Monitor neonates during pregnancy and labor for signs of sedation and withdrawal.

Risk in Patients With Impaired Respiratory Function

• Closely monitor patients taking LOREEV XR for impaired respiratory function, and consider discontinuing it if signs and symptoms of respiratory depression or apnea occur.

Laboratory Tests

• Leukopenia and elevations of lactase dehydrogenase (LDH) have developed in patients receiving lorazepam tablets. Periodic blood counts and liver function tests are recommended during long-term therapy.

ADVERSE REACTIONS
Most frequent adverse reactions in clinical trials were sedation (15.9%), dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%).

DRUG INTERACTIONS
Avoid initiation of UDP-glucuronosyltransferase (UGT) inhibitors. Dose reduction requires switching to lorazepam tablets for dose adjustment.

USE IN SPECIFIC POPULATIONS
Because of the potential for serious adverse reactions, breastfeeding is not recommended during treatment with LOREEV XR.

For additional safety information about LOREEV XR, visit loreevxrHCP.com for the LOREEV XR Full Prescribing Information.

Please see the accompanying Brief Summary.

You are encouraged to report negative side effects of prescription drugs to Almatica at 1-877-447-7979 or the FDA at www.fda.gov/medwatch, or call 1-800-FDA-1088.


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LORE-P-002
LOREEV XR™ (lorazepam) extended-release capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please consult Full Prescribing Information before use.

WARNING: CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, ADDICTION; and DEPENDENCE AND WITHDRAWAL
Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant use for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

LOREEV XR exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse commonly involve concomitant use of other medications, alcohol, and/or illicit substances, all of which are associated with an increased frequency of serious adverse outcomes. Before prescribing LOREEV XR and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction.

Continued use of LOREEV XR may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of LOREEV XR after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR, or reduce the dosage.

INDICATIONS AND USAGE
LOREEV XR is indicated for the treatment of anxiety disorders in adults who are receiving stable, evenly divided, three times daily dosing with lorazepam tablets.

DOSAGE AND ADMINISTRATION
Recommended Dosage
Initiate LOREEV XR in those being treated with lorazepam tablets, administered three times daily in evenly divided doses. Discontinue lorazepam tablets and administer the first dose of LOREEV XR in the morning on the day after the final dose of lorazepam tablets.

Administration Information
Administer LOREEV XR orally once daily in the morning. Do not crush or chew. Swallow LOREEV XR capsules whole, or open the capsule and sprinkle over a tablespoon of applesauce, followed by drinking water. Consume sprinkled LOREEV XR in its entirety within 2 hours; do not store for future use.

Dosage Increase for Inadequate Clinical Response
If the clinical response to LOREEV XR is inadequate and a dosage increase is needed, discontinue LOREEV XR and switch to lorazepam tablets. If an adequate clinical response is achieved with a stable, evenly divided three times daily dosage of lorazepam tablets, resume LOREEV XR once-daily dosing with the total daily dose of lorazepam tablets.

Discontinuation or Dosage Reduction
To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR, or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly.

Concomitant Use with UDP-glucuronosyltransferase (UGT) Inhibitors
If a UGT inhibitor is initiated during treatment with LOREEV XR, discontinue LOREEV XR and switch to lorazepam tablets to reduce the dosage.

CONTRAINDICATIONS
LOREEV XR is contraindicated in patients with:
- hypersensitivity to benzodiazepines or to any of the ingredients in LOREEV XR
- acute narrow-angle glaucoma

WARNINGS AND PRECAUTIONS
Dependence and Withdrawal Reactions
Acute Withdrawal Reactions
LOREEV XR may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction after continued use or administration of flumazenil may precipitate acute withdrawal reactions, which can be life-threatening.

Protracted Withdrawal Syndrome
In some cases, benzodiazepine users have withdrawal symptoms lasting weeks to more than 12 months.

Central Nervous System (CNS) Depression
LOREEV XR may produce CNS depression. Caution patients against engaging in hazardous occupations/activities requiring complete mental alertness, such as operating machinery or driving a motor vehicle. Alcohol should be avoided and other CNS depressant drugs used with caution.

Patients With Depression or Psychosis
LOREEV XR is not recommended for patients with a primary depressive disorder or psychosis. Preexisting depression may emerge or worsen during use. In patients with depression, a possibility for suicide should be borne in mind. LOREEV XR should not be used in such patients without adequate antidepressant therapy.

Risk of Paradoxical Reactions
Paradoxical reactions (agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) have been reported during benzodiazepine use. Such reactions may be more likely to occur in the elderly. Discontinue LOREEV XR if the patient has these reactions.

Allergic Reactions to FD&C Yellow No. 5
LOREEV XR 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of sensitivity is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Neonatal Sedation and Withdrawal Syndrome
Use of LOREEV XR during the later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate. Monitor neonates during pregnancy and labor for signs of sedation and neonates exposed to LOREEV XR during pregnancy for signs of withdrawal; manage these infants accordingly.

Risk in Patients With Impaired Respiratory Function
In patients with impaired respiratory function, respiratory depression and apnea have been reported with benzodiazepines. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression or apnea occur, consider discontinuing LOREEV XR.

Laboratory Tests
Leukopenia and elevations of lactate dehydrogenase (LDH) have developed in patients receiving lorazepam tablets. Periodic blood counts and liver function tests are recommended for patients on long-term therapy.

ADVERSE REACTIONS
In a sample of approximately 3,500 patients treated for anxiety, the most frequent adverse reactions to lorazepam tablets were sedation (15.9%), dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%). The incidence of sedation and unsteadiness increased with age. The following reported adverse reactions are categorized by System Organ Class (SOC):

- Blood and Lymphatic System Disorders: agranulocytosis, leukopenia, pancytopenia, thrombocytopenia;
- Endocrine Disorders: SIADH;
- Eye Disorder: eye function/visual disturbance (including diplopia and blurred vision);
- Gastrointestinal Disorder: constipation and gastrointestinal symptoms, including nausea;
- General Disorders and Administration Site Conditions: asthenia, fatigue, hypothermia;
- Hepatobiliary Disorders: jaundice;

(Cont’d)
Immune System Disorders: anaphylactoid reactions, hypersensitivity reactions;
Investigations: increase in bilirubin, increase in liver transaminases (including elevated LDH), increase in alkaline phosphatase;
Metabolism and Nutrition Disorders: change in appetite, hypotenatemia;
Nervous System Disorders: ataxia, autonomic manifestations, coma, convulsions/seizures, drowsiness, dysarthria/siurred speech, extrapyramidal symptoms, headache, tremor, vertigo, memory impairment;
Psychiatric Disorders: amnesia, change in libido, confusion, decreased orgasm, depression, disinhibition, disorientation, euphoria, suicidal ideation/attempt, unmasking of depression;
Reproductive System and Breast Disorders: impotence;
Respiratory Thoracic and Mediastinal Disorders: apnea, respiratory depression, worsening of obstructive pulmonary disease, worsening of sleep apnea;
Skin and Subcutaneous Tissue Disorders: allergic skin reactions, alopecia, dermatological symptoms.
Paradoxical reactions—including anxiety, excitement, agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, and/or hallucinations—may occur.
Small decreases in blood pressure and hypotension have been reported with immediate-release lorazepam.

Many adverse reactions are dose-dependent, with more severe effects occurring with high doses.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Available data from observational studies have identified a small increased relative risk with benzodiazepine use in early pregnancy and miscarriage, and a small increase in relative risk with benzodiazepine use later in pregnancy and preterm birth. In animal studies, administration of lorazepam during the organogenesis period of pregnancy resulted in increased incidences of fetal malformations at doses greater than those used clinically. Data for benzodiazepines suggest the possibility of increased neuronal cell death and long-term effects on neurobehavioral function, based on findings in animals following prenatal or early postnatal exposure at clinically relevant doses.

Lactation
There are reports of sedation, poor feeding, and poor weight gain in infants exposed to benzodiazepines through breast milk. Advise patients that breastfeeding is not recommended during treatment with LOREEV XR.

Pediatric Use
Safety and effectiveness of LOREEV XR has not been established in pediatric patients.

Geriatric Use
In general, dose selection for an elderly patient should start at the low end of the dosing range. Greater sensitivity (eg, sedation) of some older individuals cannot be ruled out.

Hepatic Impairment
LOREEV XR may worsen hepatic encephalopathy. Use with caution in patients with severe hepatic insufficiency and/or encephalopathy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
LOREEV XR contains lorazepam, a Schedule IV controlled substance.

Abuse
LOREEV XR is a CNS depressant with a potential for abuse and addiction. Even taking as prescribed may put patients at risk for abuse and misuse of their medication. The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo. The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use.

Dependence

Physical Dependence
LOREEV XR may produce physical dependence from continued therapy. Abrupt discontinuation or rapid dosage reduction or administration of flumazenil may precipitate acute withdrawal reactions, including seizures, which can be life-threatening.

Acute Withdrawal Signs and Symptoms
Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (eg, nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Protracted Withdraw Syndrome
Protracted withdrawal syndrome is characterized by anxiety, cognitive impairment, depression, insomnia, formation, motor symptoms (eg, weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months.

Tolerance
Tolerance to LOREEV XR may develop from continued therapy.

OVERDOSAGE

Clinical Experience
In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs. Manifestations of overdose include varying degrees of CNS depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, paradoxical reactions, and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, cardiovascular depression, respiratory depression, hypnотic state, coma, and death.

In case of an overdose, consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

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LOR-PR-004
Hello, From the Other Side: Psychiatric Complications in a Future Postpandemic World

Leah Kuntz

We all know that psychiatry, and the health care field at large, have been greatly impacted by the COVID-19 pandemic, but John J. Miller, MD, Editor in Chief of Psychiatric Times, shared a little bit more about how psychiatry will be impacted in a postpandemic world during his presentation at the 2021 Annual Psychiatric TimesTM World CME Conference.

“This virus has impacted virtually everybody,” said Miller wistfully. “The health effects of the individual who’s infected. The effects on family and friends of the infected individual. Individuals who modify their life in many ways because of a fear of getting infected. The stress, the unknown, the guilt, the anxiety of first responders. Health care providers often with overwhelming situations and not enough staff and too many patients.”

Miller shared a range of psychiatric symptoms that can occur as a result of COVID-19, as published in the American Journal of Psychiatry, including anxiety, depression, insomnia, fear, grief, phobias, posttraumatic stress disorder, social avoidance, increased substance abuse, suicidality, psychosis, and obsessive-compulsive disorder.

Miller also shared a list specific to children and adolescents, based on a study published in JAMA Pediatrics. Of about 81,000 participants included in 29 studies, 25% had clinically elevated depression and 20% had clinically elevated anxiety, and it was estimated that the degree of depression and anxiety in older children was double that of what would be expected prior to the pandemic.

An Attack on the Brain

Disturbingly, Miller shared that COVID-19 could have a more direct effect: “This is clearly in the early stages of understanding, but based on what is out there now, we do know that it appears the virus can directly attack the brain.” The SARS-CoV-2 virus can access the brain through 3 tracks: the olfactory tract, the vagus nerve, or the trigeminal nerve, Miller explained. If SARS-CoV-2 traverses the olfactory mucosa, it can cause the loss of smell while gaining access to the brain.

Miller shared a number of ways the virus can damage the brain. Damage to endothelial cells that abut the brain can lead to inflammation in thrombi and thus cause direct brain damage. Astrocytes, the primary type of brain cell affected, play an important role in brain fog and fatigue. Also well known is the neuroinflammation caused by COVID-19, which can cause an aggressive, systemic cytokine storm in serious COVID-19 infections. This storm can damage the blood-brain barrier and make it more permeable, allowing in more cells and potential active viruses. Furthermore, Miller shared, cytokines in the brain can activate microglia and enact astrocytes, which puts a further stress on the brain and can result in damage.

“In an ideal situation, there would be a recovery. But sometimes there’s a partial recovery, and other times, there’s no recovery, such as if there was a subsequent stroke,” Miller added.

Other Concerns

Substance abuse is another of Miller’s COVID-19–related concerns. The stress, trauma, and grief, compounded by a reduced access to treatments for substance use disorders, caused a rise in drug overdose deaths with more than 92,000 deaths according to the National Center for Health Statistics.

Furthermore, the antivaccine movement poses a significant threat to the safety of the general populace, Miller fears, as described in the Journal of Clinical Psychiatry editorial written by Joseph Goldberg, MD. Miller calls it “mass hysteria.”

“When these mass groups with mass hysteria mistrust, or frankly develop pure paranoia, and the secondary behaviors intrude into the realm of public safety, society needs to engage in a serious ethical debate as to what actions should be taken to protect [against] harm or risk to the many from the distortions or actions, or lack thereof, from the few,” said Miller.

Concluding Thoughts

Miller called COVID-19 a “modern medical challenge of the first order,” as it was described by authors in a Lancet editorial, and one that will continue to affect psychiatry and the health care field as a whole for many years to come. Miller offered some common-sense suggestions: Individuals should get vaccinated and educate others compassionately and accurately, and the number of vaccines available to the global community should be increased—that way, everyone can be safe.

REFERENCES
Chronic Adolescent THC Exposure: Mental Health Crisis?

Leah Kuntz

“Adolescence is a critical period, with increased risk for use of cannabis and, in particular, high tetrahydrocannabinol (THC)-potency cannabis. This may represent a public health crisis,” Christopher J. Hammond, MD, PhD, shared with attendees of the 2021 Annual Psychiatric Times™ World CME Conference.

In his presentation, “Impact of THC on Adolescents: Neurodevelopment,” Hammond shared that chronic adolescent THC exposure across animal and human studies is associated with disruptions or alterations in brain development. Furthermore, it is associated with adverse mental health outcomes, including depression and anxiety.

“Contrary to a lot of what the popular media messaging has communicated to us, data across studies of young people show that adolescents who use cannabis regularly and [then] cut down or stop using cannabis show reductions in depression and anxiety and improvements in cognition,” said Hammond.

Abstinence from cannabis for 3 to 4 weeks could reduce anxiety and depression, improve sleep, and boost cognition in adolescent regular cannabis users.1,2 Cannabis is the most commonly used federally illicit drug by US youth, and it accounts for more than 75% of teen admissions to substance use treatment programs. About 1.4 million adolescents try cannabis for the first time each year.3 Early-onset cannabis use, according to Hammond, can lead to numerous health issues, including major depressive disorder, alcohol use disorders, substance use disorders, suicidality, anxiety disorders, bipolar disorders, psychosis, and delinquent behaviors.4,5

“There appears to be a relatively consistent pattern of findings showing that adolescent cannabis use is associated in a dose-dependent manner with poor outcomes in academic and occupational functioning, in cognition, and in psychiatric and substance use outcomes, and that these may be worse for young people with mental health problems,” said Hammond.

Adolescent cannabis use could also lead to potential long-term brain effects, like dysfunction in white matter tracts, altered brain waves, and decreased blood flow in the brain. These effects are larger and more consistent with earlier age of onset and heavy use.

“As more data come in, we can further update and inform this field, but using the data as they exist now is important,” concluded Hammond.

REFERENCES
Finding Antidotes to Burnout Through Contradictory Truths

Heidi Anne Duer, MPH

“For us to say that this has been a time of change, stress, and loss is an understatement,” Alana Iglewicz, MD, told attendees, “because the COVID-19 pandemic has fundamentally taken the rug from underneath our feet. [It has] changed the fabric of how we live our lives [and] how we work, and understandably, the amount of change and stress is very palpable and the amount of loss is even more.”

Iglewicz, assistant clinical professor of psychiatry at the University of California San Diego, shared insights on COVID-19’s impact on health care workers. In addition to the regular stressors, health care professionals faced many challenges during the height of the pandemic. Work-life balance was disrupted, shifts were longer, and fears about personal risk and risk to family members abounded, she said. There also were increased home-life demands associated with children’s virtual schooling, caregiver burdens, and a general sense of lack of control.

A recent study of COVID-19 and stressors of almost 21,000 health care professionals between May and October 2020 and discovered alarming rates of burnout and stress, Iglewicz reported. Investigators found that 61% feared virus exposure or transmission, 38% reported anxiety or depression, 43% reported work overload, and 49% reported burnout. Not surprisingly, there were some gender and racial differences, she said. Higher rates of burnout were found among females and minorities.

Iglewicz reminded attendees that burnout has been an issue for years and has even garnered media attention due to its very real consequences. In health care, burnout can affect patients, the health care system, and the individual, she explained. In patient care, burnout leads to worse patient outcomes and increased medical errors. On a systems level, there is a drop in productivity as well as a great cost in replacing clinicians. On an individual level, burnout can lead to substance use and abuse, depression and suicidal ideation, and even an increase in motor vehicle accidents, Iglewicz said.

Fortunately, improvement in burnout started before the pandemic. Iglewicz said, noting a study by Tait D. Shanafelt, MD, and colleagues that looked at rates of burnout and stress, Iglewicz said. Electronic health records, excessive workloads, and clerical burdens were addressed. Although these are important aspects, they still involved finger-pointing. She suggested it would be more productive to move to an understanding and self-introspective perspective.

Iglewicz entertained the idea of changing the term burnout to “loss of meaning.” People enter medicine with idealistic notions and then their work no longer matches those notions and loses meaning. Similarly, she suggested considering burnout as unresolved grief. In other words, she said, there is so much to mourn in terms of why people entered the medical field. This dilemma allows you to face the limitations and begin to accept the issues.

Additionally, burnout in the health care field may be code for depression, she suggested. There is no stigma associated with the term burnout; it is tossed around casually in conversations, the media, and the like. However, there is still stigma associated with depression.

Iglewicz added there is a very fine line between depression and burnout.

“So what can be done? The first step, she said, is that clinicians must become reformed perfectionists. “The same traits that helped us get into medical school come with a price,” she said. Perfectionism, detail-oriented focus, desire for control, empathy, and competitiveness are among those traits. When ever possible, clinicians should try to turn down the level of perfectionism. Let the struggles, hurdles, and adversities refine you, not define you, she urged.

It is also important to engage in system level change, she added. And although it should not be a singular focus, self-care is vital.

She then shared 5 antidotes to burnout: find a healthy relationship with anger, pick your battles, practice ordinary kindness and compassion, support one another and seek out support when needed, and live with contradictory truths.

Iglewicz took the opportunity to conclude her talk with a contradictory truth that rings very true on the subject of burnout: “We’re all stronger than we know. Simultaneously, we are all more vulnerable than we’d like to acknowledge.”

REFERENCES
Borderline Personality Disorder:  
3 Things You Need to Do for Patients

Heidi Anne Duerr, MPH

There are 13 million adults with borderline personality disorder (BPD) in the United States and, of that number, 1.5 million are adolescents, according to Carl Fleisher, MD. To best support patients with BPD, there are 3 important tasks to consider, explained Fleisher, assistant clinical professor of psychiatry at University of California Los Angeles Health.

To kick off the discussion, Fleisher shared the case example of “Hannah,” a girl aged 16 years, who presents wondering if she has BPD after Googling her experience. Specifically, she has rapid mood swings, feels numb more often than sad, and cuts herself superficially several times a week. She has 1 friend and spends all of her time with that friend out of fear that the friend will desert her. She is interested in boys, but avoids them. Hannah does not voice her needs to parents, teachers, or friend; instead, she goes along with whatever they want or like.

The first task, therefore, is to make the diagnosis, Fleisher said. There are 9 criteria to consider, and sometimes it feels like they are all over the map. As such, the patient might not see the connections, so it is important to help draw them for patients. One way to do that, he explained, is to use a model of interpersonal hypersensitivity. Since we all want and need to be in relationships, and we all are hypersensitive, we may have a fear of abandonment. From there, you can talk about the other symptoms.

Fleisher also likes the McLean Screening Instrument for rapid assessment of patients. It helps patients think things through, he explained. It also provides an opportunity for further discussion, as the clinician may have a different perspective than the patient does on a particular item.

Most patients are relieved when they finally receive a diagnosis, Fleisher said. He shared the following patient perspective: “It explained a lot of things and I felt an enormous sense of relief that there was an explanation for the way I was.”

The second task is to refer patients to helpful resources, including psychoeducation, support, and treatment strategies, Fleisher said. He recommended a number of resources both for patients and their clinicians: the National Education Alliance for Borderline Personality Disorder, Mentalizing Initiative, the Anna Freud National Centre for Children and Families, and McLean Hospital’s Borderline Personality Disorder Training Institute.

In terms of treatments, Fleisher said, there are 4 evidence-based psychotherapy modalities: dialectical behavioral therapy, transference-focused psychotherapy, mentalizing-based therapy, and good psychiatric management, which is not an orientation but more of a framework for clinicians. “It is also possible also that plain old talk therapy is an adequate treatment for borderline personality disorder, especially if you have nothing else,” he told attendees.

It is also important to consider psychoeducation and family support, Fleisher added. He shared the results of a study looking at the impact of 6 weeks of psychoeducation on patients with BPD. The investigators found that symptom presentation was reduced by about half and stayed low for 2 months after the intervention protocol. Similarly, since caregivers and family members of those with BPD are often under a lot of stress and strain, it is important to broaden the treatment lens and provide support to them, too.

Unfortunately, Fleisher noted that no medications are approved by the US Food and Drug Administration to treat BPD specifically, and no medication is uniformly helpful. Too often, patients find themselves on multiple medications, he said, and polypharmacy poses a significant danger because of adverse effects, like weight gain associated with antipsychotics.

“We can do a whole hour-long talk on just medication for BPD, but the short of it would be this: If you’re going to use medication to treat one of the comorbid illnesses that BPD presents with, as opposed to the BPD itself, then you can try that,” Fleisher told attendees. “But if we’re going to try to treat the symptoms of BPD itself like lability, paranoia, that sort of thing, then it may be that we want to consider a brief trial of medication to get people through a crisis.” After using a medication in a way that is helpful, it is important to consider reducing then eliminating it, because they are not expected to be helpful in the long term and want to avoid polypharmacy problems, he added.

The third task is to monitor the effectiveness of the treatment, Fleisher said. Start with baseline measurements on the areas you want to avoid polypharmacy problems, he added. It is also important to consider psychoeducation and family support, Fleisher added. He shared the results of a study looking at the impact of 6 weeks of psychoeducation on patients with BPD. The investigators found that symptom presentation was reduced by about half and stayed low for 2 months after the intervention protocol. Similarly, since caregivers and family members of those with BPD are often under a lot of stress and strain, it is important to broaden the treatment lens and provide support to them, too.

Most patients are relieved when they finally receive a diagnosis, Fleisher said.

REFERENCES
How Did Virtual Schooling Affect Youth?

Heidi Anne Duerr, MPH

Virtual schooling during the pandemic presented challenges that might have long-term effects on children and adolescents, according to Karen Dineen Wagner, MD, PhD.

Wagner, who is professor and chair in the Department of Psychiatry and Behavioral Sciences at University of Texas Medical Branch, reported results from studies indicating increases in anxiety, obsessive compulsive disorder, conduct problems, prosocial behavioral problems, sleep issues, and worsening of pre-existing mental health disorders. This, in turn, resulted in increased mental health-related visits to the emergency department. Children at highest risk for increased psychiatric and behavioral problems included youth who were disadvantaged or refugees as well as those who had a chronic disorder, adverse childhood experiences, and a preexisting mental health disorder, noted Wagner.

Virtual schooling affected other areas of well-being, Wagner said. For example, in a nationwide survey of parents (N = 1290) with children aged 5 to 12 years, youth who attended virtual school were more likely to have decreased physical activity compared with students attending school in person and those attending combined in-person and virtual school (62.9%, 30.3%, and 52.1%, respectively).1 Virtual students also reported spending less time outdoors, less time with friends virtually, and less time with friends in person. Similarly, 24.9% of students attending virtual school reported worsened depression and anxiety compared with 24.7% of those in combined schooling and 15.9% of those attending school in person.

The effects were also felt by the parents. Compared to parents whose children attended in-person or combined schooling, parents whose children attended virtual school were more likely to report loss of work, childcare challenges, conflict between working and providing childcare, emotional distress, and difficulty sleeping.1

Negative effects on youth were seen in countries around the world. Wagner discussed the results of a cross-sectional survey of 367 students in Saudi Arabia.2 The investigators found 55% of respondents had moderate stress, and 30.2% had high stress levels.

Youth with attention-deficit/hyperactivity disorder (ADHD) and their parents especially struggled, Wagner added. In one study of 239 adolescents, 118 of whom had ADHD, those with ADHD had fewer routines and more difficulties with remote learning.3 Parents of adolescents with ADHD reported more difficulty in supporting home learning and home school communication. Even parents whose children with ADHD had an individual education program reported increased challenges. As a result, 22% of families incurred financial costs.4 Wagner noted the American Academy of Child & Adolescent Psychiatry and the American Psychiatric Association developed a list of recommendations for virtual schooling.5 The organizations noted that education, including school attendance, is an essential component of health development. While classroom-based education is not possible, they said it is a priority to optimize social interaction. They noted additional resources should be made available for children with special needs, and the mental health of students must be continuously addressed. They also advocated for systems that effectively and efficiently identify issues early and have means for interventions.

Ultimately, certain things are needed to better support a virtual schooling system. “There needs to be access to mental health services, as well as individual educational programs. There also needs to be resources for disadvantaged youth,” Wagner concluded. “Attention has to be directed toward the importance of physical activity and also participation in extracurricular activities as well as other peer group activities.”

REFERENCES


The Challenges and Rewards of Working With Culturally Different Patients

Leah Kuntz

Working with culturally different patients can be challenging and rewarding, and it is rarely avoided in current-day psychiatry, Larry Merkel, MD, PhD, told 2021 Annual Psychiatric Times™ World CME Conference attendees.

“Everyone’s backgrounds are very complicated, multilayered, and dynamic,” said Merkel, who is a professor of psychiatry and neurobehavioral sciences and the director of outreach at the University of Virginia.

“No person has influences these days from just 1 culture—we live in multiple cultures.”

Cultural distance is, essentially, qualitatively thinking about the difference between doctor and patient: How many facets of your background are and are not similar to facets of theirs?6

“Research [results have shown] that the greater the cultural difference between the psychiatrist and the patient, the more likely there are to be mistakes of all sorts,” Merkel said.

Merkel also covered models for managing cultural differences, including the Cultural Formulation Interview (CFI) from DSM-5, which patients seem to value over traditional interactions.7 Field trials in a variety of locations (ie, United States, Canada, Netherlands, India, Kenya, and Peru) showed CFI is feasible, acceptable, and useful, and it sensitizes clinicians to cultural issues.8 An implementation study in an outpatient psychiatric clinic demonstrated that CFI is an integral part of cultural competence training; there was a 50% reduction in discontinuation rate vs treatment as usual after 1 training session.9

CFO does have some potential problems, Merkel noted. CFI can help with direction of therapy, but not diagnosis. Additionally, it is not able to be used with a patient who has a cognitive disability or such severe symptoms as acute psychosis, suicidal behavior, or aggression.

Further, the concept of identity may be difficult to translate, according to Merkel. “We all have multiple identities. We’re fathers, mothers, children, physicians, barbers, Protestants, Catholics, Jews—all sorts of identities. We use those identities in different ways at different times. Sometimes, if you ask a person what their identity is, they may have no idea what you’re talking about.”10

REFERENCES

Major Depressive Disorder
Understanding Treatment-Resistant Depression

Heidi Anne Duerr, MPH

“There appear to be at least 3 types of major depressive disorder [MDD] based on pharmacology,” Sheldon H. Preskorn, MD, told attendees. Preskorn, a professor in the Department of Psychiatry and Behavioral Sciences at University of Kansas School of Medicine in Wichita and psychopharmacology section editor of Psychiatric Times™, was named Educator of the Year at the conference.

The first type of MDD responds to biogenic amine antidepressants, Preskorn said, and represents approximately 60% to 65% of patients. The second group is nonresponsive to biogenic amine antidepressants but responsive to glutaminergic [NMDA] antidepressants. It represents approximately 25% of patients with MDD. The third group is nonresponsive to both biogenic amine and glutaminergic antidepressants and represents approximately 15% of patients with MDD.

To get a clearer understanding of this philosophy, Preskorn turned to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which was funded by the National Institute of Mental Health to determine the effectiveness of treatments for MDD in patients who failed to respond to initial treatment with an antidepressant. In the study, the initial treatment was bupropion. If MDD was nonresponsive to treatment, patients were switched to bupropion SR, sertraline, or venlafaxine XR, or their treatment was augmented with bupropion SR or bupirone. 

In cases that remained unresponsive, patients were switched to mirtazapine or nortriptyline, or they were given augmentation with lithium or triiodothyronine. Finally, if treatment still failed, participants were switched to tranylcypromine or mirtazapine combined with venlafaxine SR.

What was noteworthy, Preskorn explained, was that acute outcomes worsened with increasing number of prior treatment failures. In the group with no or limited prior medications, 27.5% achieved remission as measured by HAM-D 17. Patients in the group with 1 prior failure had remission rates of 21.1%. And those with 2 and 3 prior failures had remission rates drop of 16.2% and 6.9%, respectively.

“If you’re like me, you see these patients every day in the clinic, because we usually get patients after they have already been tried on an antidepressant in primary care,” Preskorn said. “So we always are getting someone who has probably not benefited from treatment. And not only did they not benefit [but] they also were much more likely to relapse.”

In looking at current treatment strategies, Preskorn said the vast majority of patients initially receive a selective serotonin reuptake inhibitor. The next step most likely is either a serotonin-norepinephrine reuptake inhibitor or a norepinephrine dopamine reuptake inhibitor, he said. If that does not work, he explained there is the likelihood of augmentation with atypical antipsychotics or other kinds of medications, or a new drug such as esketamine. If there still is not a proper response, the patient would move into monoamine oxidase inhibitors or various kinds of electrical treatments such as transcranial magnetic stimulation.

So, why is there so little benefit from switching among the various antidepressants, Preskorn asked the audience. “First and foremost, you have to realize that the FDA only requires superiority over placebo for approval. There is no requirement that a new drug is superior to antidepressants, be it superior either in efficacy or tolerability…new does not mean improved.”

“The second thing is psychiatric drug development for antidepressants and antipsychotics has, for 60 years, mainly been reshuffling the relative receptor binding affinity of biogenic amine mechanisms of action. So they all work on the same neurotransmitter system.”

To better help understand the situation Preskorn gave the example of a patient with pneumonia. A certain percentage of patients treated with penicillin will get better. Those who do not are then given penicillin 2, and a smaller percentage likely will improve because the infectious agent causing the pneumonia does not respond to penicillin. The same thing happens with antidepressants. If you keep using the same type of antidepressants, the chance of response will continue to diminish because the depression is not responding to that mechanism of action.

Although shuffling identical mechanisms has not necessarily improved efficacy, it has improved safety and tolerability.

REFERENCES

Listening to Terry Gross
Richard Berlin, MD

1. Dear Terry
Back in the 70s, before I knew my own voice, I listened to yours while we learned our trades—you with comics and writers and rock stars, me with locked-ward psych patients. I can still hear us pepper questions, quick to interrupt, not yet knowing how silence can spark our work. And we both got bruised—Gene Simmons taunting you like a teenager inflaming his mom, my patients slamming doors when I pressed them to tell me, “How does that make you feel?”

2. The Way We Work
I almost fell out of my Stressless chair when I learned your guests sit in distant studios, your connection like a blind musician tuned into rhythm and tone, me in soundproofed, sweat-soaked exam rooms, high-beam eye contact, mirrored bodies, my head nodding yes, my hand circling. Tell me more, you and I coaxing people to reveal themselves with words.

3. Laughter
Your two laughs are specialized tools—the first, deep, spontaneous, seductive, impossible to fake, a laugh that says, I love you! You have my attention! My All-Time Favorite Interview John le Carré, bored by his book promotion tour, stood offish as a kid in the vice principal’s office, British monotone, one-word answers, nothing revealed until you focused on his growing up with a con man father, le Carré grudging a few details, you laughing with appreciation, le Carré spilling more, a spy coming in from the cold, opening up as if he had been waiting all his life to have this conversation with you, two mates knocking down pints at the pub.

4. Psychoanalysis
Speaking of sex, I love to hear you work when your guest is a psychoanalyst, our godparents in the interview family, a reflective tribe with an allergy to giving direct answers, like the analyst promoting her book about sex in the elderly, how you tiptoed around her, each word, every question chosen with the care of a sapper cutting wires on an unexploded bomb. But other guests aren’t quite so guarded, and I shift to the edge of my seat when I hear you make your graceful turn into questions about parents and childhood, your arc like a pilot’s approach to a runway tucked in a mountain valley, Springsteen’s Oh Terry! awe when you connected his developmental dots.

5. Saying Goodbye
Now that I’ve listened to you longer than Prozac or Freud, I’ve learned saying goodbye can be hard, my endings with patients signaled by a glance at the clock, a summary of our session, the next appointment time, yours closing when you roll the credits with a list of names my ears savor like a man with Tourette’s who ticks on sounds: Ann Marie Baldonado Molly Seavy-Nesper, Mooj Zadie. But most of all I wait to hear your Thank You, Goodbye Voice reveal exactly how much you love your guest, which reminds me how much I love my patients, the way strangers enter our lives and revive us with a breath of fresh air.

6. Overcoming Vaccine Hesitancy
Continued from Cover

Overcoming Vaccine Hesitancy

into our profession’s collective unconscious. Instead, I will endeavor to gain an understanding of our “culture of hesitancy” by invoking the “nocebo effect,” a pharmacotherapeutic construct that is carefully considered by clinical researchers who perform randomized controlled trials of new medications.

The nocebo effect is at play when individuals receiving an inert or effective medical treatment harbor the expectation that the therapeutic intervention will harm them. Just as placebos have the potential to cure, nocebos can cause pain. These days, many anticipate and imagine that a potentially life-preserving inoculation is likely to be harmful. The psychic pain engendered by this negative expectation may qualitatively act as an anticipatory nocebo effect, akin to anticipatory anxiety.

Regarding COVID-19 immunizations, Amanzio et al link vaccine hesitancy in European populations to the presence of potent nocebo effects, especially when individuals are offered specific vaccines with efficacy that is lower than that of the best-performing vaccines. These authors go on to suggest that a psychoeducational approach that acquaints the public with the countertherapeutic nocebo effect has the potential to overcome vaccine hesitancy.

Kristensen et al describe how potent nocebo effects interfere with the efficacy of biosimilar agents. They suggest that carefully coordinated multidisciplinary communication plans may help to overcome patients’ negative expectancies. Most psychiatrists have a great deal of experience helping mentally ill patients overcome their reluctance to take psychiatric medications. Sharing our hard-earned wisdom with colleagues in other specialties has the potential to be quite beneficial.

Bagus et al, in Spain, have written extensively about the relationship between nocebo effects, fear, anxiety, and mass hysteria. Their view is that media outlets and governments may inadvertently spread a contagion of fear and anxiety that culminates in a set of pathological beliefs and behaviors akin to mass hysteria. This “infectious” disease of pathological belief systems may spread virally through social media and culminate in a shared anticipatory nocebo effect that may manifest as vaccine hesitancy.

Ironically, this discussion of nocebos, a relevant concept in today’s world of randomized controlled trials, has led us to re- treat to the somewhat retro and uncomfortable territory of poorly understood sociological phenomena like mass hysteria.
Psychosocial speculation of this sort harks back to expansive and speculative works of Sigmund Freud like *Totem and Taboo* (1913), *Civilization and Its Discontents* (1929), and *Moses and Monotheism* (1939).

Psychiatry, a field once dominated by psychoanalytic theory, has robustly embraced neuroscience, brain chemistry, and pharmacotherapy in the past 4 decades. Countless mentally ill patients have benefited greatly from biological psychiatry’s advances. Although we have transcended our mid–20th century love affair with all concepts Freudian, it may be important for us to tap into old-fashioned techniques, such as careful listening, psychosocial formulation, and precise communication, to help patients and colleagues manage better in this challenging era of pseudo-information and reductionistic thinking.10

Dr Adelman is a coaching and consulting psychiatrist and is board-certified in psychiatry, addiction medicine, and coaching. He launched www.AdelMED.com after spending 8 years directing Physician Health Services, Inc. On the faculty of the University of Massachusetts Medical School, he is a consultant in psychiatry in the Division of Alcohol and Drug Abuse of McLean Hospital, an affiliate of Harvard Medical School.

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The population of older adults (65 years or older) in the United States is increasing rapidly. It is estimated that their population will nearly double from 15% in 2014 to 24% (98 million) of the total population by 2060.1 Currently, 1 in 5 older adults in the United States has a diagnosable mental health disorder, with personality disorders, anxiety disorders, mood disorders, and substance use disorders being the most common.2 It is also estimated that the total number of individuals with Alzheimer disease in the United States will rise from 5 million in 2013 to approximately 14 million by 2050.1

During the initial stages of the COVID-19 pandemic, older adults were more likely to be infected with the virus and have worse outcomes than their younger counterparts (Figure).3 Similarly, morbidity and mortality rates were highest among older adults who had cooccurring conditions such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease, and chronic kidney disease.4 Older adults were also susceptible to loneliness and social exclusion.5 The risk factors that were associated with worsening of physical, psychological, and social well-being among these individuals included age, ageism, isolation, loneliness, lack of security, frailty dependency, sexism, stigma, abuse, and cognitive and sensory impairments. The pandemic also had a significant effect on the mental health of older adults.6

COVID-19 infection presented as altered mental status in the absence of respiratory symptoms or fever. Worsening of confusion, agitation, disorientation, refusing care, and apathy were also presenting symptoms among this population. Older adults also reported greater rates of loneliness, depression, risk for substance use disorders, and suicide.7-6 In addition, worsening of psychiatric symptoms was noted among older adults who were admitted to hospitals during the lockdown periods.10 To care for older adults with mental health disorders during the pandemic and to minimize the effects of sustained social isolation, many alternative methods to providing care were developed.11,12 Electronic devices or platforms to conduct virtual interactions for social, profession, or clinical interactions became important tools. Telephone evaluations were conducted for older adults who were not able to use technology. In addition, community connection websites were established to provide a searchable directory of organizations that provided essential daily services for older adults. Older adults were also encouraged to participate in social, spiritual, or religious interactions using electronic means/platforms.

Despite the difficulties they endured during the pandemic, older adults with mental health disorders in the United States have done fairly well, compared to younger adults.13 Families, friends, clinicians, social support systems, health care agencies, health care systems, and governmental and nongovernmental agencies have rallied together during this period of uncertainty to ensure that the provision of care for older adults continues.
Recognizing and Addressing Psychiatric Implications of Sleep Disorders

Christine Juang, PhD; Colleen Mills-Finnerty, PhD; Erin Cassidy-Eagle, PhD; DBSM; Makoto Kawai, MD; and Christine Gould, PhD

Sleep complaints are common among older adults. Such complaints may reflect their concerns about normative age-related changes in sleep, such as reduced total sleep time, lighter sleep, and increased wakefulness at night, as well as the prevalence of common sleep disorders in late life, including sleep-disordered breathing and chronic insomnia. Table 1 displays common sleep disorders in older adults and associated risk factors and correlates.

Sleep-disordered breathing describes respiratory events that occur during sleep, ranging from simple snoring to pathologic hypopneas (decreased air flow) and/or apneas (temporary breathing cessation). Obstructive sleep apnea (OSA) is defined as the apnea-hypopnea index (average hypopnea and apnea events rate per hour) being above 5. The general prevalence rate of OSA is approximately 22% in men and 17% in women, and it increases with age. Chronic insomnia, characterized by difficulties initiating and maintaining sleep, is also prevalent in the older population, with estimates of insomnia symptoms close to 50%, although estimates of insomnia diagnosis are variable.

Both OSA and chronic insomnia are linked with various psychiatric concerns. OSA is associated with increased risks of vascular dementia, Alzheimer disease, and major depressive disorder. Insomnia is also associated with the onset of depression, anxiety, alcohol abuse, and psychosis. Sleep disturbances may potentiate symptoms of mental illness via several mechanisms: disruptions of memory consolidation processes that normally occur during sleep; increases in irritability and fatigue; and negative impacts on cognitive function.

It is important to note the bidirectional relationship between sleep disorders and psychiatric disorders in older adults. That is, psychiatric disorders can be both the cause and consequence of sleep disturbances. Therefore, the challenge is to determine whether sleep disruption should be the primary target for intervention or whether there are also comorbid psychiatric symptoms that need to be addressed for treatment to be successful.

Assessment of Sleep Disorders
It is helpful to start with a detailed history regarding the nature of the patient’s sleep complaints, other areas of functioning, and any other comorbid conditions that might be impacting their sleep. It can be helpful to walk through a typical 24-hour period to review sleep problems in greater detail, including onset, duration, frequency of disturbances, and possible contributions of sleep environment (eg, temperature, noise, etc.). A sleep diary can also provide a sampling of a typical week of sleep. Reported sleep difficulties often have daytime consequences, so it is important to ask about their daytime behaviors (eg, napping, canceling plans) used to counteract or cope with perceived real sleep loss. This information sheds light on the patient’s relationship with their sleep, including whether sleep impacts their ability to function and their level of concern surrounding the possible downstream effects of sleep loss. The Figure summarizes the assessment flow.

Medical conditions, medications, pain level, and alcohol or drug use should be discussed, as these factors can adversely affect sleep. Table 2 shares screening measures that are useful for gathering information about other contributing factors to poor sleep, including possible comorbid sleep disorders. For example, the Pittsburgh Sleep Quality Index, a global measure of sleep quality, may help identify the presence of potential sleep disturbance due to medical comorbidities (eg, pain, waking to use bathroom), psychiatric comorbidities (eg, nightmares), and use of sleep medications, including over-the-counter sleep medications. Furthermore, assessment of daytime sleepiness and screening for sleep apnea may be helpful to determine whether a sleep study is needed.

To make a diagnosis of OSA, home study (level 3 study) or in-lab polysomnography (PSG; level 1 sleep study) are required. In-lab polysomnography is considered a gold-standard sleep study; home study is less accurate because fewer sensors are involved. Home study is usually indicated for the confirmation of OSA diagnosis in patients with a high pretest probability of OSA. In-lab PSG is recommended for patients with comorbidities such as congestive heart failure, chronic lung disease, or neurologic conditions.

Finally, it is crucial to ask the patient what they are currently doing to manage their symptoms and their level of optimism around efforts to help.
information will be helpful in designing a treatment plan that not only improves the quality and quantity of their sleep, but also addresses the psychological impact through psychoeducation, support, and problem solving.

**Treatment for Sleep Disorders**

**Obstructive sleep apnea.** Positive airway pressure (PAP), a device that helps keep the airway open during sleep through a stream of compressed air, is the first-line medical treatment for moderate or severe sleep apnea. Several types of PAP devices exist; the most commonly used is continuous PAP, and other advanced options include bilevel PAP. For individuals with difficulty adhering to PAP use, other treatment options can be considered, including oral appliances (eg, mandibular advancement devices) and surgical options (either soft or hard tissue surgery or implantation of a nerve stimulation device). Improvements in sleep quality, daytime symptoms, and cognitive functions are often observed when OSA is adequately addressed.

**Chronic insomnia: pharmacological approaches.** There are several US Food and Drug Administration-approved prescription hypnotics for insomnia, including benzodiazepines (eg, eszolam, temazepam), nonbenzodiazepines (eg, eszopilocne, zolpidem), melatonin receptor ago-

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**Table 1. Sleep Disorders in Older Adults**

<table>
<thead>
<tr>
<th>Primary sleep disorders</th>
<th>Symptoms</th>
<th>Risk factors and correlates</th>
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<tbody>
<tr>
<td>Sleep-disordered breathing (eg, obstructive sleep apnea)</td>
<td>Respiratory events occurring during sleep, including snoring, hypopneas, and apneas; accompanied by daytime sleepiness</td>
<td>Older age, male gender, obesity, snoring, use of sedating medications or alcohol, race, smoking, family history, configuration and aging-related changes of upper airway configuration, loss of tissue elasticity</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Persistent difficulty initiating or maintaining sleep, with daytime impairment in functioning</td>
<td>Psychiatric disorders (eg, anxiety, depression), chronic medical conditions (eg, arthritis, diabetes, chronic pain, cancer)</td>
</tr>
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**Sleep-related movement disorders:**

- **Restless legs syndrome**
  - Abnormal sensations in leg(s) when resting, often in bed when falling to sleep
  - Older age, gender (women)

- **Periodic limb movement**
  - Repeated kicking or jerking of legs during sleep throughout the night; may cause sleep fragmentation or daytime sleepiness
  - Older age

- **Parasomnias:**
  - **Nightmares**
    - Vivid, disturbing dreams occurring during Rapid eye movement (REM) sleep; results in distress upon awakening
    - Depression, anxiety, insomnia

- **REM sleep behavior disorder**
  - Absence of muscle atonia normally found during REM sleep, resulting in body movements during dreams (ie, acting one’s dreams)
  - Lewy body dementia, Parkinson disease, narcolepsy

- **Circadian rhythm sleep-wake disorders (eg, advanced phase sleep disorder)**
  - Becoming sleepy in early evening and waking in early morning. Circadian rhythms do not align with societal norms for wake/sleep, causing distress
  - Older age

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**Table 2. Sleep-Related Screening Questions**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Cut-point</th>
<th>How to access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>19 items, scored to create 7 components, measure global sleep quality</td>
<td>Poor sleeper &gt; 5</td>
<td><a href="http://www.sleep.pitt.edu/instruments/">www.sleep.pitt.edu/instruments/</a></td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
<td>7 items measure severity of insomnia symptoms</td>
<td>• 0-7, no insomnia;</td>
<td><a href="http://www.ons.org/sites/default/files/InsomniaSeverityIndex_ISI.pdf">www.ons.org/sites/default/files/InsomniaSeverityIndex_ISI.pdf</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 8-14, subthreshold insomnia;</td>
<td></td>
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<td></td>
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<td>• 15-21, moderate clinical insomnia;</td>
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<tr>
<td></td>
<td></td>
<td>• 22-28, severe clinical insomnia</td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>8 items assess the likelihood of falling asleep in varied situations</td>
<td>Excessive daytime sleepiness &gt; 10</td>
<td><a href="https://epworthsleepinessscale.com/">https://epworthsleepinessscale.com/</a></td>
</tr>
<tr>
<td>STOP-BANG ([Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, and Gender)]</td>
<td>8 items that assess risk for obstructive sleep apnea</td>
<td>Yes to 3-4 questions indicates intermediate risk; yes to 5-8 questions indicates high risk</td>
<td><a href="http://stopbang.ca/osa/screening.php">http://stopbang.ca/osa/screening.php</a> Site contains additional scoring information.</td>
</tr>
</tbody>
</table>
nists (eg, ramelteon, orexin/hypocretin receptor antagonists (eg, sapienexant), and an antihistamine (doxepin). Other pharmacological drugs with sedating effects that are commonly prescribed for sleep include trazodone, mirtazapine, gabapentin; other sedative antipsychotics include quetiapine. However, many sedative hypnotics have negative side effects. Benzodiazepines, in particular, are not recommended for late-life insomnia due to their increased risks of cognitive impairment and falls.18 Nonpharmacological approaches are therefore regarded as the first line of treatment for insomnia, as they have been found to be more effective, with minimal side effects.19

**Nonpharmacological approaches.** Cognitive behavioral therapy for insomnia (CBTI) is an evidence-based, multicomponent therapy that is recommended as the first line of treatment for insomnia, with strong empirical support for the general population20 and elderly populations.21 In the context of medical and psychiatric comorbidities, CBTI was found to improve sleep and comorbid psychiatric symptoms.22 To optimize CBTI for older adults with comorbid psychiatric symptoms, Table 3 illustrates CBTI intervention components as well as adaptation considerations for older adults23 and modifications in the context of comorbid depression and anxiety.

For older adults with psychiatric comorbidities, additional modifications may be warranted. Depressive symptoms, such as low motivation and energy, may be associated with lower adherence in the behavioral recommendations of CBTI, highlighting the need for motivational enhancement strategies. Incorporating positive mood strategies into CBTI, such as behavioral activation (eg, daily pleasant activity scheduling), cognitive reframing (eg, thought records focusing on depression-related thoughts), and positive affirmation (eg, positive data logs and cue cards), could all help address comorbid insomnia and depression.23

For older adults who have anxiety, considerations include assessing sleep anxiety, as certain CBTI strategies may become less effective among those who are significantly anxious about sleep. For example, sleep restriction, intended to promote sleep drive, may be less effective in consoli-
dating sleep due to heightened arousal levels masking sleep drive.24 To address heightened arousal at night, there may be benefits in introducing relaxation exercises (eg, diaphragmatic breathing or progressive muscle relaxation) and other cognitive-behavioral strategies for managing anxiety (eg, constructive worry).

More research is needed to better understand whether to treat these comorbid conditions sequentially or concurrently in order to optimize treatment outcomes for both sleep and psychiatric symptoms. Recent data support further development of transdiagnostic treatments that concurrently target common cognitive, behavioral, and biological underpinnings across psychiatric disorders, such as sleep disturbances. One example is the Transdiagnostic Sleep and Circadian Intervention, a transdiagnostic treatment targeting sleep and circadian problems for individuals with comorbid psychiatric disorders.25 This approach is informed by CBTI and other circadian optimization strategies. Although more studies on transdiagnostic treatments are underway, CBTI is appropriate for older adults with comorbid insomnia and psychiatric disorders.

### Table 3. CBTI and Adaptations for Older Adults23

<table>
<thead>
<tr>
<th>CBTI intervention component</th>
<th>Adaptation considerations</th>
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</table>
| **Sleep restriction:** Involves reducing time in bed to approximately total time asleep by adjusting patient’s sleep schedule, with the aim to consolidate sleep | • Sleep compression is an alternative that decreases the patient’s time in bed gradually in small increments (eg, 30 minutes) per week. As opposed to reducing time in bed to a significantly shorter duration all at once, which can be difficult for some older adults to tolerate.  
• Identifies activities to do around the new sleep schedule, such as morning activities and nonstimulating activities before bedtime, to prevent lingering in bed in the morning due to boredom or dozing off too early before bedtime. |
| **Stimulus controls:** A set of recommendations, such as using the bed for sleep only and getting out of bed after prolonged wakefulness, aiming to strengthen the association between bed and sleep based on classical conditioning | • Assessing fall risks and environmental modifications (eg, remove area rugs) to reduce fall risks when getting out of bed after prolonged awakenings.  
• Counter control is an alternative that instructs patients to engage in relaxing activities in bed in a different position (eg, sitting up), as opposed to tossing/turning in bed or getting out of bed entirely after prolonged awakenings. |
| **Cognitive therapy:** Cognitive restructuring involves challenging and reframing dysfunctional thinking patterns that contribute to insomnia | • Common unhelpful beliefs around sleep in older populations, such as “I’m going to get dementia if I don’t sleep tonight” or “I should not be waking up in the middle of the night,” will need to be addressed through Socratic questioning or sleep education.  
• Value-based actions can be emphasized to promote daytime wellness, regardless of their sleep. |
| **Relaxation training:** Involves teaching structured relaxation exercises (eg, diaphragmatic breathing, progressive muscle relaxation techniques, and guided imagery) to reduce arousal levels at nighttime | Suggest passive methods for muscle relaxation when pain is more pronounced. |
| **Sleep hygiene techniques:** Commonly recommended sleep habits that can be useful for maintaining sleep, eg, minimizing alcohol use before bedtime and increasing physical exercise during the day; although poor sleep hygiene can disrupt sleep, good sleep hygiene is often not enough to be a stand-alone treatment for chronic insomnia | Place more emphasis on the pros and cons of each sleep hygiene recommendations, as well as ways to realistically implement them. For example, recommending no screen use before bedtime may not be helpful for older adults with visual impairment who use reading devices. |
| **Process-level considerations:** To enhance older adults’ learning of CBTI, providers need to be aware of common age-related fluctuations, such as changes in vision, hearing, fine-motor skills, processing speed, and memory | • User-friendly treatment materials with large fonts and writing spaces  
• Reduce content covered  
• Review and repetition of content  
• Encourage note-taking or use of other memory aids  
• Reminder calls between sessions  
• Family support outside of treatment sessions |
Concluding Thoughts
Sleep disturbance often co-occurs among older adults with psychiatric symptoms and disorders. A thorough assessment, looking at difficulty initiating and maintaining sleep, daytime sleepiness/dysfunction, and other physical markers (eg, snoring), will help providers identify the presence of sleep disorders, such as OSA or chronic insomnia, that co-occur with psychiatric conditions. Modifications can optimize the treatment of sleep disturbance in the presence of such psychiatric conditions as depression and anxiety.

Appropriate treatment is essential, as the long-term consequences of not addressing sleep disturbances may be severe. Interactions between sleep disruption and mental health symptoms even may set into motion a cascade of neurodegeneration that can ultimately lead to dementia. Mood disorders also increase risk of dementia, potentially through accelerated brain aging from stress exposure that leads to pathological changes in the brain, termed the brain-age gap. Sleep disturbances may constitute a type of stressor that increases the brain-age gap. Treatment of these common, yet complex, patients with evidenced-based methods is essential to improving their symptoms, quality of life, and brain health.

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REFERENCES

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POLARIS
Evaluating safety and efficacy of Mazindol ER in clinical trials for the treatment of narcolepsy.

Now enrolling
NLS-1021: A Four-week, Double-blind, Placebo-controlled, Randomized, Multicenter, Parallel-group Study of the Safety and Efficacy of NLS-2 (Mazindol Extended Release) in Adults for the Treatment of Narcolepsy.

NLS-1022: An Open Label Extension study available the day after completion of patient four-week treatment cycle of NLS-1021, in which the patient will roll in and take Mazindol ER once-daily as an oral tablet for up to 6 months.

POLARIS program
POLARIS is comprised of two concurrent clinical studies, NLS-1021 and NLS-1022.

The NLS-1021 program has a simple, straightforward, patient friendly study design. NLS-1022 is an Open Label Extension study offering patients enrolled in NLS-1021 the possibility to take Mazindol ER once-daily as an oral tablet for up to 6 months.

The drug substance Mazindol, with a long history of clinical use, has a unique dual mechanism of action, acting as an Orexin-2 receptor partial agonist and as inhibitor of reuptake of dopamine, norepinephrine, and serotonin.

Key inclusion criteria
- Males and females between 18 and 65 years of age, inclusive
- Diagnosis of narcolepsy according to ICSD-3 (International Classification of Sleep Disorders, 3rd Edition) or Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria
- Body mass index from 18 to 40 kg/m², inclusive
- Consent to use a medically acceptable method of contraception
- Willing and able to provide written informed consent

Key exclusion criteria
- Female subjects who are pregnant, nursing, or lactating
- Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness
- History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria
- Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness
- Use of any medications that could affect the evaluation of cataplexy
- Received an investigational drug in the past 30 days or five half-lives (whichever is longer)

To learn more about this study, visit polaris.nlspharma.com
COVID-19, Cognition, and Dementias: What Role Has the Pandemic Played?

>> Eric E. Brown, MD, MSc; Tarek K. Rajji, MD; and Benoit H. Mulsant, MD, MS

By the time COVID-19 was characterized as a pandemic, it was clear that older adults in general, and those with Alzheimer disease and related dementias (ADRD) in particular, would be severely impacted both directly by the virus and indirectly by the social consequences and responses.1 Now, approaching 2 years since SARS-CoV-2 emerged, we are starting to measure the impact of COVID-19 on older patients with cognitive impairment and ADRD. Further, we can begin to review neurobiological issues associated with COVID-19 in older adults, and consider how COVID-19 may contribute to cognitive impairment and future cases of dementia.

The Impact of COVID-19 on Older Adults

The demographics of COVID-19 cases have shifted over time, with older adults being most impacted early in the pandemic, and later waves involving younger individuals.2 Similarly, risk varied by setting, with an early wave of COVID-19 cases in congregate settings including nursing homes, retirement homes, and hospitals. These frequent and widespread outbreaks were associated with significant morbidity and mortality. Despite campaigns to vaccinate nursing home residents, they still account for a large proportion of the total deaths due to COVID-19.3,4

The severity of COVID-19 spans the spectrum from asymptomatic carrier state to severe illness and death, with age being the strongest demographic risk factor for a more severe illness: Age has an exponential relationship with infection fatality rate, reaching 15% at age 85.5 Older adults with cognitive impairment are doubly at risk, with age and cognitive impairment independently contributing to illness severity.6 Cognitive impairment has been associated with double the risk of COVID-19 mortality in nursing homes.7 Even when controlling for residence in a nursing home, those with dementia had twice the risk of acquiring COVID-19.8

We had anticipated that rates of behavioral and psychologic symptoms associated with dementia (BPSD) would increase as a result of indirect factors such as disruption to care, social isolation, and disruption to routine.9 Unfortunately, this has been borne out, with studies reporting increases in BPSD including anxiety, depression, insomnia, wandering, and agitation.9

Alongside the risk of mortality, the pandemic is also affecting mental health negatively, both via the direct effect of the virus and indirectly via the massive disruption to society in response to the pandemic. Early and ongoing mental health consequences of the pandemic include increased rates of symptoms of depression, anxiety, substance use, and suicidal ideation. However, paradoxically, younger individuals may be more impacted than older ones.10 Similarly, while the pandemic may have increased BPSD in some individuals with dementia, this has not been universally true. For example, in New Brunswick, Canada, despite a marked reduction in family visits and periods of lockdown (mitigated by virtual visits and volunteer services), there was no change in rates of agitation, and a reduction in rates of depression among nursing home residents, with more than half of them having dementia.11

The availability of safe and effective COVID-19 vaccines is thought to be a key element to ending the pandemic. Early on, in the context of limited supply, governments prioritized vaccination for high-risk groups such as the elderly and those living in long-term care (LTC) facilities. Thus, most individuals with dementia were prioritized for vaccination. For example, in Ontario, Canada, despite only 0.5% of the population living in LTC facilities, vaccination initially was reserved for LTC residents and health professionals when vaccines first became available in December 2019.12 By March 2020, more than 92% of LTC residents had received at least 1 dose of a COVID-19 vaccine, which was estimated to have reduced mortality by 96%.13 The recent approval by the US Food and Drug Administration of booster shots for older persons (ie, a third dose) may offer them further protection and also deepen current inequities when vaccination remains unavailable due to supply constraints in some jurisdictions.

The Neurobiology of COVID-19

SARS-CoV-2 is transmitted person to person via inhalation of respiratory droplets and their deposition on mucous membranes, and to a lesser extent by contaminated hands contacting mucous membranes.14 The virus enters cells via the angiotensin-converting enzyme 2 receptor, present not only in the respiratory and gastrointestinal tract but also in other organs, including the brain and blood vessels.15,16 Thus, COVID-19 can potentially lead to neuropathology via systemic and inflammatory indirect effects and by its direct action on the nervous system.

Although most cases of COVID-19 are classified as mild, severe cases occur in individuals of all ages, most commonly in older adults. Common acute symptoms include cough, fever, fatigue, headache, myalgias, and diarrhea.17 Symptoms can progress and involve hypoxemia and acute respiratory distress syndrome.18 In addition, injury to all organ systems due to severe inflammation, thromboembolic events, and neurologic complications can occur.19

The neurologic consequences of severe COVID-19 are common and involve both the central nervous system (CNS) and peripheral nervous system (PNS) (Table).20 Dizziness and headache are the most common CNS manifestations, which can also include cerebrovascular disease (eg, ischemic stroke, hemorrhage), ataxia, and seizures. Delirium is a common presentation of older adults with COVID-19; it has a very poor prognosis and is associated with permanent cognitive impairment.21 Anosmia and ageusia are the most common PNS manifestations.22 Neurologic manifestations can occur within the first days of illness and persist months after hospital discharge.23 Isolating the virus in cerebrospinal fluid is rare.24 Cognitive impairment is a commonly reported symptom in survivors of severe COVID-19 at 60 days post discharge.25 Although research is needed to confirm the neuropsychiatric sequelae of COVID-19, a broad spectrum of neuropsychiatric symptoms have been reported, including headaches, sleep disorders, encephalopathy, myalgia, and ageusia.21 The term long COVID refers to the persistence of symptoms after the resolution of the acute infection, and a broad range of symptoms have been reported, including neuropsychiatric symptoms such as cognitive impairment, insomnia, impaired concentration, posttraumatic symptoms, and headache.26 Long COVID is not always associated with the severity of acute COVID-19 or risk factors for severe COVID-19, and it may involve multiple organ damage by other direct mechanisms.27 Long COVID is thought to be relatively common, but estimates of its prevalence vary widely depending on definition and time since infection. It may also depend on the SARS-CoV-2 genetic variant.28

There is evidence for both structural and functional brain changes following COVID-19, and these changes may be associated with the neuropsychologic symptoms of long COVID. Various studies have reported heterogeneous findings. A recent systematic review summarizing the neuroimaging findings associated with COVID-19 in older adults reported widespread neuropathological issues typically associated with cerebrovascular damage, most consistently in white matter, brainstem, and...
frontotemporal cortical areas. A case-control study of patients who recovered from COVID-19 found hypometabolism in frontotemporal regions, which was associated with neurological symptoms. A study of United Kingdom Biobank participants by Douaud et al found changes in 394 individuals who had brain imaging before and after a COVID-19 infection, compared with 388 matched controls without a history of COVID-19. Among those who had survived COVID-19, Douaud et al identified gender differences in grey matter in the left parahippocampal gyrus, left lateral orbitofrontal cortex, and left insula.

The Long-Term Consequences of COVID-19

Although it is staggering that approximately 1 in 500 Americans has died of COVID-19, mortality is the tip of the iceberg. The Centers for Disease Control and Prevention estimates that as of May 29, 2021, there had been more than 100 million individuals with symptomatic COVID-19 in the United States, 10 million of them 65 years or older. The sequelae from severe COVID-19 are risk factors for dementia, and they may increase the growing number of individuals living with dementia. Understanding the specific contribution of a past COVID-19 infection on future risks of dementia will require longitudinal studies. These risks may be substantial given the cerebrovascular changes associated with past infection. During the next few years, post-COVID-19 issues may occur mostly in older adults. However, COVID-19 may also increase the risk of future cognitive impairment and dementia in younger individuals, because early-life experiences and exposures contribute to the risk of dementia, as is the case in other risk factors for dementia such as low level of education or depression early in life. The magnitude of the current and future barriers for certain patients who are at high risk for COVID-19 is essential.

REFERENCES

When your adult patients struggle with treatment-resistant depression (TRD), relief can’t come soon enough.

At Week 4, SPRAVATO® + oral antidepressant (AD) demonstrated superior improvement with a 4-point greater reduction in MADRS total score (-19.8) (n=114) vs placebo + oral AD (-15.8) (n=109) (P=0.020)²·⁴*

- Most of the treatment difference between SPRAVATO® and placebo was observed at 24 hours, and both groups continued to improve through Day 28, while the difference between the two generally stayed the same²·⁴

Identify your patients who may be appropriate for SPRAVATO® and find a treatment center in your area at spravatohcp.com/find-a-center

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).

SPRAVATO® (esketamine) CLI 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 in Study 1, a Phase 3, short-term (4-week), randomized, double-blind, multicenter, placebo-controlled study in adult patients with TRD (in current depressive episode and had not responded adequately to ≥2 oral ADs).²·⁴

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MADRS=Montgomery-Åsberg Depression Rating Scale.

Identify your patients who may be appropriate for SPRAVATO® and find a treatment center in your area at spravatohcp.com/find-a-center

Indications and Important Safety Information

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Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for SPRAVATO® on the following pages.
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.SPRAVATO.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 or 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 psychotherapeutics (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 the prior and following pages.
Important Safety Information (continued)

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 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.

PREGNANCY, EMBRYO-FETAL TOXICITY, AND LACTATION
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. Advise women of reproductive potential to consider pregnancy planning and prevention.

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/.

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

SELECT USE IN SPECIFIC POPULATIONS

Geriatric Use: 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. At the end of a 4-week, randomized, double-blind study, there was no statistically significant difference between groups on the primary efficacy endpoint.

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.

ADVERSE REACTIONS
The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were:

TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, for SPRAVATO® on the following pages.
SPRAVATO®
(eskenatide) nasal spray, CII

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, misuse of SPRAVATO is only approved 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
• 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 [see Clinical Studies (14.3) in Full Prescribing Information] Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience 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.

CONTRAINDICATIONS
SPRAVATO is contraindicated in patients with:
• Anomalous vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation [see Warnings and Precautions]
• History of, or use within 2 weeks following, anesthesia [see Warnings and Precautions]
• Hypersensitivity to eskenatide, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS

Sedation
In clinical trials, 4% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer’s Assessment of Alertness/Sedation scale (MOAA/S) [see Adverse Reactions], and 0.3% to 0.4% 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 Interactions].

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 84% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale [CADS-Scale] and/ or the Short Form Dissociative Experiences Scale (SFDES). Given potential to induce dissociation, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the psychosis is under control [see Warnings and Precautions].

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 eskenatide, 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 caution in such patients. Consider the potential for misuse of sedative drugs and the potential 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 and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings. Monitoring providers (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 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 under the program.

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

SPRAVATO® (eskenatide) nasal spray, CII

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 25-64 treated with placebo was greater than in patients age 65 and older treated with placebo). The risk of suicidal thoughts and behaviors among young adults, but there was an increased risk identified in young children and adolescents (18-24 years old) for most studies. This increased risk was observed primarily in randomized controlled trials of antidepressants and included several antidepressants and across different indication. The risk was increased in patients with major depressive disorder (MDD). The drug-placebo differences in the numbers of cases of suicidal thoughts and behaviors among patients 18-24 years old are presented 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

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Decreases Compared to Placebo</th>
<th>Increases Compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>1 fewer patient</td>
<td>14 additional patients</td>
</tr>
<tr>
<td>18-64</td>
<td>6 fewer patients</td>
<td>5 additional patients</td>
</tr>
</tbody>
</table>

* 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 delaying recurrence is itself 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 to monitor for changes in behavior and alerting the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO and/or the concomitant or underlying, in patients with signs of depression is worsening persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure
Because of the possibility of delayed or prolonged sedation, dissociation, and abuse. SPRAVATO 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 4% to 19% of SPRAVATO-treated patients and 1% to 4% of placebo-treated patients experienced an increase of greater than or equal to 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 a BP increase in BP or intracranial pressure poses a serious risk (e.g., arterial and/or intracranial and/or intracerebral hemorrhage) [see Contraindications].

Because of increased BP 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 and 1 hour 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 and operate machinery (14.8; in Full Prescribing Information). The maximum-effect time for sedation was comparable to placebo at 6 hours and 18 hours post-dose. However, both placebo- and 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.

Ulcereative or Intestinal Cystitis
Cachexia, ulcerative or intestinal 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 (e.g., hematuria, urgency, nocturia, incontinence) in SPRAVATO-treated patients than in placebo-treated patients [see Adverse Reactions]. No cases of eskenatide-related intestinal cystitis were observed in any of the studies, which included treatment duration up to a year.

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

Extrapyramidal Toxicity
Based on published findings from pregnant animals treated with ketamine, the ramicemic mixture of ketamine 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].
SPRAVATO® (esketamine) nasal spray, CIII

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]
- Increased 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 Intestinal Cynosis [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.

Treatment-Resistant Depression

SPRAVATO was evaluated for safety in 1709 adults diagnosed with treatment-resistant depression (TRD) [see Clinical Studies (14.1) 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 46% 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 56% and 31%, 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 (0.9%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscle weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.1%), sedation (0.1%), and vertigo (0.1%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in 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, hypnosis, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Table 2 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with placebo nasal spray plus oral AD.

Most Common Adverse Reactions

The most commonly observed adverse reactions in 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, hypnosis, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Table 3 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO plus oral AD and greater than patients treated with placebo nasal spray plus oral AD.

Table 3: Adverse Reactions Occurring in ≥2% of Adult Patients with MDD and Acute Suicidal Ideation or Behavior Treated with SPRAVATO + Oral AD at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

<table>
<thead>
<tr>
<th>CARDIAC DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia* 6 (2%) 1 (0.5%)</td>
</tr>
<tr>
<td><strong>EAR AND LARYNX DISORDERS</strong></td>
</tr>
<tr>
<td>Vertigo* 78 (23%) 6 (2%)</td>
</tr>
<tr>
<td><strong>GI TRACT DISORDERS</strong></td>
</tr>
<tr>
<td>Nausea 96 (29%) 19 (9%)</td>
</tr>
<tr>
<td>Vomiting 31 (9%) 4 (2%)</td>
</tr>
<tr>
<td>Diarrhea 23 (7%) 13 (6%)</td>
</tr>
<tr>
<td><strong>MOUTH DISORDERS</strong></td>
</tr>
<tr>
<td>Dry mouth 19 (6%) 7 (2%)</td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</strong></td>
</tr>
<tr>
<td>Constriction 11 (3%) 3 (1%)</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</strong></td>
</tr>
<tr>
<td><strong>NURSING SYSTEM DISORDERS</strong></td>
</tr>
<tr>
<td>Tension 14 (4%) 0 (0%)</td>
</tr>
<tr>
<td>Mental impairment 11 (3%) 2 (1%)</td>
</tr>
<tr>
<td><strong>PSYCHIATRIC DISORDERS</strong></td>
</tr>
<tr>
<td>Disorientation* 142 (41%) 21 (9%)</td>
</tr>
<tr>
<td>Anxiety* 45 (13%) 14 (6%)</td>
</tr>
<tr>
<td>Insomnia 29 (8%) 16 (7%)</td>
</tr>
<tr>
<td>Euphoria 15 (4%) 2 (1%)</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE, THORACIC AND MEDIANSTINAL DISORDERS</strong></td>
</tr>
<tr>
<td>Nausea 7 (2%) 1 (0.5%)</td>
</tr>
<tr>
<td>Vomiting 20 (6%) 6 (3%)</td>
</tr>
<tr>
<td>Diarrhea 12 (3%) 2 (1%)</td>
</tr>
<tr>
<td><strong>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</strong></td>
</tr>
<tr>
<td>Hyperhidrosis 14 (4%) 5 (2%)</td>
</tr>
</tbody>
</table>

* 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; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucinations; hyperventilation; jitters; lightheadedness; loss of auditory sensation; lipoatrophy; lipoatrophy, oral; dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment
- Depression includes: dizziness; dizziness exertional; dizziness postural; procedural dizziness
- Dysarthria includes: dysarthria; speech; speech disorder
- Dyspnea includes: dyspnea; hypoxia
- Hypothyroidism includes: hypothyroidism, hyperthyroidism
- Hyperhidrosis includes: hyperhidrosis; hypohidrosis
- Hyperkalemia includes: hyperkalemia; normokalemia
- Hypoglycemia includes: hypoglycemia; hyperglycemia
- Hypothermia includes: hypothermic; hypothermic, normothermic
- Hypoxia includes: hypoxia; hypocapnia
- Hypovolemia includes: hypovolemia; hypovolemic
- Hypothyroidism includes: hypothyroidism; hypothyroidism, hyperthyroidism
- Hypothermia includes: hypothermia; hypothermic
- Hypothyroidism includes: hypothyroidism; hypothyroidism, hyperthyroidism
- Hyperglycemia includes: hyperglycemia; hypoglycemia
- Hypothermia includes: hypothermic; hypothermic, normothermic
- Hypothyroidism includes: hypothyroidism; hypothyroidism, hyperthyroidism
- Hypothermia includes: hypothermia; hypothermic
- Hyperglycemia includes: hyperglycemia; hypoglycemia
- Hypothermia includes: hypothermia; hypothermic
- Hyperglycemia includes: hyperglycemia; hypoglycemia
- Hypothermia includes: hypothermia; hypothermic
- Hyperglycemia includes: hyperglycemia; hypoglycemia
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- Hypothermia includes: hypothermia; hypothermic
- Hyperglycemia includes: hyperglycemia; hypoglycemia
- Hypothermia includes: hypothermia; hypothermic
- Hyperglycemia includes: hyperglycemia; hypoglycemia
- Hypothermia includes: hypothermia; hypothermic
SPRAVATO® (esketamine) nasal spray, CIII

Sedation
Sedation was evaluated by adverse event reports and the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S). In the MOAA/S, “5” means “responds readily to name spoken in normal tone” and “6” means “no response after painful truncal squeeze.” Any decrease in MOAA/S from pre-dose is considered to indicate the presence of sedation, and such a decrease occurred in a higher number of patients on SPRAVATO than placebo during the short-term TRD studies. Dose-related increases in sedation (MOAA/S score ≤ 5) were observed in a fixed-dose study with patients ≥65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD. See Table 7 for the incidence of sedation (MOAA/S score ≤ 5) in patients treated with SPRAVATO plus oral AD compared to patients treated with placebo plus oral AD, similar to the TRD study results in Table 4.

Dissociation/Perceptual Changes
Dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions) were observed in a fixed-dose TRD study (see Warnings and Precautions). Table 4 presents the incidence of dissociative symptoms (MOAA/S score ≤ 5) in a fixed-dose study with patients ≥65 years of age with TRD and a flexible-dose study with patients ≥65 years of age with TRD.

Table 4: Incidence of Sedation (MOAA/S Score ≤ 5) in Double-blind, Randomized, Placebo-controlled Studies (Fixed-dose Study with Adult Patients ≥65 Years of Age with TRD and Flexible-dose Study with Patients ≥65 Years of Age with TRD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sedation (MOAA/S score ≤ 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>N=112</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 56 mg</td>
<td>N=114</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 84 mg</td>
<td>N=114</td>
</tr>
<tr>
<td>Patients ≥65 years</td>
<td>N=63</td>
</tr>
<tr>
<td>N=72</td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients evaluated with MOAA/S

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, there was a higher incidence of sedation (MOAA/S score ≤ 5) in patients treated with SPRAVATO plus oral AD compared to patients treated with placebo plus oral AD, similar to the TRD study results in Table 4.

Table 5: Incidence of Dissociation (CAODS Total Score ≥ 4 and Change >0) in Double-blind, Randomized, Placebo-controlled Studies (Fixed-dose Study with Adult Patients ≥65 Years of Age with TRD and Flexible-dose Study with Patients ≥65 Years of Age with TRD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dissociation (CAODS total score ≥ 4 and change &gt;0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>N=113</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 56 mg</td>
<td>N=113</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 84 mg</td>
<td>N=113</td>
</tr>
<tr>
<td>Patients ≥65 years</td>
<td>N=65</td>
</tr>
<tr>
<td>N=72</td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients who were evaluated with CAODS

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral AD also demonstrated a higher number (84%) with dissociation (CAODS total score ≥ 4 and change >0) compared to patients treated with placebo plus oral AD (16%).

Increase in Blood Pressure
The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time from baseline to the first week of treatment in the short-term studies, as well as over time with long-term treatment, are presented in Table 6.

Table 6: Increases in Blood Pressure in Double-blind, Randomized, Placebo-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Oral AD in the Treatment of TRD in Adult Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Increase in Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>SBP 84 mg</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 56 mg</td>
<td>N=346</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 84 mg</td>
<td>N=222</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 28 mg</td>
<td>N=72</td>
</tr>
<tr>
<td>Patients ≥65 years</td>
<td>91%</td>
</tr>
<tr>
<td>N=66</td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients who were evaluated with CAODS

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral ADs demonstrated similar mean placebo-adjusted increases in SBP and DBP compared to patients treated with TRD, as well as similar rates of increases to SBP ≥180 mmHg or ≥40 mmHg increases in SBP and similar rates of increases to DBP ≥10 mmHg or ≥25 mmHg increases in DBP, compared to the TRD study results shown in Table 6.

Nausea and Vomiting
SPRAVATO® can cause nausea and vomiting. 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. Rarely 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 7 presents the incidence and severity of nausea and vomiting in a short-term study with patients treated with SPRAVATO and placebo. In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral ADs demonstrated similar incidence and severity of reported nausea and vomiting compared to the TRD study results described above.

Table 7: Incidence and Severity of Nausea and Vomiting in a Double-blind, Randomized, Placebo-controlled, Fixed-dose Study in Adult Patients with TRD

<table>
<thead>
<tr>
<th>Group</th>
<th>Nausea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>N=56</td>
<td></td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 56 mg</td>
<td>N=115</td>
<td></td>
</tr>
<tr>
<td>SPRAVATO + Oral AD 84 mg</td>
<td>N=116</td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD 28 mg</td>
<td>N=72</td>
<td></td>
</tr>
<tr>
<td>N=66</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients who were evaluated with CAODS

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with SPRAVATO plus oral ADs demonstrated similar incidence and severity of reported nausea and vomiting compared to the TRD study results described above.

Sensation
Sensation 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).
SPRAVATO® (esketamine) nasal spray, CIII

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 Cmax 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-Åsberg Depression Rating Scale (MADRS).

Hepatic Impairment

The mean esketamine AUC and t1/2 values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function (see Clinical Pharmacology (12.3) in Full Prescribing Information). SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

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

Abuse

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

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

Abuse Potential Study

A cross-over, double-blind abuse potential study of SPRAVATO and ketamine was conducted in recreational polydrug users (n=34) who had experience with perception-altering drugs, including ketamine. Ketamine, the racemic mixture of esketamine and esketamine, is a Schedule I controlled substance under the Controlled Substances Act.

Abuse

There was no difference in the scores for “Hallucinating,” “Floating,” “Detached,” and “Spaced Out” than the 84 mg dose of intranasal SPRAVATO (94 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 Overdose

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 overdose (1-800-222-1222 or www.poison.org).

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cp-81105v6
**NO “COOKIE CUTTER” PATIENTS**
**MANAGING TREATMENT-RESISTANT DEPRESSION**

* Leah Kuntz

In an installment of Psychiatric Times™ custom Case Based Psych Perspectives, Lisa Harding, MD, and Angelos Halaris, MD, PhD, APA, ACNP, CINP, provided insight into how to diagnose treatment-resistant depression (TRD), summarized available treatment options, and offered recommendations on how to best help patients with this disorder.

Through examination of 2 case presentations, Harding and Halaris came to the agreement that each patient must be handled as a unique individual. A thorough psychiatric and developmental history must be performed for each patient to ensure the diagnosis of TRD, they said.

“There’s no cookie cutter patient that fits into a scenario [of TRD],” said Harding, who is a board-certified psychiatrist and clinical instructor of psychiatry at the Yale School of Medicine in New Haven, Connecticut.

### Treatment Options

Additionally, the experts discussed 2 nonpharmacological modalities for the treatment of TRD, the former “mainstay” electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS), which is Halaris’ second top choice.

“[ECT] is very effective, there’s no doubt about it. But again, the effect doesn’t last forever, and the issue of maintenance ECT is acknowledged,” Halaris said. “The potential for some kind of cognitive impairment is still an issue.”

On the other hand, TMS is time consuming. Patients come into the office a minimum of 3 days a week, preferably 5 days a week for Halaris. TMS also requires maintenance.

“The response is generally quite good. Even after the first few treatments, we can get a response. But I have also witnessed the loss of efficacy after termination of the initial acute treatment phase of about 35 sessions,” admitted Halaris, professor of psychiatry at Loyola University Chicago Stritch School of Medicine in Maywood, Illinois. Nonetheless, he considers it a viable and important treatment option in the TRD arsenal.

### Intranasal Esketamine

Clinicians can also consider pharmacological treatment options; however, Halaris stressed the importance of ensuring a patient has true TRD, and not presumptive TRD. “In my book, true TRD is the one that has ruled out all potential contributory factors...If all these criteria have been met, then we have a true TRD patient,” he said.

“Then I would consider intranasal esketamine.”

Halaris began using intranasal esketamine during phase 3 clinical trials before the US Food and Drug Administration (FDA) approval and still uses it.

“I had a maintenance patient just an hour ago, and another one coming back for maintenance intranasal esketamine right after we’re done with this discussion,” Halaris said. “It’s a very interesting approach, not so much the classic neurotransmitters or serotonin-norepinephrine-dopamine, but at the end NMDA [N-methyl-D-aspartate] receptor blockade that involves predominantly, but not exclusively, glutamatergic transmission.”

Off-label intravenous ketamine is a treatment that Halaris does not use. He cited 3 reasons for this decision: 1) it is not FDA approved, 2) it is costly, and 3) it is not as well-regulated as intranasal esketamine by the Risk Evaluation and Mitigation Strategy (REMS) program.

Halaris, who helped establish REMS-certified treatment centers both in university medical centers and private practice settings, considers the REMS certification process easily achievable. “The process is fairly simple. It takes an application. The company...is very helpful in assisting prospective sites, whether a medical center or a private practice setting to achieve REMS certification. Certain conditions needed to be met; the equipment—there’s no equipment other than a suitable chair for the patient to rest comfortably. Monitoring vital signs, installing a safe, because the medication needs to be under double-lock with limited access with a code that the REMS certified provider,” Halaris explained. “It’s not that cumbersome. I know it sounds scarier than it really is.”

The ideal candidates for intranasal esketamine are those who are on an oral antidepressant concomitantly with some response but not full remission, according to Halaris and Harding. Contraindications include cardiovascular, intracerebral, intraabdominal, and aneurysmal vascular disease, and histories of hemorrhages.

It is also important to have a conversation with patients about substance abuse, Harding said. She asks patients whether they are going to support groups, and if so, what they look like, as well as simply extending the conversation as you would before any schedule III substance prescription.

In terms of costs for intranasal esketamine, the way to obtain reimbursement is still unclear. Getting insurance companies to cover it is a challenge and requires extensive paperwork, Halaris noted. However, there is assistance through CarePath.

“Once we obtain the insurance information with patients’ written consent, their data are passed on to CarePath, and they are amazingly efficient...It saves our staff tons of time,” Halaris stated.

Harding and Halaris shared that patients have had copays as little as $10 to $20.

For clinicians who are considering intranasal esketamine as a therapeutic option for their patients, Halaris shared this advice: “It works as long as you do it right, for the right patient, in the right constellation.”

Dr Harding is a board-certified psychiatrist and clinical instructor of psychiatry at the Yale School of Medicine, in New Haven, Connecticut. She is also part of the Janssen Speaker Bureau. Dr Halaris is a board-certified psychiatrist and professor of psychiatry at Loyola University Chicago Stritch School of Medicine in Maywood, Illinois. He reports no conflicts of interest regarding the subject matter of this article.
BIPOLAR UPDATE

Sorting Out Comorbidities

David N. Osser, MD

The last column discussed how to improve precision in the diagnosis of mania and hypomania and how to identify likely prebipolar depressions that may evolve into a diagnosis of bipolar disorder (BD) following the onset of a subsequent manic or hypomanic episode. It is important to identify comorbid disorders that add to the symptoms of BD, so that these symptoms can be targeted appropriately. Some prescribers tend to target symptoms (eg, anxiety, insomnia, and irritability) with medications while leaving the underlying disorder(s) unrecognized and/or untreated.1

Taking Time for Diagnosis

When there is a comorbidity, one should first delineate the various DSM-5 diagnoses that are present (Table). The evaluation may require several meetings to reach the initial diagnostic impression, and it can take 90 minutes to evaluate a complex new patient, including reviewing the previous record and writing the assessment.2 Clinicians who are employed may not be allowed this much time, or if in private practice, they may elect to take less time because of financial considerations and pressures. Experienced clinicians may convince themselves that they can do an adequate assessment in less time and choose the correct medications for the correct diagnoses. However, a competent and comprehensive psychiatric evaluation requires time. Brief evaluations, followed by quick prescribing, are often experienced by patients as rushed and unsatisfying. Confidence in and respect for our profession is ten experienced by patients as rushed and unsatisfying. Confidence in and respect for our profession is undermined by these practices.3 The first clinical encounter is an important moment that sets the stage for the ongoing therapeutic alliance.

After establish the diagnoses, determine (with the patient) those that may be contributing the most to the patient’s distress or dysfunction, and treat those first with what the evidence best supports. For example, active and severe substance use disorders may deserve priority management. Cannabis use disorder can exacerbate BD,4 and it may be important to persuade the patient to address this before introducing or modifying the medications prescribed for the BD and other disorders.

Treating Common Comorbidities

Posttraumatic stress disorder (PTSD) is a common comorbidity, especially in veterans. The irritability in PTSD—which can be triggered by events, interactions, or memories of their trauma—is easily mistaken for the irritable mood that is one of the mood types in the A criteria for bipolar mania (along with elevated or expansive mood) in the DSM-5. Valproate is often prescribed for irritable mood thought to be associated with mania, but the PTSD symptoms, including irritability, will likely not respond to it, as was demonstrated in 2 negative controlled studies.5 Determine whether the irritable mood occurs in discrete episodes of mania that last at least several days and are accompanied by the other manic symptoms in the mania criteria (noting that 4 other symptoms are needed if the mood is only irritable). If not, and the irritable mood is invariably occurring when triggered by events that produce reexperiencing and the fight-or-flight adrenalized immediate reactions to those triggers, then it is likely due to PTSD. For these patients, the treatment would likely be more effective with an antiadrenaline agent in the PTSD armamentarium such as prazosin or clonidine.

Attention-deficit/hyperactivity disorder (ADHD) is another comorbidity with BD. Most adults with ADHD have emotional dysregulation, which presents as chronic over-reactiveness to stresses.6 This, too, can be confused with the irritable mood of a manic episode. Stimulants have been found effective for this emotional dysregulation as well as for the focus, concentration, and hyperactivity associated with ADHD.7 It is important to make this diagnosis, using the DSM-5 criteria, and consider which symptoms could be attributed to ADHD and which occur mostly or to a greater extent during discreet manic episodes. Stimulants can, in fact, be used to treat ADHD in patients with comorbid BD.4

Sleep impairment is seen in comorbid diagnoses. In mania, there is decreased need for sleep, and the treatment of choice would be an antimanic agent rather than a hypnotic. However, often sleep impairment has other causes. There are medical causes, such as sleep apnea, restless leg syndrome (RLS), caffeine, nocturia from prostate hypertrophy or diabetes, and pain syndromes, etc. Among psychiatric comorbidities, PTSD, which is associated with sleep disturbance, including difficulty initiating sleep and difficulty maintaining it due to nightmares, disturbed awakenings, and night terrors. A thorough evaluation of insomnia is indicated to identify the leading cause(s), including asking about all examples of PTSD-related sleep disturbance. This is a much better approach than the shortcut of treating the insomnia symptom by proceeding through a list of hypnotics that might inclu...
PSYCHIATRIC VIEWS ON THE DAILY NEWS

Banning Alcohol, but Not the Unvaccinated, on Airplanes

I have just taken a flight on Spirit Airlines, which continues to allow the drinking of spirits. Southwest and American Airlines, however, both continue to ban alcohol, with the reasoning that alcohol has contributed to increased disruptive behavior of passengers.

On the other hand, unvaccinated passengers are still allowed to fly, which also means that they are in airports with fellow passengers for long periods of time. I found that the shuttle buses to rental cars were jam packed. In contrast, when I went to an outdoor music festival, proof of vaccination was required.

Doesn’t it seem that the unvaccinated should also be banned on airplanes and in airports for health and mental health reasons, and that health care professionals should support such a mandate? How else are we now going to end the pandemic without mandates where possible? Or, is this another case of profits taking priority over health, as it does in so many of our health insurance systems?

We Need to Care About the Mental Health of Police, Too

On Monday, September 13, 2021, loved ones and colleagues gathered to share memories of former Milwaukee police officer Tom Kline, who took his own life a year ago. National data indicate that more law enforcement officers have died by suicide than in the line of duty over the past 5 years. Police have very high burn out rates, approaching the epidemic rate experienced by physicians.

The root reasons for the suicides are many. Some are similar to those suffered by mental health caregivers. Burnout is one; family problems are another. There may be guilt, perhaps unconscious at times, from the public charge of racism. There is the trauma.

As one former police officer said, “I can still picture every baby that has passed away or has been killed. When I’m sleeping, I can picture them in my dreams. That’s an image I’m never going to forget.”

Perhaps he could forget them with beneficial treatment. But treatment has been hard to get, and there is often a reluctance to admit that it is needed.

Posttraumatic stress disorder in police is especially challenging because it often does not qualify them for workers’ compensation. Thank-fully, on October 1 a bill in my home state of Wisconsin went into effect to provide just that. Besides the financial compensation, the bill will make it easier to get needed psychiatric treatment. These and other related developments for police well-being are long overdue.

Minor League Baseball Players With Major Mental Health Problems

On September 30, ESPN published an article titled: “Can a Union Fix This? Minor Leaguers Say Poverty-Level Pay, Poor Housing Are Driving a Mental Health Crisis.”

The article began with the description of a failed suicide attempt of a minor league baseball player, Kieran Lovegrove, who had financial and other problems. He then felt that he was meant to speak out about mental health in the minor leagues. Most players are reluctant to jeopardize their careers by doing so.

In the midst of starting the highly profitable Major League Baseball (MLB) playoffs and World Series, whose players often have multimillion-dollar, multiyear contracts, we have the minor leagues—the feeding grounds to MLB—suffering from financial and mental health crises. It sort of parallels the more general great and growing divide in our country between the rich and poor. Moreover, although psychiatric and psychological care has infused MLB, it has not been readily available for the minor leaguers. Fortunately, the works and actions of Lovegrove and other minor leaguers seem to be getting the attention of MLB owners. May this also get the attention of the rest of society as another underserved group in mental health care.

Professional baseball has legal protection against the use of unions. So do businesses involved in health care, such that psychiatrists and other physicians cannot unionize. Without that, the courage of speaking out against mental harm takes on added weight and necessity wherever it is in such systems, the latest being about Facebook. The desired outcome, of course, is better mental health in those systems and their users.

A Modern Day Cain and Abel Story

One of the well-known Biblical stories is that of brothers Cain and Abel,
who were said to be the children of the first parents, Adam and Eve. Cain killed Abel, and when confronted by God, he responded, “Am I my broth-
er’s keeper?”

The media recently reported that Jeffrey Burnham also was not his brother’s keeper. On September 29, he allegedly killed his pharmacist brother and 2 others because his brother was “killing people with the COVID shot.”

Leading up to this tragedy, the news reported him worrying his mother about his possible intentions. She apparently called the local po-
lice more than once with concerns about her son’s mental stability. At some point, the police sent out an alert, but Burnham was not seen until he was arrested the day after the killings, when he confessed his guilt.

Besides the unknown individual and family history of Burnham and his brother, several social psychiatric issues and questions come readily to the fore:

1. Was Burnham influenced by any of the hundreds of websites reporting misinformation about COVID-19?
2. Given that mental illness is associated with increased violence only if it is severe and untreated, was that the case here?
3. Did the police unit in this case have mental health professionals embedded in their system to help assess the original concerns of the mother and perhaps prevent this outcome?
4. More generally, are we failing as a society and sometimes as a “family to be our brothers’ and sisters’ keepers?”

**REFERENCES**


Dr Moffic is an award-winning psychiatrist who has specialized in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received the one-time designation of Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. He is an advocate for mental health issues relate to climate insta-
bility, burnout, Islamophobia, and anti-Semitism for a better world. He serves on the Editorial Board of Psychiatric Times™.
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Heal Thyself, Then Heal Others?
The Power of Lived Experiences

Simona Karbouniaris, MsC;
Jim van Os, MD, PhD

Although about 45% to 75% of mental health professionals have personal experience with mental health care services, overall the cultural norm has been not to be open about this fact.1 Indeed, professionals often perceive personal mental health problems as a weakness, feeling they should be able to cope on their own.2 Similarly, psychiatrists have been trained to separate the personal from the professional, yet they have a tendency to self-diagnose and self-treat.3 Correspondingly, they may experience shame, embarrassment, and fear of being judged negatively if they disclose their own mental health histories.

Findings from a recent randomized controlled trial, however, reveal that physician self-disclosure of lived experience improves mental health attitudes among medical students.4 Patients may also profit from professionals harnessing lived experiences.

However, little is known on how to disclose and use experiential knowledge in a professional and appropriate fashion.5 Research illustrates that the mental health systems in many Western countries (eg, Australia, United Kingdom, United States, the Netherlands, and Israel) have struggled to meaningfully incorporate the lived experiences of professionals.5 To address this deficit, several pilot studies in the Netherlands have focused on the implementation of experiential knowledge in mental health contexts, including peer consultation groups for psychiatrists whose personal experiences could inform their medical practice.

Defining and Exploring Experiential Knowledge
Experiential knowledge can be defined as the ability to handle or resolve a problem based on an individual’s own experience.6 It may refer to the emotional impact or to practical, spiritual, and existential insights that come with coping with certain types of distress. It has been introduced as a new source of knowledge next to professional and scientific knowledge and has been increasingly acknowledged and formalized.7,8 A small body of literature has studied how traditional mental health professionals have used experiential knowledge. To date, these studies have mainly looked at applied professions, such as social workers and nurses who followed postbachelor trainings, stimulating the integration of the personal-professional identity.7

Being aware of one’s vulnerabilities is basic to the training of psychoanalysts and the Rogerian tradition. However, the explicit use of lived experiences in mental health care practice to date has been limited to in vivo self-disclosures.7 Although some psychiatrists like Ahmed Hankir, MBChB, MRCPsych, portray themselves as “wounded healers,” exposing a personal weakness generally has a negative connotation. At the same time, a broader research project in the Netherlands is now exploring the use of experiential knowledge by psychiatrists.4 The psychiatrist is often the lead member of a care team, so harnessing lived experiences may be considered a particularly risky investment. They may feel concerned about losing authority or blurring the boundaries between professionals and patients. There may also be overidentifying with and projecting issues onto patients.7 Anecdotal evidence suggests that psychiatrists seem wary or do not know how to navigate this.8

The Many Challenges of Sharing Personal Experiences
Many potential obstacles keep mental health professionals, particularly psychiatrists, from harnessing lived experiences in clinical practice. Although there is growing empirical evidence that

What are your thoughts? Have you (or would you) shared lived experiences to support a patient’s journey? Let us know what you think at PTEditor@mjlifesciences.com.
patients feel well supported by caretakers who share their experiences, no evidence exists that would also apply in the case of psychiatrists using their lived experience. Using lived experience is also often associated with (inappropriate) disclosures and labeled as unprofessional. The fear is that it may undermine the supposed neutrality of the clinician. Consequently, psychiatrists are not trained to transform their lived experiences into experiential knowledge. Without proper training, many are insufficiently equipped to use their own experiences as part of their treatments.

Furthermore, they were taught that personal disclosures may put additional stress on, and thus further burden, already vulnerable patients. They may fear it will lead to role confusion and are more comfortable in a role as unimpaired professional, especially when facing difficult decisions, such as (forensic) risk assessments.

Finding a Way Forward
In the Netherlands, psychiatrists recently joined a broader movement in which mental health professionals reveal their lived experience. They come together in peer consultation groups with colleagues to explore the meaning of their personal experiences in a professional context.

Their reflections have given rise to a few preliminary observations and guidelines. The use of experiential knowledge does not necessarily entail disclosing one’s entire private life. It requires assessing what would be useful to patients as they recover from (severe) mental health distress and trauma. If psychiatrists choose to make personal disclosures, they should take place in a training or peer consultation context, often starting with sharing a personal recovery story and unraveling its key elements.

When implicitly or explicitly using their personal experiences as a resource for patients, psychiatrists may contribute to a culture change in which stigma and shame around mental distress are relieved. Lived experiences are related to not only a specific diagnosis but also broader insights related to life, such as knowing how it is to live in different realities, surviving emotional or physical trauma, and suffering from loneliness or social injustice. Psychiatrists who talk about their own struggles in these areas could serve as positive role models for their team and patients.

In general, patients express appreciation when nurses and social workers talk about their own recovery paths. Sharing personal experience can humanize and strengthen therapeutic relationships.

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When implicitly or explicitly using their personal experiences as a resource for patients, psychiatrists may contribute to a culture change in which stigma and shame around mental distress are relieved. Lived experiences are related to not only a specific diagnosis but also broader insights related to life, such as knowing how it is to live in different realities, surviving emotional or physical trauma, and suffering from loneliness or social injustice. Psychiatrists who talk about their own struggles in these areas could serve as positive role models for their team and patients.

In general, patients express appreciation when nurses and social workers talk about their own recovery paths. Sharing personal experience can humanize and strengthen therapeutic relationships.

The Bottom Line
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Mirrors and Jeweled Nets

When I was a kid, I took dance lessons for a decade and a half. As a senior in high school, I performed a dance solo to the song “The Music and the Mirror” from my favorite musical, A Chorus Line. “All I ever needed was the music and the mirror, and the chance to dance for you,” an auditioning dancer pleads to a casting director. Then the music abruptly changes to mark her dance solo. She turns around toward a line of mirrors near the back of the stage to dance, leading the audience to watch not her body, but her reflection. At 17, I left it all on that stage, popping with jazz hands, in homage to the show that made me want to move to New York City to become a dancer.

I did move to NYC a decade later, not to dance on Broadway, but to complete my residency training in psychiatry. Nevertheless, over the course of my career as a psychiatrist, mirroring has been one of the most essential tools I need to perform at my best. After my residency training at Columbia University, where I studied Kohut’s theories on the mirror transference, I moved to far grittier settings (but, sadly, none of them a stage). I have come to experience the act of reflecting my clients’ inner light back to them as a main objective of my work. It is a little like the concave mirror a dentist uses to look at the back of your mouth, but instead of searching for black holes as markers of cavities of pathology, I just look for the light, try to magnify it, and reflect it back. When it happens, it is beautiful, and much more powerful than any medication I have ever prescribed.

Reflections of a Jeweled Net

Far away in the heavenly abode of the great god Indra, there is a wonderful net that stretches out infinitely in all directions. There is a single glittering jewel in each “eye” of the net, and since the net itself is infinite in dimension, the jewels are infinite in number. There hang the jewels, glittering like stars in the first magnitude, a wonderful sight to behold. If we now arbitrarily select one of the jewels, so that there is an infinite re-creation called Uncaged Minds Detroit. I hope to be able to purchase property on the upper east side of Detroit. I hired a team of like-minded therapists to hire one of them to handle this project. It is a project that requires the same level of focus as a dance studio, but with the added challenge of using the same space as a dance studio for my office, if no one else. This would require the studio to have a large wall mirror. I have been to some yoga studios with mirrors, some without; they have their pros and cons in that setting, so I have been wafting a bit on whether I want one. Today I decided, yes, I definitely want a mirror.

Seeing the Light

To explain why, I will have to rewind a bit to last December. I evaluated a new client in my telehealth practice: “Sarah” was a single Black mother of two young children who had reached out for mental health treatment for the first time in her life because her anxiety symptoms had become unbearable. Sarah had been working as a nursing assistant at one of Detroit’s main hospitals, and her floor was one of the first in the hospital to be declared a COVID-19 ward. Almost overnight, the job she once enjoyed became a daily barrage of suffering and death. In the wake of George Floyd’s murder, the idea of those stacked bodies in Detroit hospitals, most of them Black, traumatized many of my clients, but Sarah was my first client who had actually been on the front lines.

I gave her a diagnosis of posttraumatic stress disorder (PTSD); I am no stranger to treating PTSD after 6 years working in the US Department of Veterans Affairs system. However, I am much more familiar with treating the kind of PTSD that affects veterans, not the kind that hits soldiers on active duty. Sarah’s trauma was still happening, every day, and her choices were to continue to endure it or be out of a job. I told her, honestly, that medication might help, and that using her medical leave from work would definitely help. I reassured her, before we were even done with our interview, that I would be happy to sign her paperwork. The look of relief on Sarah’s face confirmed that my immediate gesture of material support would help me forge a therapeutic alliance. (This is of the utmost importance for me as a White psychiatrist in situations like these, in which I am the first mental health professional a Black client has ever met; here, I am working against many years of deep-seated and perfectly reasonable mistrust of individuals who look like me and do the job I do.)

In our initial interview, when I asked Sarah about childhood sexual abuse, she told me that, when she was 6 years old, the man her grand-
mother married molested her. Afterward, Sarah had told her grandmother it hurt “down there.” Her grandmother stood up, took a can of Crisco out of the kitchen cupboard, and rubbed it on Sarah as a soothing balm. No words were spoken about it, that day or any to follow, but her grandmother never let her out of her sight again when she came to visit. As I took notes during the interview, under the developmental history section, I simply jotted down the word Crisco, knowing I would recall her story immediately when I sat down to write her evaluation note. The gesture seemed so tender and yet so heartbreaking, so careful and yet not careful enough.

A couple of months into our work together, Sarah emailed me to let me know she had just found out her own 6-year-old daughter had been molested by her father; Sarah had broken up with him several years prior while she had been living in Georgia. They had no formal custody agreement, but Sarah allowed her daughter to stay with him in Florida for a couple of weeks every summer. She was devastated she had “let this happen” to her own daughter, despite it being one of her greatest fears, given what she herself had experienced at that same age. At Sarah’s first visit after that email, I invited her to elaborate about what her daughter had told her, and how it all came to light. She took a deep breath and told me, “You’re the first person I’m going to tell.” I will not retell an unspeakable story here.

Sarah kept it together until she told me something her daughter had said: “I thought parents are supposed to protect us.” I am not sure, even now, she understands her daughter was not talking about her. It is clear to anyone with just enough distance from this mother’s tortured soul that her daughter was referring to the other parent—the father who had abused her.

Sarah broke down a second time during the interview, when she brought up the upcoming fourth anniversary of her mother’s death. Her mother had been her best friend, and she told me how desperately she needed to talk through this with her, like they would talk through every problem together: “My mom did it all. She was everything for everybody. I need her now.”

COVID-19 stacked up the bodies in Detroit hospitals and gave Sarah PTSD. COVID-19 was also the underlying necessity foraging the invention, or at least the rapid advent, of teletherapy. As it turns out, telehealth is incredibly convenient and efficient, and I took pretty easily to it. That being said, therapy over Zoom is not without its challenges; technological issues pop up occasionally, and I have spoken to more than one client while they were seated on their toilet (the only private place they could manage for our session).

On this particular day, the uniquely telehealth therapeutic quirk was around camera positioning. At this point in the interview, while Sarah spoke of how she longed for her mother, her camera was positioned in such a way that the light from the lamp behind her glared like a radiant burst that filled the entirety of the rest of the screen. I saw only Sarah’s face and that light. And I listened to 2 voices at once—Sarah’s, telling me her terrible story, and the one coming from the light behind her, holding space for it for all 3 of us. I could see it, that glaring light behind her. But I knew she could not.

After she was done speaking, I waited a moment, then pointed out how her lamp was affecting her appearance in the Zoom screen. She chuckled and apologized, reaching to adjust her camera, but I stopped her and told her that for me, the light behind her helped me feel her mother’s presence very powerfully. Sarah started to cry. It was simple. I saw light. I reflected it back to her. I did not feel like a medium, but I also did not feel like a psychiatrist. I was just a mirror. I sort of started to cry too.

I told Sarah what I could hear her mother trying to say from behind her. She was saying, as she told me how she longed to speak to her: "Girl! You’re talking to me right now!"

Her mom was saying, "No one can be everything for everybody. But look around. We do the best we can. We lift, and we are lifted. Look around."

Her mom was saying, "Look behind you, you see that light?"

"Look below you, you see that diamond?"

"Look around. We are a jeweled web. We are everywhere. We are everything."

Dr. Dykema is the cofounder and clinical director of Uncaged Minds Detroit, a mental health and wellness resource for low-income Detroiters, with a special focus on the LGBTQ+ community and those impacted by the criminal justice system. She is also a part-time law student and public psychiatry fellow at Wayne State University.

Majority of Americans favor president’s vaccine mandate: poll

Jeff Bendix

Six in 10 Americans support the vaccine mandates announced by President Joe Biden, although support is divided sharply along party lines, a survey finds.

According to the Axios-Ipsos poll, conducted September 10 to 13, 2021, 60% of Americans favor requiring COVID-19 vaccinations for federal employees and businesses and organizations with 100 employees or more. However, only about 30% of Republicans support the requirements compared with more than 80% of Democrats and 60% of independents.

From a political perspective, the support among independents is especially important, according to Cliff Young, president of Ipsos US Public Affairs.

“No. 1 issue for Biden has been COVID, and he’s been losing ground on it, especially among independents. This is an initiative that could help bolster him there,” Young said in a statement.

The poll also found that increasing numbers of Americans are experiencing vaccine and masking requirements at work and in public places. Twenty-five percent of respondents said their employers now require all employees be vaccinated compared with 16% in a survey conducted August 10 to 13.

Similarly, 58% of respondents said their employers require mask wearing at work, up from 51% in the August survey, and 43% said their state or local government requires masks to be worn in public places, up from just 33% in August.

Also, there is growing concern over the spread of the Delta coronavirus, with 53% of respondents saying they are “extremely” or “very” concerned compared with 35% in late June. A plurality of Americans (38%) said the federal government’s top priority should be getting more people vaccinated, rather than providing booster shots (28%) or sending vaccines to developing countries (19%).

Interestingly, support for school masking mandates has increased slightly; 70% of respondents supported them compared with 69% in mid-August. Similarly, support for childhood vaccination is up but still lukewarm; 44% of respondents, compared with 38% in mid-August, said they were “very” or “somewhat” likely to get their child vaccinated when a vaccine becomes available for the child’s age group.
Important dosing considerations for ARISTADA INITIO and ARISTADA

- For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating ARISTADA® (aripiprazole lauroxil) or ARISTADA INITIO® (aripiprazole lauroxil)†
- ARISTADA INITIO and ARISTADA are only to be administered as an intramuscular injection by a healthcare professional†
- There are 2 ways to start treatment with ARISTADA. If not starting ARISTADA with the ARISTADA INITIO regimen, administer 21 consecutive days of oral aripiprazole with the first ARISTADA injection†
- Adjust ARISTADA dose as needed. When making dose and dosing interval adjustments, consider the pharmacokinetics and prolonged-release characteristics of ARISTADA. ARISTADA INITIO is a single dose, and adjustments are not possible†
- If/when a dose of ARISTADA is missed, administer the next injection as soon as possible. Concomitant supplementation following a missed dose may be recommended depending on the time elapsed since last injection. See full Prescribing Information for more information†

INDICATION and IMPORTANT SAFETY INFORMATION for ARISTADA INITIO® (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

INDICATION
ARISTADA INITIO, in combination with oral aripiprazole, is indicated for the initiation of ARISTADA when used for the treatment of schizophrenia in adults.

ARISTADA is indicated for the treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

Please see additional Important Safety Information and Brief Summaries of full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA on the following pages.
IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA (continued)

Contraindications: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Reactions, Including Stroke: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, have been reported in placebo-controlled trials of elderly patients with dementia-related psychosis treated with risperidone, aripiprazole, and olanzapine. ARISTADA INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

Potential for Dosing and Medication Errors: Medication errors, including substitution and dispensing errors, between ARISTADA INITIO and ARISTADA could occur. ARISTADA INITIO is intended for single administration to ARISTADA which is administered monthly, every 6 weeks, or every 8 weeks. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex may occur with administration of antipsychotic drugs, including ARISTADA INITIO and ARISTADA. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental state, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, flushing, or cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible and to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing antipsychotics should be consistent with the need to minimize TD. Discontinue ARISTADA if clinically appropriate. TD may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Antipsychotic drugs have been associated with metabolic changes that include:

- Hyperglycemia/Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with oral aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

- Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

- Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pathological Gambling and Other Compulsive Behaviors: Compulsive or uncontrollable urges to gamble have been reported with use of aripiprazole. Other compulsive urges less frequently reported include sexual urges, shopping, binge eating and other impulsive or compulsive behaviors which may result in harm for the patient and others if not recognized. Closely monitor patients and consider dose reduction or stopping aripiprazole if a patient develops such urges.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension which can be associated with dizziness, lightheadedness, and tachycardia. Monitor heart rate and blood pressure, and warn patients with known cardiovascular or cerebrovascular disease and risk of dehiscence and syncope.

Falls: Antipsychotics including ARISTADA INITIO and ARISTADA may cause somnolence, postural hypotension or motor and sensory instability which may lead to falls and subsequent injury. Upon initiating treatment and recurrently, complete fall risk assessments as appropriate.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue ARISTADA INITIO and/or ARISTADA at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Seizures: Use with caution in patients with a history of seizures or in conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: ARISTADA INITIO and ARISTADA may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that therapy with ARISTADA INITIO and/or ARISTADA does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use; use caution in patients at risk for aspiration pneumonia.

Concomitant Medication: ARISTADA INITIO is only available at a single strength as a single-dose pre-filled syringe, so dosage adjustments are not possible. Avoid use in patients who are known CYP2D6 poor metabolizers or taking strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, or strong CYP3A4 inducers, antihypertensive drugs or benzodiazepines.

Depending on the ARISTADA dose, adjustments may be recommended if patients are 1) known as CYP2D6 poor metabolizers and/or 2) taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers for greater than 2 weeks. Avoid use of ARISTADA 662 mg, 882 mg, or 1064 mg for patients taking both strong CYP3A4 inhibitors and strong CYP2D6 inhibitors. (See Table 4 in the ARISTADA Full Prescribing Information.)

Commonly Observed Adverse Reactions: In pharmacokinetic studies the safety profile of ARISTADA INITIO was generally consistent with that observed for ARISTADA. The most common adverse reaction (≥3% incidence and at least twice the rate of placebo reported by patients treated with ARISTADA 441 mg and 882 mg monthly) was akathisia.

Injection-Site Reactions: In pharmacokinetic studies evaluating ARISTADA INITIO, the incidences of injection-site reactions with ARISTADA INITIO were similar to the incidence observed with ARISTADA. Injection-site reactions were reported by 4%, 5%, and 2% of patients treated with 441 mg ARISTADA (monthly), 882 mg ARISTADA (monthly), and placebo, respectively. Most of these were injection-site pain and associated with the first injection and decreased with each subsequent injection. Other injection-site reactions (induration, swelling, and redness) occurred at less than 1%.

Dystonia: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy/Nursing: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider of a known or suspected pregnancy. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO and/or ARISTADA during pregnancy. Aripiprazole is present in human breast milk. The benefits of breastfeeding should be considered along with the mother’s clinical need for ARISTADA INITIO and/or ARISTADA and any potential adverse effects on the infant from ARISTADA INITIO and/or ARISTADA or from the underlying maternal condition.

Please see the Brief Summaries of Full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA on the following pages.
INDICATIONS AND USAGE: ARISTADA INITIO is contraindicated in patients with a known hypersensitivity reaction to aripiprazole. Hypersensitivity reactions have ranged from pruritus/urticaria to anaphylaxis.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS:
• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonitis) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

ARISTADA INITIO is contraindicated for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. ARISTADA INITIO is not approved for the treatment of patients with dementia-related psychosis.

Potential for Dosing and Dispensing Errors: Medication errors, including substitution and dispensing errors, between ARISTADA INITIO and ARISTADA could occur. ARISTADA INITIO is intended for single administration only. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur in association with antipsychotic drugs, including ARISTADA INITIO. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, or cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both the symptoms of NMS and the symptoms of the underlying illness. In patients treated with atypical antipsychotics who develop NMS, the diagnosis should be confirmed by laboratory tests. In one retrospective study of more than 4000 patients treated with atypical antipsychotics, 3% of patients developed NMS. In another retrospective study of 1716 patients treated with atypical antipsychotics, 1% of patients developed NMS. The symptoms of NMS appear to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with antipsychotics, consider discontinuation of the antipsychotic drug. However, some patients may require antipsychotic treatment despite the presence of the syndrome.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia/Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with oral aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pathological Gambling and Other Compulsive Behaviors: Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other compulsive urges, reported less frequently include: sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, and other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm for the patient and others if not recognized. If compulsive urges develop, consider discontinuing aripiprazole.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions related to orthostatic hypotension can include dizziness, lightheadedness and tachycardia. Generally, these effects are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naive. In such patients, monitor orthostatic vital signs.

Fails: Antipsychotics including ARISTADA INITIO may cause somnolence, postural hypotension, or motor and/or extrapyramidal symptoms (EPS), which may be associated with and/or, consequence of treatment with antipsychotics. As with other antipsychotics, consider discontinuation of the antipsychotic drug. However, some patients may require antipsychotic treatment despite the presence of the syndrome.

Leukopenia, Neutropenia, and Agranulocytosis: In clinical trials and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of clinically significant WBC/ANC and/or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of antipsychotics at the first sign of a clinical significant decline in WBC or ANC. The factors leading to a leukopenic event are not well understood.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue antipsychotics in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.
Seizures: As with other antipsychotic drugs, use ARISTADA INITIO cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment: ARISTADA INITIO, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ARISTADA INITIO does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ARISTADA INITIO for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. ARISTADA INITIO and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Clinical Studies 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 practice.

The safety of ARISTADA INITIO, in combination with oral aripiprazole, for the initiation of ARISTADA when used for the treatment of schizophrenia in adults has been established and is based on clinical trials of ARISTADA (aripiprazole lauroxil) including 1019 adult patients with schizophrenia.

Patient Exposure: ARISTADA INITIO has been evaluated for safety in 170 adult patients in clinical trials in schizophrenia. In pharmacokinetic studies, the safety profile of ARISTADA INITIO was generally consistent with that observed for ARISTADA.

ARISTADA (Aripiprazole Lauroxil) Trials in Adults with Schizophrenia

Commonly Observed Adverse Reactions with Aripiprazole Lauroxil: The most common adverse reaction (incidence >5% and at least twice the rate of placebo in patients treated with aripiprazole lauroxil) was akathisia.

Adverse Reactions Occurring at an Incidence of 2% or More in Aripiprazole Lauroxil-Treated Patients: Adverse reactions associated with the use of aripiprazole lauroxil (incidence of 2% or greater, rounded to the nearest percent and aripiprazole lauroxil minus placebo incidence greater than placebo) that occurred were: injection site pain, increased weight, increased blood creatinine phosphokinase, akathisia, headache, insomnia, and restlessness.

Injection Site Reactions

ARISTADA INITIO

In pharmacokinetic studies evaluating ARISTADA INITIO, the incidences of injection site reactions with ARISTADA INITIO were similar to the incidence observed with aripiprazole lauroxil.

ARISTADA (Aripiprazole Lauroxil)

Injection site reactions were reported by 4% of patients treated with 441 mg aripiprazole lauroxil and 5% of patients treated with 882 mg aripiprazole lauroxil compared to 2% of patients treated with placebo. Most of these were injection site pain (3%, 4% and 2% in the 441 mg aripiprazole lauroxil, 882 mg aripiprazole lauroxil and placebo groups, respectively). Other injection site reactions (induration, swelling and redness) occurred at less than 1%.

Extrapyramidal Symptoms: In a schizophrenia efficacy study in aripiprazole lauroxil–treated patients, the incidence of other EPS-related events, excluding akathisia and restlessness, was 5% and 7% for patients on 441 mg and 882 mg, respectively, versus 4% for placebo-treated patients.

Dystonia: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions Observed in Clinical Studies with Aripiprazole Lauroxil: The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Cardinal – angina pectoris, tachycardia, palpitations
Gastrointestinal disorders – constipation, dry mouth
General disorders – asthenia
Musculoskeletal – muscular weakness
Nervous system disorders – dizziness
Psychiatric disorders – anxiety, suicide

Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole: The following is a list of additional adverse reactions that have been reported in clinical trials with oral aripiprazole and not reported above for ARISTADA INITIO or aripiprazole lauroxil.

Cardiac Disorders: Bradyarrhythmias, atrial flutter, cardiac arrhythmias, atrioventricular block, atrial fibrillation, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders: photophobia, diplopia
Gastrointestinal disorders: gastroesophageal reflux disease
General Disorders and Administration Site Conditions: peripheral edema, chest pain, face edema
Hepatobiliary Disorders: hepatitis, jaundice
Immune System Disorders: hypersensitivity
Injury, Poisoning, and Procedural Complications: fall, heat stroke
Investigations: weight decreased, hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased, blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased
Metabolism and Nutrition Disorders: anorexia, hypokalemia, hypoglycemia
Musculoskeletal and Connective Tissue Disorders: muscle tightness, rhabdomyolysis, mobility decreased
Nervous System Disorders: memory impairment, cogwheel rigidity, hypokinesia, bradykinesia, akinesia, myoclonus, coordination abnormal, speech disorder, chorea, ataxia
Psychiatric Disorders: aggression, loss of libido, delirium, libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking
Renal and Urinary Disorders: urinary retention, nocturia
Reproductive System and Breast Disorders: erectile dysfunction, gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism
Respiratory, Thoracic, and Mediastinal Disorders: nasal congestion, dyspnea
Skin and Subcutaneous Tissue Disorders: rash, hyperhidrosis, pruritus, photosensitivity
Vascular Disorders: hypertension, hypotension

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-966-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Table 1: Clinically Important Drug Interactions With ARISTADA INITIO

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors</th>
<th>Clinical Impact</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of oral aripiprazole alone</td>
<td>Avoid concomitant use of ARISTADA INITIO with strong CYP3A4 or CYP2D6 inhibitors because the dosage of ARISTADA INITIO cannot be modified</td>
<td></td>
</tr>
</tbody>
</table>

Examples: Itraconazole, clarithromycin, quindoline, fluoxetine, paroxetine

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inducers</th>
<th>Clinical Impact</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone</td>
<td>Avoid concomitant use of ARISTADA INITIO with strong CYP3A4 inhibitors because the dosage of ARISTADA INITIO cannot be modified</td>
<td></td>
</tr>
</tbody>
</table>

Examples: Carbamazepine, rifampin

Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents</td>
<td>Avoid concomitant use of ARISTADA INITIO with antihypertensive drugs because the dosage of ARISTADA INITIO cannot be modified</td>
</tr>
</tbody>
</table>

Examples: Carvedilol, lisinopril, prazosin

Benzodiazepines

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone</td>
<td>Avoid concomitant use of ARISTADA INITIO with benzodiazepines because the dosage of ARISTADA INITIO cannot be modified</td>
</tr>
</tbody>
</table>

Examples: Lorazepam

Due to its potential to enhance the effect of certain antihypertensive agents, use ARISTADA INITIO cautiously in patients with hypertension.

Strong CYP3A4 Inhibitors

Clinical Impact: Concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of oral aripiprazole alone.

Examples: Itraconazole, clarithromycin, quindoline, fluoxetine, paroxetine

Strong CYP3A4 Inducers

Clinical Impact: Concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone.

Examples: Carbamazepine, rifampin

Antihypertensive Drugs

Clinical Impact: Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Examples: Carvedilol, lisinopril, prazosin

Benzodiazepines

Clinical Impact: The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.

Examples: Lorazepam

Drug Interactions
Risk Summary: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Limited published data on aripiprazole use in pregnant women are not sufficient to inform any drug-associated risks for birth defects or miscarriage. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at doses up to 8 and 23 times, respectively, the maximum recommended human dose (MRHD) of 675 mg based on body surface area (mg/m²). However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits. The background risk of major birth defects and miscarriage for the general population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies was 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations: Fetal/Neonatal Adverse Reactions: Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recover within hours or days without specific treatment; others required prolonged hospitalization.

Data: Animal Data for ARISTADA (Aripiprazole Lauroxil): Aripiprazole lauroxil did not cause adverse developmental or maternal effects in rats or rabbits when administered intramuscularly during the period of organogenesis at doses of 18, 49, or 144 mg/kg/day in pregnant rats which are approximately 1 to 8 times the MRHD of 675 mg based on mg/m², and at doses of 241, 723, and 2893 mg/kg in pregnant rabbits which are approximately 2 to 23 times the MRHD based on mg/m². However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits [see Data below].

Animal Data for Aripiprazole: Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day which are approximately 1 to 10 times the oral MRHD of 30 mg/day based on mg/m² of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight, and undescended testes. Delayed skeletal ossification was observed at 3 and 10 times the oral MRHD based on mg/m². At 3 and 10 times the oral MRHD based on mg/m², delivered offspring had decreased body weights. Increased incidences of hepatodisparagmatic nodules and diaphragmatic hernia were observed in offspring from the highest dose group (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to the highest dose. Postnatally, delayed vaginal opening was seen at 3 and 10 times the oral MRHD based on mg/m² and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rabbits treated with oral doses of 10, 30, and 100 mg/kg/day which are 2 to 11 times human exposure at the oral MRHD based on AUC and 6 to 65 times the oral MRHD based on mg/m² of aripiprazole during the period of organogenesis decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternebrae were observed at 3 and 11 times the oral MRHD based on AUC. In rats treated with oral doses of 3, 10, and 30 mg/kg/day which are 1 to 10 times the oral MRHD based on mg/m² of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at the highest dose. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

Lactation: Risk Summary: Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARISTADA INITIO and any potential adverse effects on the breastfed infant from ARISTADA INITIO or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of ARISTADA INITIO in pediatric patients have not been established.

Geriatric Use: Safety and effectiveness of ARISTADA INITIO in patients ≥65 years of age have not been evaluated. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA INITIO is not approved for the treatment of patients with dementia-related psychosis.

CYP2D6 Poor Metabolizers: Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Avoid use of ARISTADA INITIO in these patients because dosage adjustments are not possible (it is only available in one strength in a single-dose pre-filled syringe).

Hepatic and Renal Impairment: No dosage adjustment for ARISTADA INITIO is required based on a patient's hepatic function (mild to severe hepatic impairment, Child–Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute).

Other Specific Populations: No dosage adjustment for ARISTADA INITIO is required on the basis of a patient’s sex, race, or smoking status.

OVERDOSAGE

Human Experience: Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or in combination with other substances) include acidosis, agitation, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdose: In case of overdose, call the Poison control center immediately at 1-800-222-1222.

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-866-274-7623 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ARISTADA INITIO.

This Brief Summary is based on ARISTADA INITIO Full Prescribing Information Rev March 2021.

Manufactured and marketed by Alkermes, Inc., Waltham, MA 02451-1420.

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ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
(For complete details, please see full Prescribing Information and Medication Guide.)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death

• ARISTADA is not approved for the treatment of patients with dementia-related psychosis

INDICATIONS AND USAGE: ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.

CONTRAINDICATIONS: ARISTADA is contraindicated in patients with a known hypersensitivity reaction to aripiprazole. Hypersensitivity reactions have ranged from pruritus/urticaria to anaphylaxis.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients With Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in elderly patients taking antipsychotic drugs, revealed a risk of death in drug-treated patients of approximately 1.6 to 1.7 times that of placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the increase in mortality in observational studies may be attributed to the antipsychotic drug as opposed to other characteristics of the patients is not clear.

ARISTADA is not approved for the treatment of patients with dementia-related psychosis.

Cardiovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was an increased risk of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. ARISTADA is not approved for the treatment of patients with dementia-related psychosis.

Potential for Dosing and Medication Errors: Medication errors, including substitution and dispensing errors, between ARISTADA and ARISTADA INITIO® (aripiprazole lauroxil) could occur. ARISTADA INITIO is for single administration in contrast to ARISTADA which is administered monthly, every 6 weeks, or every 8 weeks. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur in association with antipsychotic drugs. NMS is a differential diagnosis that includes central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop and occur at any time during treatment at low doses, although this is uncommon.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ARISTADA should be prescribed in a manner that is likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with ARISTADA, drug discontinuation should be considered. However, some patients may require treatment with ARISTADA despite the presence of the syndrome.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia/Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with oral aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weight gain. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved following drug discontinuation; however, for some patients, drug discontinuation is required to continue treatment despite discontinuation of the atypical antipsychotic.

In the long-term, open-label schizophrenia study with ARISTADA, 14% of patients with normal hemoglobin A1C (<5.7%) at baseline developed elevated levels (≥5.7%) post-baseline.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

In the long-term, open-label schizophrenia study with ARISTADA, shifts in baseline fasting total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL) were reported in 1% of patients; shifts in baseline fasting LDL cholesterol from normal (<100 mg/dL) to high (≥160 mg/dL) were reported in 1% of patients; and shifts in baseline fasting triglycerides from normal (<150 mg/dL) to high (≥200 mg/dL) were reported in 6% of patients. In the same study, shifts in baseline fasting total cholesterol from borderline (<200 mg/dL) to high (≥240 mg/dL) were reported in 15% of patients; shifts in baseline fasting LDL cholesterol from borderline (<100 mg/dL) and <160 mg/dL to high (≥160 mg/dL) were reported in 8% of patients; and shifts in baseline fasting triglycerides from borderline (<150 mg/dL) and <200 mg/dL to high (≥200 mg/dL) were reported in 38% of patients. In addition, the proportion of patients with shifts in fasting HDL cholesterol from normal (≥40 mg/dL) to low (<40 mg/dL) was reported in 15% of patients.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

The proportion of adult patients with weight gain ≥7% of body weight is presented in Table 1.

Table 1: Proportion of Adult Patients With Shifts in Weight in the 12-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trial

<table>
<thead>
<tr>
<th>Placebo N = 207 (%)</th>
<th>ARISTADA 441 mg N = 207 (%)</th>
<th>ARISTADA 882 mg N = 208 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>≥7% increase from baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathological Gambling and Other Compulsive Behaviors: Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other compulsive urges, reported less frequently include sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm for the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

Orofacial Hypotension: Aripiprazole may cause orofacial hypotension, perhaps due to its c5 antagonistic receptor antagonist. Associated adverse reactions related to orofacial hypotension can include dizziness, lightheadedness, and tachycardia.
Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose, and monitor orthostatic vital signs.

Orthostatic hypotension was reported for 1 patient in the ARISTADA 882 mg group (0.5%) and no patients in the ARISTADA 441 mg and placebo groups in the 12-week schizophrenia efficacy study. In the long-term open-label schizophrenia study, orthostatic hypotension was reported for 1 (0.2%) patient treated with ARISTADA. Orthostatic hypotension was defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values.

For patients with dehydration, hypovolemia, or cardiovascular compromise, treatment with an antihypertensive agent is recommended.

In clinical trials and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis has also been reported.

Risk Summary:

Aripiprazole Lauroxil is contraindicated in patients with a history of a clinically significant low WBC/ANC or history of drug-induced leukopenia/neutropenia, in patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, who perform a complete blood count (CBC) frequently during the first few months of treatment. In such patients, consider discontinuation of ARISTADA at the first sign of a clinical or laboratory decline in WBC or history of other causative factors. Discontinue ARISTADA in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. ARISTADA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonitis.

ADVERSE REACTIONS

Clinical Studies 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 practice.

Patient Exposure: ARISTADA has been evaluated for safety in 1180 adult patients in clinical trials in schizophrenia.

Commonly Observed Adverse Reactions: The most common adverse reaction (incidence ≥5% and at least twice the rate of placebo in patients treated with ARISTADA) was akathisia. Adverse Reactions Occurring at an Incidence of 2% or More in ARISTADA-Treated Patients: Adverse reactions associated with the use of ARISTADA (incidence of 2% or greater, rounded to the nearest percent and ARISTADA incidence greater than placebo) that occurred are shown in Table 2.

Table 2: Adverse Reaction System Organ Class Preferred Term

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N = 207 (%)</th>
<th>Aripiprazole Lauroxil 441 mg N = 207 (%)</th>
<th>882 mg N = 208 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site pain 2 3 4</td>
<td>Investigations</td>
<td>Increased weight 1 2 2</td>
</tr>
<tr>
<td></td>
<td>Increased blood creatine phosphokinase 0 2 1</td>
<td>Nervous system disorders</td>
<td>Akathisia 4 11 11</td>
</tr>
<tr>
<td></td>
<td>Headache 3 3 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In an open-label pharmacokinetic study, the adverse reactions associated with the use of 441 mg monthly, 882 mg every 6 weeks, and 1064 mg every 2 months were similar across the dose groups.

Injection-Site Reactions: Injection-site reactions were reported by 4% of patients treated with 441 mg ARISTADA and 5% of patients treated with 882 mg ARISTADA compared to 2% of patients treated with placebo. Most of these were injection-site pain (3%, 4%, and 2% in the 441 mg ARISTADA, 882 mg ARISTADA, and placebo groups, respectively), and most were associated with the first injection and decreased with each subsequent injection to less than or equal to 1% for both doses of ARISTADA and placebo. Other injection-site reactions (induration, swelling, and redness) occurred at less than 1%. In an open-label pharmacokinetic study evaluating 441 mg monthly, 882 mg every 6 weeks, and 1064 mg every 2 months, injection-site reactions were similar across the dose groups.

Extrapyramidal Symptoms: In the 12-week schizophrenia efficacy study, for ARISTADA-treated patients, the incidence of other EPS-related events, excluding akathisia and restlessness, was 5% and 7% for patients on 441 mg and 882 mg, respectively, versus 4% for placebo-treated patients (Table 3).

Table 3: Incidence of EPS Compared to Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction Term</th>
<th>Placebo N = 207 (%)</th>
<th>ARISTADA 441 mg N = 207 (%)</th>
<th>882 mg N = 208 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>4 11 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>1 3 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other EPS</td>
<td>4 5 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>1 2 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>3 3 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dystonia: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions Observed in Clinical Studies: The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be noninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Cardiac—angina pectoris, tachycardia, palpitations

Gastrointestinal disorders—constipation, dry mouth

General disorders—asthenia

Musculoskeletal—muscular weakness

Nervous system disorders—dizziness

Psychiatric disorders—anxiety, suicide

Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole: The following is a list of additional adverse reactions that have been reported in clinical trials with oral aripiprazole and not reported above for ARISTADA.

Cardiac Disorders: atrial flutter, cardiorespiratory arrest, atrioventricular block, atrial fibrillation, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders: photophobia, diplopia

Gastrointestinal Disorders: gastrointestinal reflux disease

General Disorders and Administration Site Conditions: peripheral edema, chest pain, face edema

Hepatobiliary Disorders: hepatitis, jaundice

Immunologic System Disorders: hypersensitivity

Injury, Poisoning, and Procedural Complications: fall, heat stroke

Investigations: weight decreased, hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transpeptidase increased, blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders: anorexia, hypokalemia, hypomagnesemia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders: muscle tightness, rhabdomyolysis, mobility decreased

Nervous System Disorders: memory impairment, cogwheel rigidity, hypokinesia, myoclonus, bradykinesia, akinesia, coordination abnormal, speech disorder, choreoathetosis

Psychiatric Disorders: aggression, loss of libido, delirium, libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

PSY1121_040-A010_Akermes.indd 46
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Renal and Urinary Disorders: urinary retention, nocturia
Reproductive System and Breast Disorders: erectile dysfunction, gynecomastia, menstruation irregular, amenorrhea, breast pain, priapism
Respiratory, Thoracic, and Mediastinal Disorders: nasal congestion, dyspnea
Skin and Subcutaneous Tissue Disorders: rash, hyperhidrosis, pruritus, photosensitivity, reaction, alopecia, urticaria
Vascular Disorders: hypotension, hypertension

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngeal edema, pruritus, urticaria, oropharyngeal edema), pathological gambling, hiccups, blood glucose fluctuation, electrolyte disorder, and drug reaction with eosinophilia and systemic symptoms (DRESS).

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions With ARISTADA

Table 4: Clinically Important Drug Interactions With ARISTADA

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors</th>
<th>Clinical Impact:</th>
<th>The concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of oral aripiprazole alone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td></td>
<td>With concomitant use of ARISTADA with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, exposure of aripiprazole was reduced.</td>
</tr>
<tr>
<td>Examples:</td>
<td></td>
<td>Irinotecan, diltiazem, quindine, fluoxetine, paroxetine.</td>
</tr>
</tbody>
</table>

Strong CYP3A4 Inducers

<table>
<thead>
<tr>
<th>Clinical Impact:</th>
<th>The concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>With concomitant use of ARISTADA with a strong CYP3A4 inducer for more than 2 weeks, consider increasing the ARISTADA dose.</td>
</tr>
<tr>
<td>Examples:</td>
<td>Carbamazepine, rifampin.</td>
</tr>
</tbody>
</table>

Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Clinical Impact:</th>
<th>Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Monitor blood pressure and adjust dose accordingly.</td>
</tr>
<tr>
<td>Examples:</td>
<td>Carvedilol, lisinopril, prazosin.</td>
</tr>
</tbody>
</table>

Benzodiazepines

<table>
<thead>
<tr>
<th>Clinical Impact:</th>
<th>The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Monitor sedation and blood pressure. Adjust dose accordingly.</td>
</tr>
<tr>
<td>Example:</td>
<td>Lorazepam.</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2383 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Limited published data on aripiprazole in pregnant women are not sufficient to inform any drug-associated risks for birth defects or miscarriage. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at doses up to 5 and 15 times, respectively, the maximum recommended human dose (MRHD) of 1064 mg based on body surface area (mg/m²). However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits [see Data]. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations: Fetal/Neonatal Adverse Reactions: Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity and have included increased state (e.g., crying, irritability, crying), feeding difficulties, and decreased interest in extrauterine stimuli. These symptoms are believed to be the result of both exposure to antipsychotic drugs and withdrawal of pregnancy-related placental estrogen. Cessation of these symptoms typically follows delivery. The management of these symptoms should be determined on an individual basis. Discriminate the clinical significance of the symptoms and manage symptoms appropriately. Some neonates recover within hours or days without specific treatment; others required prolonged hospitalization.

Data: Animal Data for Aripiprazole Lauroxil: Aripiprazole lauroxil did not cause adverse developmental or maternal effects in rats or rabbits when administered intramuscularly during the period of organogenesis at doses of 18, 49, or 144 mg/m² in pregnant rats which are approximately 0.6 to 5 times the maximum recommended human dose (MRHD) of 1064 mg ARISTADA on mg/m² basis and at doses of 241, 723, and 2893 mg animal in pregnant rabbits which are approximately 1 to 15 times the MRHD on mg/m² basis. However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits.

Animal Data for Aripiprazole: Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day, which are approximately 1 to 10 times the oral maximum recommended human dose (MRHD) of 300 mg/day on mg/m² basis of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight and, unrecorded tests. Delayed sexual maturation was observed at 3 and 10 times the oral MRHD on mg/m² basis.

At 3 and 10 times the oral MRHD on mg/m² basis, delivered offspring had decreased body weights. Increased incidences of hepatoatriphycal nodules and diaphragmatic hernias were observed in offspring from the highest dose group (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to the highest dose. Postnatally, delayed vaginal opening was seen at 3 and 10 times the oral MRHD on mg/m² basis and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rabbits treated with oral doses of 10, 30, and 100 mg/kg/day, which are 2 to 11 times human exposure at the oral MRHD based on AUC and to 6 to 65 times the oral MRHD on mg/m² basis of aripiprazole during the period of organogenesis, decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternebrae were observed at 3 and 11 times the oral MRHD based on AUC. In rats treated with oral doses of 3, 10, and 30 mg/kg/day which are 1 to 10 times the oral MRHD on mg/m² basis of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged recovery during gestation were seen at the highest dose. An increase in stillbirths and decreases in pup weights (persisting into adulthood) and survival were also seen at this dose.

Lactation: Risk Summary: Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARISTADA and any potential adverse effects on the breastfed infant from ARISTADA or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of ARISTADA in patients <18 years of age have not been evaluated.

Geriatric Use: Safety and effectiveness of ARISTADA in patients ≥65 years of age have not been evaluated. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA is not approved for treatment of patients with dementia-related psychosis.

CYP2D6 Poor Metabolizers: Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 6% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM).

Hepatic and Renal Impairment: No dosage adjustment is required for a patient’s hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute).

Other Specific Populations: No dosage adjustment for ARISTADA is required on the basis of a patient’s sex, race, or smoking status.

OVERDOSAGE

Human Experience: Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, CRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdose: In case of overdose, call the Poison control center immediately at 1-800-222-1222.

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-866-274-5823 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ARISTADA.

This Brief Summary is based on ARISTADA Full Prescribing Information Rev March 2021 and marketed and marketed by Alkermes, Inc., Waltham, MA 02451-1420

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Addiction & Substance Use

CLINICAL REFLECTIONS

Benzodiazepines:
It’s Time to Prescribe Caution

» Steve Adelman, MD

The opioid epidemic has grown increasingly deadly, yet it is possible that an important component has been overlooked (Figure). It has been estimated that concurrent use of benzodiazepines and opioids may occur in as many as 50% of opioid overdose deaths.1 However, more and more patients leave their doctors’ offices with prescriptions for benzodiazepine medications. Across the medical profession, the percentage of outpatient visits resulting in a benzodiazepine prescription has increased from 3.8% in 2003 to 7.4% in 2015.2 This startling statistic suggests that more cautious and conservative use and prescription of benzodiazepines has the potential to save thousands of lives per year.

Benzodiazepine Misuse
During the time period studied by Agarwal et al.,3 outpatient psychiatrists manifested a stable pattern of benzodiazepine prescribing, delivering benzodiazepine prescriptions to the patient in 30% of psychiatric visits. Overall, prescriptions written by psychiatrists account for approximately one-sixth of the more than 25 million prescriptions that are written each year.4 In 2015 and 2016, 30.6 million US adults reported benzodiazepine use in the past year; of these, 5.3 million were deemed to be misusing them.5 The most common type of misuse occurs when prescribed medications are diverted and utilized by individuals who did not receive them for a legitimate medical indication. Thus, data suggest that some benzodiazepines prescribed by psychiatrists end up being misused by individuals who are also misusing opioids, and that some of these opioid overdose deaths are potentiated by benzodiazepines prescribed by a trusting psychiatrist. Are these benzodiazepines that originate in mental health settings a factor in hundreds, or thousands, of annual opioid overdose deaths? Although the magnitude of this problem is not known, it is likely that psychiatrists who exercise more caution can play a role in doing less inadvertent harm.

Nearly a decade ago, Jones et al.6 conducted a comprehensive review of studies on the combined use of opioids and benzodiazepines and concluded that “the co-abuse of opioids and benzodiazepines is ubiquitous around the world.” They further found that benzodiazepines are utilized by those who abuse opioids to potentiate opioid intoxication, and that the co-abuse of opioid and benzodiazepines “has negative consequences for general health, overdose lethality, and treatment outcome.” Perhaps their 2012 conclusion that physicians should exercise more caution and vigilance in prescribing is reflected in the fact that psychiatrists have paid attention, and we have not increased our rate of benzodiazepine prescribing. Whereas psychiatric prescriptive practices have remained stable, other physicians, especially primary care providers, are delivering nearly twice as many benzodiazepine prescriptions to patients.7 However, in view of the subsequent progression of the opioid crisis and the mounting overdose death toll, reducing the rate of benzodiazepine prescriptions in psychiatric practice may indeed be a worthwhile, lifesaving consideration.

By adhering to universal precautions in pain medicine, Gourlay et al.8 suggested that physicians are able to routinize a cautious, nonstigmatizing clinical approach that facilitates their ability to limit opioid prescriptions. It might be helpful for psychiatrists to adopt a parallel set of best practices and universal precautions with regard to prescribing benzodiazepines.

It might be helpful for psychiatrists to adopt a parallel set of best practices and universal precautions with regard to prescribing benzodiazepines.

Table: 8 Universal Precautions for Psychiatrists

1. Make a diagnosis with an appropriate differential. Patients complaining of anxiety and/or insomnia may have an underlying substance use disorder (SUD) that mimics an anxiety disorder. They may experience drug adverse effects (AEs) that may be ameliorated without adding a benzodiazepine.

2. Conduct a comprehensive assessment including risk of substance use disorders and/or chronic pain, including family SUD histories.

3. Ensure proper informed consent. The possibility of synergistic AEs, including somnolence and respiratory depression, should routinely be covered.

4. Create and ratify a treatment agreement.

5. Carefully consider nonpharmacological anxiety reduction strategies as well as nonbenzodiazepine alternatives that lack addiction liability. Modalities like cognitive behavioral therapy, dialectical behavioral therapy, and meditation should be considered, as should less risky pharmacological options like buspirone, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors.

6. Conduct pre- and postintervention assessment of anxiety symptoms as well as level of functioning. Prescribing medications with potentially dangerous AEs is meant to improve a patient’s level of functioning. If functional level is deteriorating or simply not improving, a consultation or second opinion may be needed.

7. Periodically review all psychiatric diagnoses and comorbid conditions, including SUDs.

8. Remember the importance of documentation. All data that speak to the presence or absence of active SUDs, especially opioid use disorder and aberrant use of benzodiazepines, should be carefully documented in the medical record. Whenever possible and feasible, nonmental health providers involved with each patient should be privy to relevant data. The withholding of information from medical providers may indicate a significant current problem.

Early on, and throughout the course of psychiatric treatment, routinely employ patient-centered urine drug screens, prescription monitoring program database reviews, and pill counts.

Discussion

Epidemiological studies suggest that individuals with untreated anxiety and mood disorders may be prone to self-medicate with nonmedical use of opioids. Unfortunately, use and misuse of opioid

CLInICAL reFLeCTIonS

Benzodiazepines:
It’s Time to Prescribe Caution
Addiction & Substance Use

Dr Adelman is a coaching and consulting psychiatrist and is board-certified in psychiatry, addiction medicine, and coaching. He launched www.AdelMED.com after spending 8 years directing Physician Health Services, Inc. on the faculty of the University of Massachusetts Medical School, he is a consultant in psychiatry in the Division of Alcohol and Drug Abuse of McLean Hospital, an affiliate of Harvard Medical School.

REFERENCES

7. Vaillant GE. Natural history of male alcoholism: VI. alcoholism the card or the horse to sociopathy? Br J Addict. 1983;78(3):317-326.

Dr. Adelman cites a study that benzodiazepine use among patients with opioid use disorder may worsen symptoms of anxiety. It is not surprising, then, that outpatient psychiatrists sometimes prescribe benzodiazepines to patients who may covertly be suffering from opioid use disorder. Substance use disorders (SUDs) have long been associated with behaviors that may be deemed antisocial, including deceptive communication; therefore, community-based psychiatrists in high-volume clinic settings may be at risk of being fooled by patients who are drug-seeking.

The ease of integrating some or all of the 8 suggested universal precautions for initiating or continuing benzodiazepine pharmacotherapy will vary from treatment setting to treatment setting. At the very least, this aspirational approach to the treatment of co-occurring psychiatric disorders and SUDs. Integrated treatment of co-occurring disorders is the accepted standard of care for this challenging, high-risk patient population.

Figure. National Drug Overdose Deaths Involving Opioids, by Benzodiazepine Involvement

Dr. Adelman references a study by Gourlay et al. that benzodiazepines may be used in pain medicine: a rational approach to the treatment of chronic pain. A study by Martins et al. also references the natural history of male alcoholism.

Dr. Adelman also refers to a study by Vaillant GE that alcoholism is a card or horse to sociopathy. Another study by Young et al. reviews common and challenging behaviors among individuals on long-term opioid therapy.

Dr. Adelman's publication is an excerpt from a larger study on benzodiazepine use among patients with opioid use disorder. The study highlights the importance of universal precautions in pain medicine.

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Schizophrenia in the Emergency Department: Psychologically and Psychodynamically Informed Practices

Anthony J. Furiato, DO, FACEP; and Mark L. Ruffalo, DPsa, LCSW

Although schizophrenia is a leading cause of suffering and disability worldwide, affecting about 1% of the global population, community services for those with chronic schizophrenic illness are lacking in many areas. As a result, the emergency department (ED) often becomes a primary location for care of this severe mental disorder.

With our combined experience as an emergency medicine physician with interest in the management of acute psychiatric presentations (Furiato) and a psychotherapist with interest in the psychotherapy of schizophrenia (Ruffalo), we believe a psychodynamically (and psychodynamically) informed guide to the management of schizophrenia in the ED that incorporates relevant research from pharmacotherapy, psychology, and psychotherapy can be very useful in the acute care of these patients.

Is It Really Schizophrenia?

Attempts to distinguish schizophrenia from the psychotic symptoms that occur in other mental and medical disorders date at least to Kraepelin’s pioneering work in the late 1800s. Another German psychiatrist, Kurt Schneider, proposed the “first-rank symptoms” of schizophrenia in 1939, and his theory held widespread popularity throughout the 20th century (Table 1). A recent Cochrane review of Schneider’s first-rank symptoms (FRS) concluded that FRS correctly identifies individuals with schizophrenia 75% to 95% of the time. While reliance on FRS alone may not be sufficient to diagnose schizophrenia, recognition of FRS can aid ED physicians and mental health workers in the triage and care of patients presenting with psychotic disturbance.

Patients presenting to EDs may be well-known to ED staff; the course of schizophrenia is generally chronic and, in many geographic regions of the United States, comprehensive mental health systems are sorely lacking. In cases wherein the patient is a poor historian, or past records are otherwise unable to be obtained, reliance on clinical skill, such as knowledge of FRS, is necessary to ascertain the diagnosis of schizophrenia.

In certain instances, such as a clinical suspicion of new-onset schizophrenia or abnormal neurologic exam findings, use of brain imaging may be necessary to rule out organic disease of the nervous system. While a comprehensive review of brain imaging in psychosis is outside of the scope of this paper, Coentre et al1 note that neuroimaging is particularly useful in first-episode psychosis when patients are elderly, have neurological symptoms, or have an atypical clinical picture.

Leveraging Psychopharmacology

In the ED setting, the first and most important consideration upon presentation of the acutely agitated patient with psychosis or schizophrenia is the level of risk of harm they pose to themselves and staff. The resulting answer will help determine the route and type of medication for the specific patient. Speed of onset can dictate the route of administration, as those who are violent will need more rapid calming. These therapies should be used with verbal de-escalation techniques or directly after such attempts have failed.

Benzodiazepines, which are pharmacologically active on the gamma-aminobutyric acid (GABA) receptors, act on the central nervous system and are among the most common medications used for calming and sedation in the ED. The largest concentrations exist in the thalamus, cortex, and cerebellum. There are many different subclasses of GABA receptors, including the main α- and β-subunits. The biochemical neurotransmitter effects include reversible binding of the excitatory neurotransmitter and neuronal firing. The primary clinical effects are anxiolysis, sedation, and amnesia.

Benzodiazepines are also commonly used as the first-line agent of emergency treatment of seizure disorders and epilepsy. Potential adverse events include respiratory depression, hypoxia, hypotension, and paradoxical excitation reaction in those with organic brain disease. Depending on the lipid solubility of the agent and route of metabolism with patient comorbidities, half-lives vary widely (Table 2).

Patients who are successfully verbally calmed and de-escalated can be considered for therapy with oral management with benzodiazepines alone or in combination with antipsychotics. Intramuscular medications combined with antipsychotics, often with the help of physical restraints, are used for those patients who cannot be de-escalated and pose a risk of injury to themselves and staff.

The 2 main categories of antipsychotics in the emergency setting are first-generation (typical) and second-generation (atypical) agents. The class distinctions are mostly important because of the associated adverse effects. First-generation antipsychotics were developed for the treatment of schizophrenia; they act on the multiple dopaminergic receptor, anticholinergic, and histamine pathways. Each drug has its own mechanism of action and level of antagonism of those pathways.

The hallmark first-generation drug is haloperidol, commonly used in the ED. It has been used with great success in treating the positive symptoms of schizophrenia. One of its main limitations, and ultimately a reason that prompted the development of the second-generation drug class, consists of extrapyramidal symptoms such as tremor, slurred speech, akathisia, dystonia, and tardive dyskinesia. The second-generation class of medications further treats the negative symptoms of schizophrenia and improves upon the adverse event profile of the first-generation group. Olanzapine and ziprasidone are common second-generation antipsychotics used in the ED. Significant adverse event of the second-generation drugs include sedation, hypotension, weight gain, and
More research is needed to further assess or ED psychiatric evaluation vs the traditional antipsychotics used in the ED include lorazepam plus haloperidol or ziprasidone; and midazolam plus haloperidol or ziprasidone. The combination of antihistamine diphenhydramine is also sometimes added to the aforementioned 2-drug cocktail for patients who are extremely violent. This practice is falling out of favor as seen in a recent retrospective cohort study.7

In the prehospital and ED literature, ketamine has also been examined for the acute management of the violently agitated patient.7 Ketamine is a dissociative agent that works at the N-methyl-D-aspartate (NMDA) receptor, which is thought to play a partial role in the development in schizophrenia. Ketamine, when given intramuscularly, can produce more rapid de-escalation and sedation vs the more traditional method of benzodiazepines plus an antipsychotic.7 The drawback to the use of ketamine is the theoretical possibility of exaggerating schizophrenic episodes due to activity on the NMDA receptors. There does not appear to be an increased need for inpatient psychiatric admission or ED psychiatric evaluation vs the traditional therapy.7 More research is needed to further assess the use of ketamine in the acute agitated schizophrenic patient.

Psychologically Informed Management

Schizophrenia is a complex, multidimensional problem that requires appreciation of both biomedical and psychosocial aspects of disease management. This is true not only in the psychiatric treatment setting but also in the ED, since patients with schizophrenia may exhibit the most severe symptoms in the acute care setting.

Of greatest importance, perhaps, is the recognition that the patient’s heightened state of anxiety has contributed to their current psychotic disintegration. The patient with schizophrenia often feels alone and afraid, isolated, and without any sense of basic trust or security. The threat of interpersonal contact is too much for them to bear, so they escape even deeper into their psychotic world. Care must be taken to avoid any unnecessary situations in which the patient’s anxiety is increased, as this will only worsen the psychotic symptoms. Any attempt to challenge or question the validity of delusional themes will result in utter failure, so the ED clinician must avoid these types of confrontations. At the same time, the clinician should not tacitly agree with the patient’s deluded ideas but instead explain empathically that there are reasons they are experiencing things differently. Again, the clinician must do everything they can to foster an environment in which some semblance of trust can be established. For the patient who is mute or otherwise difficult to engage in an interview, speaking about neutral subjects, such as the weather or sports, may help alleviate anxiety and open up the patient to answering some basic questions.

While it is, of course, necessary to gather some information from the patient to establish a history and determine appropriate disposition, the patient with schizophrenia may experience too many questions as an imposition. As Silvano Arieti, MD, noted, “The request for information is often interpreted by the patient as ‘an attempt to take something from him. The aim of the ED interview should be less the collection of detailed information and more of a process of relating to the patient, while gathering an assessment of current symptoms, an attempt to relay a sense of warmth, security, and trust which will serve as the foundation for ongoing treatment.

As previously discussed, the administration of psychotropic medications in the ED is sometimes necessary to stabilize an aggressive or violent patient. In these cases, the ED physician and mental health professional should maximize the patient’s sense of autonomy and self-determination; for example, the staff can allow the patient to choose the route of administration. Most likely, the patient feels that they have been violated in some way—either due to intrusive voices, paranoia, somatic delusions, or some other terrifying symptom—so the ED clinician should attempt to avoid coercion to the greatest degree possible.

Lastly, in many cases of schizophrenia, psychotic symptoms are ongoing, sometimes in spite of good pharmacological and psychotherapeutic management. The mere presence of psychotic symptoms in a patient who experiences such symptoms at baseline does not warrant inpatient psychiatric hospitalization, and it is unlikely that any such admission would do anything to improve the patient’s chronic illness.

Concluding Thoughts

Schizophrenia is a complex, disabling condition that presents a challenge to psychiatric and emergency medicine providers alike. Due in part to the lack of a comprehensive mental health system in the United States, patients with schizophrenia frequently present to the ED for diagnosis, treatment, and acute stabilization. Knowledge of diagnostic, pharmacological, and psychosocial elements of schizophrenia is essential for competent ED care. Of chief importance is the recognition that the patient with psychosis is in a psychologically vulnerable state, worsened by anxiety, and improved with understanding, empathy, and evidence-based symptom management.

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REFERENCES

The Fundamentals of QTc: Understanding Risks and Preventing Problems

Margo C. Funk, MD, MA; and Junyang Lou, MD, PhD

Although the ultimate goal of pharmacological treatments is to help the patient, sometimes medications can cause adverse effects. Such is the case with some psychiatric medications that can trigger torsades de points (TdP), a potentially fatal polymorphic ventricular tachycardia that arises during abnormal ventricular repolarization. Prolongation of the corrected QT interval (QTc) on the 12-lead electrocardiogram (ECG) is a primary marker of TdP risk and a major drug safety benchmark used by the US Food and Drug Administration (FDA). As such, psychiatric clinicians must be aware of the risk factors that increase risk of TdP; in addition, they must feel confident performing individual risk-benefit analyses when prescribing a medication with known risk. An important part of this process is basic proficiency in ECG interpretation, including recognition and measurement of relevant intervals and application of appropriate corrections for heart rate (HR) and QRS duration.

What Are the Mechanisms of TdP?
Medications that prolong ventricular repolarization do so through direct blockade of the inward rectifier potassium channel encoded by the human ether-a-go-go related gene. This blockade results in slowed efflux of potassium from cardiac myocytes prolonging the duration of the cardiac action potential and the QT interval on the ECG. TdP is typically triggered by early afterdepolarizations, which are ectopic activations of the ventricles arising during the prolonged repolarization phase. Most cases of TdP occur in the context of multiple risk factors, including use of more than 1 QTc prolonging medication, female sex, older age, bradycardia, personal history of structural or functional heart disease, personal or family history of sudden cardiac death, renal impairment (especially hemodialysis), hepatic impairment, and electrolyte disturbance (eg, hypokalemia, hypomagnesemia, hypocalcemia). Close attention should be given to co-administered medications that may inhibit metabolism of high-risk QTc-prolonging medications. The cardiac action potential begins with transmission of electrical activity from the sinoatrial node to the atrioventricular (AV) node, corresponding to the PR interval on the ECG. Electrical impulses then travel rapidly from the AV node through the His-Purkinje system, leading to rapid and synchronized ventricular depolarization, represented by the QRS complex. Repolarization of the ventricles occurs during the JT interval, which begins at the J-point (end of the QRS complex) and ends with termination of the T-wave. Notably, the QT interval includes the QRS complex and the JT interval, encompassing both ventricular depolarization and repolarization.

Most cases of TdP occur in the context of multiple risk factors.

What About Heart Rate Correction of the QT Interval?
It is well recognized that the QT interval is HR dependent. Since the 1920s, the Bazett formula (QTc = QT/RR1/2) has been primarily used to derive the “heart rate–corrected QT interval,” or QTc, in clinical and research settings. Most computerized ECG interpretation software uses the Bazett formula by default. Unfortunately, the Bazett formula is well known to overestimate the QTc during fast HR and underestimate it at lower HR. Recognizing this inadequacy, the FDA transitioned from use of the Bazett formula to the Fridericia formula (QTc = QT/RR1/3) in 2017 for drug monitoring studies. The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) recommend use of linear regression formulae such as Hodges, Framingham, or nomogram for HR correction. A comprehensive study of more than 6000 participants comparing 5 HR correction formulae demonstrated the most consistent QT correction (ie, HR independent) by Fridericia and Framingham. In general, the Fridericia, Hodges, and Framingham QTc formulae have the most consistent data and are found in most online or app-based QTc calculators. Although the QTc is considered abnormal when it is above 450 ms in men and above 460 ms in women, TdP does not typically occur when the QTc is < 500 ms. Most practitioners use 500 ms as an informal QTc cutoff.

Ventricular conduction delay from bundle branch block or ventricular pacing manifests as widening of the QRS (QRS > 110 ms) due to slowed, cell-to-cell depolarization of the myocardium rather than rapid conduction through the His-Purkinje system. Widening of the QRS complex artificially prolongs the QT interval without prolonging repolarization. Psychiatrists who frequently treat patients with cardiac disease should be familiar with methods to correct the QT interval for a wide QRS. Failure to correct for a wide QRS may result in inappropriate withholding or under-dosing of necessary psychotropic medication. Recommendations by the ACC/AHA/HRS suggest use of a bivariate formula using both HR and QRS as variables, or the Jc (upper limits of normal: men = 355 ms, women = 372 ms).

What About Specific Psychotropic Medications?
Many classes of medications, both psychotropics and commonly used nonpsychotropics, can prolong the QTc and increase the risk of TdP. One of the best online registries of QTc-prolonging medications is www.crediblemeds.org. CredibleMeds® catalogues medications according to 4 main categories: possible risk (evidence for QTc prolongation); conditional risk (evidence for QTc prolongation under certain conditions, such as overdose, or when combined with another drug that inhibits metabolism of the primary drug); known risk (evidence for TdP); and drugs to avoid in congenital long QT. Although CredibleMeds® is a comprehensive registry, the levels of evidence are highly variable, with many designations based only on case report. Psychiatrists must be familiar with the evidence for individual drugs to best inform a clinical decision. In the next sections, we will highlight the key medications that all psychiatrists should know.

METHADONE. Due to the rare nature of TdP, which can be silently lethal, it is difficult to study TdP as a primary outcome measure. Prolongation of the QTc serves as the closest proxy; however, QTc prolongation is only a marker of risk and not an absolute predictor of TdP. Methadone is among the few medications with TdP as a known outcome and therefore should serve as an example of the need to closely monitor patients for QTc prolongation. The only known risk factor is use of a bivariate formula using both HR and QRS as variables, or the Jc (upper limits of normal: men = 355 ms, women = 372 ms).
vigilant monitoring for cardiac risk with attention to harm-reduction strategies, such that ECG screening does not become a barrier to methadone treatment. Methadone is not recommended in patients with a QTc ≥ 500 ms. For patients with a QTc higher than 450 ms but less than 500 ms, alternatives like buprenorphine should be considered when possible. All modifiable risk factors for TdP should be evaluated and corrected prior to methadone initiation. There is not consensus on the frequency of follow-up ECGs; however, this should depend on the baseline QTc (if performed) and the presence of other risk factors. ECGs should also be performed following dose changes or when total daily dose exceeds 120 mg.

CITALOPRAM. In 2011, the FDA issued a drug safety communication regarding citalopram, noting that it should not be prescribed at doses greater than 40 mg and should not be used at doses greater than 20 mg in those with liver dysfunction or who are 60 years or older. It was further noted that 60-mg dosing was no more efficacious than 40-mg dosing. This guidance was based on a single study that demonstrated an increased QTc of 8.5 ms at 20 mg and 18.5 ms at 60 mg. In 2012, the FDA downgraded their guidance, stating that citalopram was not recommended at doses greater than 40 mg and should be discontinued in anyone with a QTc greater than 500 ms. Since the FDA recommendations, multiple studies have demonstrated similar results. However, studies examining risk of ventricular arrhythmia, sudden cardiac death, and all-cause mortality have shown no difference between citalopram and other selective serotonin reuptake inhibitors (SSRIs). Furthermore, patients on higher doses of citalopram that were reflexively reduced have increased QTc prolongation risk with citalopram is statistically significant when compared with other antidepressants, including SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs). Olanzapine and clozapine are also considered to cause QT prolongation, although no clear association has been established with the specific risk associated with the individual antipsychotic, psychiatrists may consider obtaining a baseline and steady-state ECG with vigilance for QTc greater than 500 ms or a QTc increase of 60 ms or more following medication initiation.

OTHER ANTIPTSCHYTICS. Although nearly all antipsychotics have been associated with QTc prolongation, there is significant variability across the medication class. Of the typical antipsychotics, the low-potency phenothiazines, including thioridazine and chlorpromazine, have been most consistently associated with QTc prolongation. Ziprasidone has the most QTc prolongation of the atypical antipsychotics. Other atypical antipsychotics, quetiapine is associated with mild-to-moderate QTc prolongation, with mixed data. Olanzapine, risperidone, and clozapine are considered to cause QT prolongation, with mixed data. A systematic review of 77 clinical trials of ziprasidone and risperidone has shown no difference between citalopram and other antidepressants, including SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs). Olanzapine and clozapine are also considered to cause QT prolongation, although no clear association has been established with the specific risk associated with the individual antipsychotic, psychiatrists may consider obtaining a baseline and steady-state ECG with vigilance for QTc greater than 500 ms or a QTc increase of 60 ms or more following medication initiation.

OTHER ANTIDEPRESSANTS & MOOD STABILIZERS. In healthy patients with no underlying heart disease, tricyclic antidepressants administered at therapeutic doses likely have little impact on the QTc, with low risk of TdP. However, TdP can occur in cases of overdose or when these drugs are used in patients with underlying cardiac disease, especially ventricular conduction delay or ischemic heart disease. If the other antidepressants, including SSRIs and serotonin-norepinephrine reuptake inhibitors, citalopram carries the most risk of QTc prolongation. Sertraline is the best studied and has the best cardiac safety profile for patients with heart disease. Antiepileptic medications used for mood stabilization have not been shown to prolong the QTc. The few studies of lithium have not demonstrated clinically significant QTc prolongation when serum levels are within the therapeutic range. Supratherapeutic lithium levels are associated with modest increases of QTc.

NONPSYCHOTROPIC MEDICATIONS. Some of the most common nonpsychotropic medications have significant QTc prolongation and deserve special attention. These include the macrolide antibiotics (eg, azithromycin), antifungals (eg, fluconazole), most antiemetics (eg, ondansetron), furosemide (mediated by fluctuation of potassium), and antiarrhythmics (eg, amiodarone). Many of these medications are known cytochrome P450 inhibitors of other QTc-prolonging medications, and they require vigilance, with consideration for alternatives, when used in combination.

Conclusions

When prescribing medications with known risks of QTc prolongation or TdP, psychiatrists must perform a comprehensive risk-benefit analysis, taking into consideration the QTc, risk factors for TdP, strategies to mitigate cardiac risks when possible, and potential psychiatric adverse outcomes that would arise from not prescribing a medication.

Dr Funk is the program director of the Harvard South Shore (HSS) psychiatry residency training program. Dr Lou is an interventional cardiologist at Brigham and Women’s Hospital.

REFERENCES

Read the full article and included figures online, available here.
BIPOLAR DISORDER
THE DIFFICULT DIAGNOSIS

» Leah Kuntz

In this installment of the custom Around the Practice video program, Michael Thase, MD; Gustavo Alva, MD, DFAPA; Theresa Cerulli, MD; and Tina Matthew-Hayes, DNP, FNP, PMHNP, shared their insights on the identification and management of bipolar disorder.

“Sometimes people go about without necessarily receiving an appropriate diagnosis for a while,” said Alva, medical director of ATP Clinical Research in Costa Mesa, California. “Based on the literature, sometimes people go 5 to 10 years before asserting the appropriate diagnosis.”

To highlight diagnostic challenges and discuss optimized treatment, the panel walked through 2 interesting case vignettes.

CASE VIGNETTE 1

A 27-year-old woman presents for evaluation of a complex depressive syndrome after having failed 2 recent trials of antidepressants. She has a history of attention-deficit/hyperactivity disorder (ADHD), for which she took methylphenidate during her youth. Her depressive episode occurred, as she described it, “right out of the blue.” She is taking sertraline and escitalopram at the time of initial evaluation; and escitalopram was recently reduced by her primary care provider from 20 mg to 10 mg because she believed the medicine might have been making her worse.

The patient’s symptoms include hypersexuality, hypersomnia, overeating, reactive mood, tearfulness, and trouble concentrating. On the day of her first visit, she scores 16 on the Patient Health Questionnaire-9 (PHQ-9), which is in the moderate depression range. She filled out the mood disorder questionnaire and scored a whopping 10, which is not the highest possible score but higher than 95% of people who take this inventory. The differential diagnosis for this patient included major depressive disorder, recurrent unipolar with mixed features versus bipolar II disorder, with an antecedent history of ADHD. The patient was not taking any mood-stabilizing medication.

“When we consider somebody with a major depressive episode, obviously a differential diagnosis of bipolar disorder and a depressive episode is certainly one that we should be considering. I think that this particular case is quite interesting in that it brings so many different elements to the forefront and helps us along lines of medication misadventures. And the possibility of maybe barking up the wrong tree and not necessarily addressing the underlying issues that we need to be getting to,” Alva said.

One of the complicating factors, as Cerulli explained, is the history of ADHD. “[The patient] has had recurrent depressive episodes with some mixed features that could be mixed up with things like the reactivity of ADHD, the higher energy of ADHD, and the irritability of ADHD—it’s easy to miss that this was actually a bipolar picture,” she said. “We’re really looking at risk factors to be able to help identify who are the patients that are at risk for bipolar as opposed to unipolar depression, or just an ADHD anxious irritable picture, which is so commonly where these folks get lumped into.”

The panel was then asked which treatment option they would be most likely to start with this patient: lithium, quetiapine, divalproex, lurasidone, or cariprazine.

Matthew-Hayes chose cariprazine, based on the metabolic profile, her experience with the medication, and the FDA-approved status for both depression and mania. Alva agreed, noting that cariprazine is not sedating, would not require a food alteration, and has an attractive profile for someone who has the potential to become pregnant.
CASE VIGNETTE 2

A 47-year-old male investment banker with a history of manic episodes comes for a second opinion regarding treatment of an intractable depressive episode. His initial treatment was with lithium, which was highly effective, but it aggravated his psoriasis, gave him a low-grade tremor (even at blood level of 0.6 mEq/L), and caused excessive thirst. He was switched to divalproex, which was not as effective. It was supplemented first by olanzapine, then risperidone, and then lamotrigine at the beginning of this episode. Lamotrigine had helped during a previous episode, but this time it did not help enough even when titrated up to 400 mg. Adequate trials of bupropion, fluoxetine, and duloxetine, even at high doses, did not result in a meaningful drop in the PHQ-9 score.

His symptoms included unreactive low mood, pervasive anhedonia, and passive suicidal ideation. He did not have a substance use disorder, nor was he psychotic. The interview indicated he was adherent to the treatment.

Based on the data presented, this patient meets the definition of treatment-resistant depression and bipolar I depression, for which there is only a single treatment indicated: the combination formulation of olanzapine and fluoxetine. Because of the metabolic risks associated with olanzapine, this treatment is not ideal.

Another strategy might be to add lithium to the current mood stabilizer combination, but the patient had tolerability issues with this medication. Other options include newer-generation antipsychotics, with quetiapine, lurasidone, and cariprazine having FDA approval for bipolar I depression.

After discussion, the panel thought cariprazine would be the best next option. “With cariprazine being FDA approved for treating all phases of bipolar—bipolar depression, mixed phase, and manic symptoms—you get a little assurance that you’re not going to end up triggering the manic symptoms. You may, in fact, be also treating and preventing the other phases of bipolar simultaneously, while treating this very treatment-resistant depression phase that the patient is in,” Cerulli said.

Telemedicine and Improving Outcomes

In addition, the panel discussed the positives of telemedicine in the struggle to identify and treat bipolar disorder.

“It’s a wonderful opportunity to be able to reach patients that we might not otherwise have been able to reach,” Cerulli said. “I found that this has been a nice way to be able to see patients that are at a distance from practice that I can now have an opportunity to work with.”

Matthew-Hayes added that telemedicine helps to keep matters confidential: “One of the other huge benefits is getting some of our patients, especially bipolar patients, a little more privacy.”

Matthew-Hayes also suggested reaching out to local National Alliance on Mental Illness organizations to help get patients the internet access at decreased rates so they can use telehealth appointments. Thase recommended checking out the Depression and Bipolar Support Alliance, of which he is a 30-year member, where largely free psychoeducational resources can be found.

Dr Thase is professor of psychiatry at the Perelman School of Medicine at the University of Pennsylvania. Dr Alva is medical director of ATP Clinical Research in Costa Mesa, California. He also works with Avanir, Otsuka, ACADIA, Lundbeck, Abbvie, Teva, Neurocrine Biosciences, Athers, LivNova, and Alector. Dr Cerulli is the medical director of Cerulli and Associates in North Andover, Massachusetts. She also works with Abbvie and is a speaker for Vraylar. Tina Matthew-Hayes is a dual certified nurse practitioner at the Western Pennsylvania Behavioral Health Resources in West Mifflin, Pennsylvania.

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To view the custom video series in its entirety, please visit: psychiatrictimes.com/around-the-practice/around-the-practice-identification-and-management-of-bipolar-disorder

Or scan the QR code
ONE MEDICATION APPROVED TO TREAT ALL BIPOLAR I EPISODES: DEPRESSIVE AND ACUTE MANIC OR MIXED EPISODES

Visit VRAYLARHCP.com for VRAYLAR bipolar I disorder study results and design, additional dosing information, and more.

Indications and Usage
Indicated in adults for the:
• Treatment of depressive episodes associated with bipolar I disorder (bipolar depression)
• Acute treatment of manic or mixed episodes associated with bipolar I disorder

Important Safety Information

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR is not approved for treatment of patients with dementia-related psychosis.
• Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Safety and effectiveness of VRAYLAR have not been established in pediatric patients.

Contraindication: VRAYLAR is contraindicated in patients with known hypersensitivity. Reactions have included rash, pruritus, urticaria, and events suggestive of angioedema.

Cerebrovascular Adverse Reactions, Including Stroke: In clinical trials with antipsychotic drugs, elderly subjects with dementia had a higher incidence of cerebrovascular adverse reactions, including fatalities vs placebo. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with antipsychotic drugs. NMS may cause hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary, dyskinetic movements) and the likelihood it will become irreversible may increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. If signs and symptoms of TD appear, drug discontinuation should be considered.

Late-Occurring Adverse Reactions: Adverse events may first appear several weeks after initiation of VRAYLAR, probably because plasma levels of cariprazine and its major metabolites accumulate over time. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after longer term exposures. Monitor for adverse reactions, including extrapyramidal symptoms (EPS) or akathisia, and patient response for several weeks after starting VRAYLAR and after each dosage increase. Consider reducing the dose or discontinuing the drug.

Metabolic Changes: Atypical antipsychotics have caused metabolic changes, such as:
• Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Assess fasting glucose before or soon after initiation of treatment, and monitor periodically during long-term treatment.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warnings, on the following pages, or visit https://www.rxabbvie.com/pdf/vraylar_pi.pdf
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**Important Safety Information (continued)**

- **Dyslipidemia:** Atypical antipsychotics cause adverse alterations in lipids. Before or soon after starting an antipsychotic, obtain baseline fasting lipid profile and monitor periodically during treatment.
- **Weight Gain:** Weight gain has been observed with VRAYLAR. Monitor weight at baseline and frequently thereafter.
- **Leukopenia, Neutropenia, and Agranulocytosis:** Leukopenia/neutropenia have been reported with antipsychotics, including VRAYLAR. Agranulocytosis (including fatal cases) has been reported with other antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue VRAYLAR at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.
- **Orthostatic Hypotension and Syncope:** Atypical antipsychotics cause orthostatic hypotension and syncope, with the greatest risk during initial titration and with dose increases. Monitor orthostatic vital signs in patients predisposed to hypotension and in those with cardiovascular/cerebrovascular diseases.
- **Falls:** VRAYLAR may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures, or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotics and recurrently for patients on long-term therapy.
- **Seizures:** Use VRAYLAR with caution in patients with history of seizures or with conditions that lower the seizure threshold.
- **Potential for Cognitive and Motor Impairment:** Somnolence was reported with VRAYLAR. Caution patients about performing activities requiring mental alertness (eg, operating hazardous machinery or a motor vehicle).
- **Body Temperature Dysregulation:** Use VRAYLAR with caution in patients who may experience conditions that increase body temperature (eg, strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics).
- **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotics. Antipsychotic drugs, including VRAYLAR, should be used cautiously in patients at risk for aspiration.
- **Drug Interactions:** Strong CYP3A4 inhibitors increase VRAYLAR concentrations, so VRAYLAR dose reduction is recommended. Concomitant use with CYP3A4 inducers is not recommended.
- **Adverse Reactions:** In clinical trials, the most common adverse reactions (≥5% and at least twice the rate of placebo) are listed below:

  - **Bipolar mania:** The incidences within the recommended dose range (VRAYLAR 3 – 6 mg/day vs placebo) were: EPS (26% vs 12%), akathisia (20% vs 5%), vomiting (10% vs 4%), dyspepsia (7% vs 4%), somnolence (7% vs 4%), and restlessness (7% vs 2%).
  - **Bipolar depression:** The incidences within the recommended doses (VRAYLAR 1.5 mg/day or 3 mg/day vs placebo) were: nausea (7%, 7% vs 3%), akathisia (6%, 10% vs 2%), restlessness (2%, 7% vs 3%), and EPS (4%, 6% vs 2%).

**References:**

INDICATIONS AND USAGE: VRAYLAR® is indicated for the treatment of schizophrenia in adults [see Clinical Trials in the full Prescribing Information].

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS: AND SUICIDAL THOUGHTS AND BEHAVIORS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR® is not approved for the treatment of patients with dementia-related psychosis [see WARNINGS and Precautions].

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in children, adolescents, and young adults in short-term trials of psychiatric disorders. These findings were consistent for all studies and for all antidepressant drugs used (with the exception of modafinil). The increase appeared to be greatest for the first month of treatment, and the relative risk then declined with time on treatment. Both young and old patients are at an increased risk, but older patients may be more susceptible.

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Antidepressants increased the risk of suicidal thoughts and behaviors in children, adolescents, and young adults in short-term trials of psychiatric disorders. These findings were consistent for all studies and for all antidepressant drugs used (with the exception of modafinil). The increase appeared to be greatest for the first month of treatment, and the relative risk then declined with time on treatment. Both young and old patients are at an increased risk, but older patients may be more susceptible.

ADVERSE REACTIONS:

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS: AND SUICIDAL THOUGHTS AND BEHAVIORS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR® is not approved for the treatment of patients with dementia-related psychosis [see WARNINGS and Precautions].

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ADVERSE REACTIONS:
Elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS appears in a patient on VRAYLAR, drug discontinuation should be considered. However, some patients may still develop NMS in the days or weeks following discontinuation. Whether antipsychotic treatment should be reinstated after NMS has resolved is not known. The longest duration of NMS was 32 weeks, but a correlation between duration of NMS and risk of recurrence was not seen. NMS typically begins within the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes associated with involuntary twitching of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with higher severity and higher doses of first-generation antipsychotics. An elevated risk of acute dystonia is observed in males and younger age groups.

Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and Placebo-treated Adult Patients in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=594), VRAYLAR* 1.5 - 3 mg/day (N=593), VRAYLAR* 4.5 - 6 mg/day (N=593), VRAYLAR* 9 - 12 mg/day (N=596). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 4. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and Placebo-treated Adult Patients in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=594), VRAYLAR* 1.5 - 3 mg/day (N=593), VRAYLAR* 4.5 - 6 mg/day (N=593), VRAYLAR* 9 - 12 mg/day (N=596). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 5. Adverse Reactions Associated with Discontinuation of Treatment. The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions. In 6-week schizophrenia trials, the incidence of reported events related to EPS, excluding akathisia and restlessness was 4% for VRAYLAR-treated patients versus 0% for placebo-treated patients. The incidence of akathisia was 20% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These events led to discontinuation in 2% of VRAYLAR-treated patients versus 0% of placebo-treated patients. The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 6. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 7. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 8. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=594), VRAYLAR* 1.5 - 3 mg/day (N=593), VRAYLAR* 4.5 - 6 mg/day (N=593), VRAYLAR* 9 - 12 mg/day (N=596). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 9. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=594), VRAYLAR* 1.5 - 3 mg/day (N=593), VRAYLAR* 4.5 - 6 mg/day (N=593), VRAYLAR* 9 - 12 mg/day (N=596). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 10. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 11. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 12. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 13. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 14. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 15. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 16. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 17. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).

Table 18. Change in Body Weight (kg) in 6-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=442), VRAYLAR* 3 - 6 mg/day (N=263), and VRAYLAR* 9 - 12 mg/day (N=273). The incidence of EPS in patients treated with VRAYLAR was 6%, which is 2% lower than placebo (8%).
sufficient to outweigh dose-related adverse reactions. In the two 6-week and one 8-week bipolar depression trials, there were no clinically meaningful differences between VRAYLAR-treated patients and placebo-treated patients in mean change in serum creatinine and diastolic blood pressure. Table 13 in the full Prescribing Information shows the Mean Change in Blood Pressure at Endpoint in two 6-Week and one 8-Week Bipolar Depression Trials. Values shown are: Placebo (N=499), VRAYLAR 3 mg/day (N=572), and VRAYLAR 6 mg/day (N=572); VRAYLAR 1.5 mg/day (N=572) and VRAYLAR 3 mg/day (N=546). The mean changes at endpoint are as follows: Supine Systolic Blood Pressure (mmHg): (-0.2, -0.2, -0.1), Supine Diastolic Blood Pressure (mmHg): (0.2, 0.1, -0.3). Changes in diastolic blood pressure were similar across all trials and in patients with transaminase elevations ≥3 times the upper limits of the normal reference range in 6-week schizophrenia trials ranged between 1% and 2% for VRAYLAR-treated patients, increasing with dose, and was 1% for placebo-treated patients. The proportion of patients with transaminase elevations ≥3 times the upper limits of the normal reference range in 6-week schizophrenia trials ranged between 1% and 2% for VRAYLAR-treated patients, increasing with dose, and was 1% for placebo-treated patients. The proportion of patients with elevations of creatine phosphokinase (CPK) greater than 1000 U/L in 6-week schizophrenia trials ranged between 4% and 6% for VRAYLAR-treated patients, increasing with dose, and was 4% for placebo-treated patients. The proportion of patients with elevations of CPK greater than 1000 U/L in 3-week bipolar mania trials was about 4% in VRAYLAR and placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 6-week and 8-week bipolar depression trials ranged between 0.2% and 1% for VRAYLAR-treated patients versus 0.2% for placebo-treated patients. Other Adverse Reactions Observed During the Pre-marketing Evaluation of VRAYLAR - Adverse reactions listed below were reported by patients treated with VRAYLAR at doses of ≥1.5 mg once daily since the premarketing database of 3888 VRAYLAR-treated patients. The reactions listed are those that could be of clinical importance, as well as those that are plausibly drug-related on pharmacologic or other grounds. Reactions that appear elsewhere in the VRAYLAR label are not included. Reactions are further categorized by organ class and listed in order of decreasing frequency, according to the following definition: those occurring in ≥1/100; those occurring in 1/100 to 1/1000 patients (frequent) [see Clinical Pharmacology in the full Prescribing Information]; those occurring in 1/1000 to 1/10000 patients (infrequent) in the table; and those occurring in <1/10000 patients (rare). Gastrointestinal Disorders:

- Diarrhea;

- Vomiting;

- Abdominal pain;

- Nausea;

- Anaemia;

- Metabolism and Nutrition Disorders:

- Increased lipase;

- Hypoglycemia;

- Hyperglycemia;

- Drug Interactions:

- Concomitant use of VRAYLAR with a strong CYP3A4 inhibitor may increase the exposure of cariprazine and its major active metabolite, demethylcariprazine (DCCAR, compared to VRAYLAR alone [see Clinical Pharmacology in the full Prescribing Information]; intervention: If VRAYLAR is used with a strong CYP3A4 inhibitor, reduce VRAYLAR dosage [see Dosage and Administration in the full Prescribing Information]; Examples: itraconazole, ketoconazole, CYP3A4 Inducers: Clinical Impact: CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the exposure of VRAYLAR has not been evaluated, and the net effect is unclear [see Clinical Pharmacology in the full Prescribing Information]; intervention: Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended [see Dosage and Administration in the full Prescribing Information]; Examples: rifampin, carbamazepine.

USE IN SPECIFIC POPULATIONS: Pregnancy - Pregnancy Exposure Registry - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VRAYLAR during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/. Risk Summary - Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see Clinical Considerations).There are no available data on VRAYLAR use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DCDDR, has been detected in adult patients up to 12 weeks after discontinuation of VRAYLAR [see Clinical Pharmacology in the full Prescribing Information]; intervention: Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended [see Dosage and Administration in the full Prescribing Information]; Examples: rifampin, carbamazepine.

Drug Interactions: Drugs Having Clinically Important Interactions with VRAYLAR. Table 14 in the full Prescribing Information lists the Clinically Important Drug Interactions with VRAYLAR. Strong CYP3A4 Inhibitors: Concomitant use of VRAYLAR with a strong CYP3A4 inhibitor increases the exposure of cariprazine and its major active metabolite, demethylcariprazine [DCDDR, compared to VRAYLAR alone [see Clinical Pharmacology in the full Prescribing Information]: intervention: If VRAYLAR is used with a strong CYP3A4 inhibitor, reduce VRAYLAR dosage [see Dosage and Administration in the full Prescribing Information]; Examples: itraconazole, ketoconazole. CYP3A4 Inducers: Clinical Impact: CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the exposure of VRAYLAR has not been evaluated, and the net effect is unclear [see Clinical Pharmacology in the full Prescribing Information]; intervention: Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended [see Dosage and Administration in the full Prescribing Information]; Examples: rifampin, carbamazepine.

Drug Abuse and Dependence: Controlled Substance - VRAYLAR is not a controlled substance. Abuse - VRAYLAR has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance. Dependence - VRAYLAR has not been systematically studied in animals or humans for its potential for physical dependence. Overdose: Human Experience - In pre-marketing clinical trials involving VRAYLAR in approximately 5000 patients or healthy subjects, accidental acute overdose (46 mg/day) was reported in a patient. This patient experienced no adverse reactions. No overdose deaths occurred in this patient. The patient was recovered the same day. Management of Overdose - No specific antidotes for VRAYLAR are known. In managing overdose, supportive and symptomatic care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. In case of an overdose, consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

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Cognitive/Neuropsychological Functioning and Suicidal Behavior: A Review of Research and Implications for Clinical Practice

Jerrold Pollak, PhD

S

uicidal behavior is a complex and incom-pletely understood biopsychosocial syn-
drome. It encompasses suicidal thinking (sometimes accompanied by plan and/or intent), attempted suicide, and death from suicide. Despite intensive study over decades, suicidal behavior eludes reliable prevention and prediction and, for many patients, is not a well-treated set of conditions.1

In recent years the evidence base regarding sui-cidal etiology, prevention, assessment, and inter-
vention have all expanded, and a number of prom-
ising prevention and treatment innovations for suicidal behavior have been developed.2 Still,

rates of completed suicide continue to increase among nearly all age groups.3 Since at least the start of this century, death from suicide has be-

come a well-entrenched public health epidemic with no signs of abating.

During the second half of the 20th century, clini-
cal and research studies on suicide were largely focused on the psychosocial and psycho-
dynamic underpinnings of suicidal behavior (a working definition of suicidal behavior appears in Table 1). By way of contrast, scant attention was paid to possible neurobiological correlates and causal factors.

The idea that suicidal behavior might have its
genesis, in part, in neurobiology may have emerged as early as the 1960s.4 However, the study of the interface of neurobiology and what are referred to as neuropsychiatric disorders in contemporary clinical practice began in earnest only in the 1980s. This helped to galvanize re-

search on cognitive/neuropsychological dysfunc-
tion as a possible significant risk factor for sui-
cidal behavior and, hence, its importance as a potential target for assessment and intervention. Research findings since the early 2000s have out-

lined cognitive/neuropsychological correlates of suicidal behavior, with an emphasis on the role that cognitive/neuropsychological impairment

1. Increase familiarity with the indications for psychological/neuropsychological impairment.

2. Identify 3 patient groups who are characterized by elevated rates of suicidal behavior and co-occurring cognitive/neuropsychological impairment.

3. Enhance an appreciation of a good working knowledge of neurocognitive status in assessment and treatment planning with suicidal patients.

ACTIVITY GOAL

Identify 3 patient groups who are characterized by elevated rates of suicidal behavior and co-occurring cognitive/neuropsychological impairment.

LEARNING OBJECTIVES

1. Increase familiarity with the indications for psychological/neuropsychological testing of patients with suicidal behavior and suspected or known cognitive/neuropsychological impairment.

2. Enhance an appreciation of a good working knowledge of neurocognitive status in assessment and treatment planning with suicidal patients.

3. Enhance an appreciation of a good working knowledge of neurocognitive status in assessment and treatment planning with suicidal patients.

TARGET AUDIENCE

This accredited continuing education (CE) activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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may play as both a potential diathesis and stressor with respect to susceptibility to suicidal behavior.

This research can help clinicians in the realms of assessment and intervention. For clinical assessment of risk of suicidal behavior, options include the Stress-Diathesis and Risk-Protective Factors Models. According to recent studies, 3 broad clinical groups are characterized by high base rates for both cognitive/neuropsychological impairment and suicidal behavior. Therefore, a good working knowledge of a patient’s neurocognitive status can help guide clinical assessment and intervention. Future research could clarify the relationship between cognitive/neuropsychological impairment and suicide, hopefully leading to advances in suicide prevention.

### Stress-Diathesis and Risk-Protective Factors Models

The Stress-Diathesis model conceptualizes suicidal behavior as multi-determined and the outcome of preexisting distal vulnerabilities (diathesis) interacting with recent and current proximal situational stressors/triggers. The latter can contribute to the probability and timing as well as the pattern and relative severity of suicidal behavior in the individual case.

Predisposing vulnerabilities include a blend of neurobiological factors and predisposing influences that are psychologically/psychodynamically based (Table 2). These factors can, in part, reflect the impact of multiple biological influences (including a history of neurodevelopmental difficulties) but are also thought to be significantly affected by adverse life events and trauma, especially those occurring early in life: mistreatment, neglect, abandonment, and other detrimental life experiences.

For many patients, the interaction of these biopsychosocial factors results in serious problems with the development of age-appropriate behavioral and emotional self-regulation abilities and skills, as well as more general difficulties with adaptation to the lifespan. This includes noteworthy problems coping with adversity, especially attachment and loss issues associated with situational stressors and lifespan developmental transitions.

The interplay of a patient’s diathesis and situational stressors/triggers of varied type (which are commonly experienced by patients as existential threats to their psychological and/or physical well-being) can significantly heighten the risk for suicidal behavior. The degree/severity of risk is attenuated, to some extent, by protective factors: patient’s personality assets, good social support, access to psychiatric care, and other favorable life circumstances.

The Stress-Diathesis model aligns reasonably well with the Risk-Protective Factors model both conceptually and in terms of its heuristic value for clinical assessment and intervention. This conceptual framework emphasizes the importance of the interaction of distal and proximal influences that augment vulnerability (risk factors) and influences, which reduce susceptibility to suicidal behavior (protective factors). This paradigm is employed to create an overall suicidal risk profile for patients who are seen for clinical assessment.

### Identifying 3 At-Risk Clinical Groups

Three clinical groups are at significant risk for a combination of cognitive/neuropsychological impairment and suicidal behavior: individuals with neurodevelopmental disorders, neuropsychiatric disorders, and acquired cognitive or neuropsychological disorders. Details on each of these conditions appear in Table 3.

Patients who fall into 1 or more of these 3 groups grapple with a number of challenges that can negatively impact psychosocial development, executive functioning, and quality of life. They can struggle with identity formation/consolidation, self-esteem regulation, psychological and cognitive insight, judgment, social cognition, cognitive flexibility, impulse control/response inhibition, task initiation, organization/planning, decision-making, and problem solving.

Additional difficulties often involve 1 or more components of negative affectivity, including anger, irritability, liability, anxiety, and depression. Some patients report intolerable recurrent or chronic emotional and psychological pain together with a proclivity to overreact or emotionally shut down in response to acute and chronic stressors.

This construct has considerable overlap with the term neuroticism, which is a key component of the 5-factor dimensional personality model and has applicability to DSM-5 personality disorders.

A substantial number of patients who fall into 1 or more of these 3 groups have at least mildly reduced ability to profit from experience. They may have trouble learning and successfully using coping skills for the purpose of distress tolerance, stress reduction, and responding in a flexible manner to problematic life events. Overall, these patients have significant difficulty building resilience in the face of lifespan developmental challenges and demands. Their struggles in this regard are often complicated by high rates of co-occurring mental health and substance abuse disorders.

The plethora of cognitive and emotional challenges that these patients confront on a daily basis contribute to a significant vulnerability to recurrent as well as persistent behavioral-mood instability.

Some studies have focused on the relationships between cognitive/neuropsychological functioning and suicidal thinking while others have examined the relationship of cognitive/neuropsycho-
Table 2. Neurobiological and Psychosocial Risk Factors

<table>
<thead>
<tr>
<th>Neurobiological</th>
<th>Psychosocial</th>
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<tr>
<td>1. FAMILY HISTORY OF SUICIDE. Includes first- and second-degree biological relatives with histories of suicidal behavior; can also include relatives with histories of neuropsychiatric conditions like borderline personality disorder, bipolar disorder, and schizophrenia, which are associated with relatively high rates of suicidal behavior.</td>
<td>1. PERSONALITY TRAITS. These include but are not limited to patients with significant cluster A personality difficulties, for example paranoid personality features; cluster B personality difficulties, for instance histrionic and/or borderline personality features; and cluster C personality difficulties, notably obsessive-compulsive and dependent personality features.</td>
</tr>
<tr>
<td>2. GENETICS. Includes first- and second-degree relatives with varying degrees of shared genetic endowment with the patient.</td>
<td>2. INTERPSYCHIC CONFLICTS. These include a range of longstanding internalized/psychological conflicts that contribute to a patient feeling emotionally triggered in response to certain stressors/triggers.</td>
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<tr>
<td>3. EPGENETIC AND TEMPERAMENTAL VARIABLES. Epigenetics refers to the impact of environmental influences like psychosocial trauma on gene activity and expression. These genetic alterations are potentially transmissible and may confer an increased vulnerability to the negative effects of stressors in offspring. Problematic temperaments include but are not limited to negative affectivity, rigid perfectionism, rejection-sensitivity, impulsivity, and risk-taking/recklessness.</td>
<td>3. DEFENSE MECHANISMS. These refer to longstanding intrapsychic mechanisms that manage long-term internal conflicts and situational crises/stressors. They include immature and reality-distorting defenses, for example: denial, acting out, splitting, dissociation, projection, and projective identification.</td>
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<tr>
<td>4. NEURODEVELOPMENTAL OR EARLY-ONSET ACQUIRED BRAIN DYSFUNCTION. These include patients with histories of neurodevelopmental disorders like attention-deficit disorder and autism spectrum disorder, which are associated with elevated rates of cognitive/neuropsychological dysfunction. Early-onset or acquired brain dysfunction include pre-natal or perinatal brain injury, or brain injury occurring in the childhood/early adolescent years.</td>
<td>4. COPING PATTERNS DEVELOPED THROUGH CHILDHOOD AND ADOLESCENCE. These overlap with defense mechanisms but are typically associated with considerably more self-awareness than is the case with defense mechanisms. They include various self-medicating strategies to fend off problematic feelings and impulses, including suicidal feelings and impulses: substance abuse, binge-eating, promiscuity, overspending and non-suicidal self-injury.</td>
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Other studies have found positive relationships between cognitive/neuropsychological impairment and suicidal thinking. For example, a study that employed a general population sample and a subgroup with depressive disorders found that a significant positive association between cognitive/neuropsychological impairment and suicidal thinking, including a strong link with higher frequency suicidal thinking. An investigation that assessed the cognitive/neuropsychological integrity of patients with major depressive disorder, with and without suicidal thinking, found that scores on measures of motor speed and executive functioning were significantly lower among patients with suicidal thinking. Moreover, greater compromise in cognitive/neuropsychological functioning was correlated with more severe suicidal thinking.

Other studies have compared the cognitive/neuropsychological test performance of psychiatric patients with histories of suicidal behavior (defined as 1 or more serious suicide attempts), with psychiatric controls—patients with comparable mental health difficulties but with negative histories of suicidal behavior, as well as participants with negative mental health histories (ie, healthy controls). Meta-analytic reviews of the literature comparing these 3 groups highlight an array of cognitive/neuropsychological difficulties in patients with 1 or more mental health condition(s) and histories of suicide attempts, when compared with psychiatric and nonpsychiatric controls. Such difficulties include worse performance on tests of decision-making, category fluency, and response inhibition in patients with depressive and bipolar mood disorders; they also include lower performance on tests of long-term memory and working memory in patients with depressive and bipolar disorders, schizophrenia, schizoaffective disorder, and other conditions like borderline personality disorder.

A recent literature review compared patients with diagnoses of schizophrenia, schizoaffective disorder, and major mood disorder (major depression, bipolar I, and bipolar II disorder) and a history of suicide attempts with patients with similar diagnoses but without suicide attempts. The comparison was based on a series of cognitive/neuropsychological tests, many of which can be considered measures of executive functioning. Patients with histories of 1 or more suicide attempts performed worse than those with comparable neuropsychiatric diagnoses who did not attempt suicide. Findings were mixed, however, with respect to performance on tests of decision-making and constructional praxis. Moreover, measures of working memory did not clearly discriminate between these 2 groups.

Another literature review compared patients across a broad range of neuropsychiatric diagnoses with suicidal thinking with patients who had a history of attempts as well as patients with negative histories for suicidal behavior, looking at various neuropsychological measures. Differences between patients with suicidal thinking and those who actually attempted suicide were characterized as “negligible to small.” There were, however, medium size effects between these groups for performance on 2 measures of executive functioning. Those participants who had attempted suicide performed worse in decision-making and inhibition. There were no significant effect size differences on any neurocognitive measures or indices between patients with suicidal thinking and patients without histories of suicidal behavior. The only exception was a large effect size on measures of information processing speed, in favor of the latter group.

A review of the literature that focused on performance on a wide range of tests of executive functioning in relation to suicidal thinking and/or attempted suicide across a number of neuropsychiatric diagnoses found “some evidence” and “tentative support” for links between impaired executive functioning and suicidal behavior. Associations appeared stronger for patients with depressive disorders than with patients with bipolar or psychotic disorders.

Discussing the Findings

The findings of these and other reviews offer modest support for the idea that psychiatric patients with histories of suicidal behavior have more problematic cognitive/neuropsychological functioning than non-suicidal psychiatric patients. Moreover, these difficulties with neurocognition may be conceptualized, at least in part, as trait markers, that are relatively separate and distinct from the impact of state-related affective/behavioral factors and co-occurring mental disorders, including depression, on a patient’s cognitive/neuropsychological status.

That said, other studies have not found meaningful relationships between neurocognitive status and suicidal behavior. Although counterintuitive, some studies noted better cognitive/neuropsychological functioning among those patients with schizophrenia who attempted suicide as opposed to those who did not attempt with the same diagnoses.

It is also important to consider that most medical and/or psychiatric patients with cognitive/neuropsychiatric impairment have negative histories for suicidal behavior. Substantial numbers of psychiatric patients with histories of suicidal behavior have no apparent problems with their neurocognition.

Indeed, profiles of intact and impaired cognitive/neuropsychological abilities/skills may prove...
to be more germane to risk for suicidal behavior than impaired abilities/skills per se. For example, the neurocognitive status of a sample of suicidal attempters has been characterized by relatively good problem-solving abilities/skills but relatively poor impulse control/response inhibition.  

**Lessons Derived From the Literature**

To date, there is suggestive but insufficient evidence to reliably support robust and independent cause and effect relationships between cognitive/neuropsychological impairment and elevated rates of suicidal behavior among patients with neurodevelopmental, neuropsychiatric, and/or acquired neurocognitive disorders.  

As is true of many factors that may be implicated in complex multifactorial outcomes like suicidal behavior, the possible impact of cognitive/neuropsychological impairment on the susceptibility to suicidal behavior is likely to vary as a function of an individual’s clinical profile of intact and impaired cognitive/neuropsychological abilities. A host of medical, psychosocial, psychodynamic, and situational influences might affect outcomes as well. Neuropsychiatric diagnosis may also be a relevant factor.  

Additionally, it may be that the number and relative severity and/or the stage of the neurodevelopmental, neuropsychiatric, and medical/neurologic condition(s)—as well as a patient’s particular nexus of self-harm related risk and protective factors—all play key roles. These are moderator variables, which mediate the impact of cognitive/neuropsychological impairment on the risk for suicidal behavior.  

For instance, Alzheimer disease is a risk factor for suicidal behavior, even many years after formal diagnosis. There is some evidence that patients newly diagnosed with mild neurocognitive disorder, possible Alzheimer disease, or cognitive/neuropsychological changes consistent with probable early phase Alzheimer disease may be at greater risk for suicidal self-harm than patients with more advanced illness.  

It may also be the case that at least some of the effects of a patient’s cognitive/neuropsychological status are indirect in so far as they negatively impact other risk factors which, in turn, elevate risk for suicidal behavior.  

For example, cognitive/neuropsychological impairment can sometimes result in disinhibition and impulsivity, which lead to reckless behavior or exacerbate preexisting personality trait vulnerabilities. In association with potentially destabilizing influences like substance abuse and other proximal psychosocial stressors/triggers, these difficulties would be expected to significantly raise the risk for suicidal behavior. In this scenario, a patient’s profile of cognitive/neuropsychological abilities and deficits may even facilitate the transition from suicidal thinking to a suicide attempt.  

Other cases of cognitive/neuropsychological impairment, characterized by problems with conceptual thinking, language processing, working memory, and/or anterograde memory, would likely differentially impact comprehension and retention. These issues could lead to poor understanding and follow-through with crisis/safety and treatment plans.  

In both instances, the patient’s neurocognitive profile may elevate risk for suicidal self-harm and, together with other factors, override the potentially mitigating influence of protective factors. If cognitive/neuropsychological factors can be more firmly established as an important set of causal influences in augmenting the risk of suicidal behavior, then they should be viewed as one of many significant predisposing risk factors. Accordingly, they would begin to play a more frequent and prominent role in suicide assessment and intervention. This might include the development of relatively brief and well-tolerated neuropsychological screening tests, which could be integrated into formal risk assessments to enhance predictive validity, as well as help guide clinical management and harm reduction strategies.  

**The Role of Psychological/Neuropsychological Testing**

To date, the clinical utility of cognitive/neuropsychological testing for the assessment of suicidal behavior lacks a clear evidentiary base. Therefore, the following discussion is based on clinical experience, while considering the aforementioned findings on links between cognitive/neuropsychological impairment and suicidality.  

Cognitive/neuropsychological testing may be appropriate in the context of a history of neurodevelopmental disorder, neuropsychiatric disorder, and/or acquired neurologic disorder, as well as suspicion of possible cognitive/neuropsychological impairment. Indications for cognitive/neuropsychological testing include a history of chronic or recurring suicidal thinking with 1 or more workable plans, intent, and/or evidence of preparation and/or a recent history of 1 or more serious (high risk/low rescue) suicidal attempts.  

Cognitive/neuropsychological testing is less clearly indicated for patients with histories of suicidal behavior but who do not clearly fall into 1 or more of the 3 clinical groups previously reviewed. It is also less clearly indicated for patients with negative histories for presumptive neuropsychological impairment, and when there is little to no suspicion of concerning recent/current negative change(s) in neurocognition. However, psychological testing with an emphasis on clarifying the possible temperamental, personality trait, psychosocial, and/or psychodynamic contribution to suicidal behavior should be strongly considered for this subset of patients. Because many referred individuals have a complex diathesis for suicidal behavior that reflects a mix of both neurobiological and psychosocial factors and situational stressors/triggers that have compelling psychodynamic resonance for the patient, a test battery that includes both psychological and cognitive/neuropsychological assessments is often the best choice given.  

In some instances, findings from psychometric tests may highlight the potential value of compensatory strategies to work around cognitive/neuropsychological impairments, thereby enhancing symptom management and harm reduction. In this regard, there soon may be a time when patients who have significant histories of suicidal behavior are concurrently seen for cognitive rehabilitation services. These services could target the neurocognitive impairments that appear to play a role in the recurrence and/or persistence of suicidal thinking and behavior.  

**Directions for Future Research**

A considerable amount remains to be learned about the clinical relevance of links between cognitive/neuropsychological functioning...
and suicidal behavior. Research is clearly warranted to further elucidate the putative mechanisms and pathways by which cognitive/neuropsychological impairment may heighten risk for suicidal thinking and attempts. As such, research should investigate the ways that neurocognitive status may influence and, in turn, be affected by risk and protective factors as well as contextual variables and the possible synergy between negative cognitive biases/distortions and neuropsychological impairment.

Further evidence is also needed to assess the role that cognitive and neuropsychological impairment may play in disrupting an individual’s ability to adaptively cope with adverse life circumstances and, thus, heighten the risk for suicidal behavior. Presumably, patients who have cognitive/neuropsychological impairment and a combination of neurodevelopmental, neuropsychiatric, and neurologic factors would be at greater risk for suicidal behavior than patients with fewer of these influences when controlling for the relative severity of these factors in a given case. Research would be helpful to address the possible additive or synergistic impact on the susceptibility to various types of suicidal behavior.

Impaired neurocognition (especially compromised executive functioning) may impede the ability to effectively engage in serious suicidal behavior. Evidence-based data are needed to support this idea. It would also be desirable to clarify the role of higher level cognitive/neuropsychological impairments to psychopharmacological interventions as well as nonpsychopharmacologic approaches like cognitive rehabilitation also merits further study. In addition, it would be helpful to have research that incorporates a wider demographic, this is especially true for adolescents and older adults because of well-documented risk for suicidal self-harm.

To properly address these issues, more data are needed to ascertain the ability of specific tests and/or score profiles to differentiate patients with high vs low risk for serious suicidal behavior. This would include the possible identification of test profiles that may heighten vs attenuate risk within varying time frames: imminent (days), near term (weeks), and long term (months). Future research also could identify patterns of cognitive/neuropsychological functioning related to the spectrum of suicidal self-harm behaviors. Such knowledge could facilitate the prediction of potentially serious outcomes, as well as differential response to harm reduction/safety interventions. This continuum encompasses morbid musing, passive suicidal thinking, active suicidal thinking with and without plan and/or intent, impulsive versus planned suicide attempts, high vs low lethality attempts, and completed suicide.

Imminent and short-term suicidal behavior, especially serious suicide attempts and death from suicide, continue to be unpredictable.

If tests or sets of measures have consistently good sensitivity/speciﬁcity, they may also help to further an understanding of the neuroanatomical substrates of suicidal behavior. To advance these research aims, the use of a standardized battery of cognitive/neuropsychological tests, along with good psychometric properties that tap a broad range of neurocognitive domains, would be highly desirable. This data would allow for more meaningful comparisons and conclusions across studies. Preferably, assessments should include the domain of social cognition which, to date, does not figure prominently in research on neurocognition and suicidal behavior. Screening tests like the Screen for Cognitive Impairment in Psychiatry might serve as the basis for the development of such a research battery.

Concluding Thoughts

Imminent and short-term suicidal behavior, especially serious suicide attempts and death from suicide, continue to be unpredictable. However, a good working knowledge of a patient’s neurocognitive status might enhance predictive validity and improve symptom management and safety planning. This information could be obtained from psychometric testing coupled with clinically relevant information gleaned from further research on the relationships between neurocognitive test performance and suicidal behavior. Such improvements could lead to improved quality of life for patients who are suicidal, and to lives being saved.

Dr Pollak is a clinical psychologist and neuropsychologist, Emergency Services, Seacoast Mental Health Center, Portsmouth, New Hampshire; and an allied health professional, Department of Medical Services, Section of Psychiatry, Exeter Hospital, Exeter, New Hampshire. He reports no conflicts of interest regarding the subject matter of this article.

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Schedule consists of 16 hour shifts, approximately 10 shifts per month.

Adult Outpatient Opportunity
• BE/BC provider with training/experience in a variety of mental health treatment conditions as well as Chemical Dependency and Substance Abuse. Candidate with experience in treatment of Bipolar Disorder, Borderline Personality Disorder, and Mood Disorders is preferred. Additionally, ECT training and experience is highly desirable. Staffed by psychiatrists, psychologists, clinical social workers, psychiatric nurses, licensed professional counselors, and other mental health professionals, Cape Fear Valley Behavioral Health Care provides a team approach to mental wellness. Behavioral Health Care is accredited by The Joint Commission and licensed by the State of North Carolina. The Health System is seeking providers for the following due to regional volumes and commitment to expand services:

Emergency Opportunity
• Two BE/BC providers with experience in ED or trained in EDPsychiatry. The Emergency Department maintains a Psychiatric Unit of 9 beds for patients in crisis. Support team is specially trained.
Department of Behavioral Health 
Washington, DC 
Supervisory Medical Officer (Psychiatry) 
SALARY RANGE $217,525 - $294,299 
Per Annum 

The Department of Behavioral Health (DBH) seeks an experience physician to serve as both Chief Medical Officer and Director of the Comprehensive Crisis and Emergency Program (CPEP) with responsibility for planning and directing CPEP operations and providing direct oversight and overall supervision of psychiatrists, nurses, and related direct care clinical staff. The incumbent develops a comprehensive crisis and emergency program and associated activities and makes recommendations to the Chief Clinical Officer on new policies and program activities and initiatives.

Qualifications: Applicants must meet the following requirements: 1. Graduation with degree of Doctor of Medicine from the United States School of Medicine or Canada approved by the Accreditation Council for Graduate Medical Education of the American Medical Association in the year of the applicant’s graduation or an equivalent degree from a foreign medical school certified by the Educational Commission for Foreign Medical Graduates (ECFMG); and 2. A current permanent and full or unrestricted District of Columbia license to practice medicine; and 3. Completion of an approved residency program.

Selective Placement Factors: Management prefers candidates who are Board Certified in Psychiatry by the American Board of Psychiatry & Neurology.

Education: Graduation with degree of Doctor of Medicine from the United States School of Medicine or Canada approved by the Accreditation Council for Graduate Medical Education of the American Medical Association in the year of the applicant’s graduation or an equivalent degree from a foreign medical school certified by the Educational Commission for Foreign Medical Graduates (ECFMG).

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To Apply: 1. Visit www.dchr.dc.gov 2. Click on Careers 3. Click Careers-de 4. Click view all job 5. Click on Department of Behavioral Health under the Agency Heading on left hand side 6. The job title/announcement will open up, click on Green "Apply for Job" #134242

Per Annum 

The Department of Behavioral Health (DBH) seeks an experience physician to serve as a Medical Officer (Psychiatry) with the Comprehensive Psychiatry Emergency Program. Provides mental health services for those individuals who are in need of immediate attention to minimize severity and prevent further, deterioration of their psychiatric condition. Performs initial diagnostic evaluations, medication management, and crisis evaluations while working in CPEP and may be called upon to help with Urgent Care duties. Provides services that reflect the recovery model to improve social, occupational and family functioning while mobilizing community supports and the consumer’s personal strengths. Conducts an interview with clients using techniques to develop a rapport with clients, obtain information, and understand the client. Participates with staff in the triage of clients upon arrival. May assist in case reviews, root cause analysis of case, and peer reviews as designated. Monitors clients in crisis for up to 72-hour observation and evaluation for changes in symptoms, and the effect of medication.

Qualifications: Applicants must meet the following requirements: 1. Graduation with degree of Doctor of Medicine from the United States School of Medicine or Canada approved by the Accreditation Council for Graduate Medical Education of the American Medical Association in the year of the applicant’s graduation or an equivalent degree from a foreign medical school certified by the Educational Commission for Foreign Medical Graduates (ECFMG); and 2. A current permanent and full or unrestricted District of Columbia license to practice medicine; and 3. Completion of an approved residency program.

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INGREZZA® (valbenazine) capsules

CONTRAINDICATIONS

INGREZZA® (valbenazine) capsules is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported.

WARNINGS AND PRECAUTIONS

Somnolence

INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation

INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP3P4 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3P4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Parkinsonism

INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed in patients treated with INGREZZA who are <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 3 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling, and hypokinesia. In cases where follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS

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

• Hypersensitivity
• Somnolence
• QT Prolongation
• Parkinsonism

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 practice.

Variable and Fixed Dose Placebo-Controlled Trial Experience

The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia (7%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 26% were Hispanic or Latino. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotic medications at study entry.

Adverse Reactions Leading to Discontinuation of Treatment

A total of 3% of INGREZZA treated patients and 2% of placebo-treated patients discontinued because of adverse reactions.

Common Adverse Reactions

Adverse reactions that occurred in the 3 placebo-controlled studies at an incidence of ≥2% and greater than placebo are presented in Table 1.

Table 1: Adverse Reactions in 3 Placebo-Controlled Studies of 6-week Treatment Duration Reported at ≥2% and >Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INGREZZA (n=260) (%)</th>
<th>Placebo (n=183) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnolence, fatigue, sedation)</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Balance disorders (fall, gait disturbance, dizziness, balance disorder)</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

Other Adverse Reactions Observed During the Premeier Evaluation of INGREZZA

Other adverse reactions of ≤1% incidence and greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Endocrine Disorders: blood glucose increased

General Disorders: weight increased

Infectious Disorders: respiratory infections

Neurologic Disorders: disorders of cerebrovascular origin, intracerebral hemorrhage, intracranial hemorrhage, intracranial hypertension, convulsion, encephalopathy, meningeal syndrome, sleep disorder, tremor, paresthesia, hypokinesia, akathisia

Psychiatric Disorders: anxiety, insomnia

During controlled trials, there was a dose-related increase in prolactin. Additionally, there was a dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of INGREZZA that are not included in other sections of the labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: rash

Drug Interactions

Drugs Having Clinically Important Interactions with INGREZZA

Table 2: Clinically Significant Drug Interactions with INGREZZA

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td>Concomitant use of INGREZZA with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA.</td>
<td>Examples: isocarboxazid, phenelzine, selegiline</td>
</tr>
<tr>
<td>Strong CYP2D6 Inhibitors</td>
<td>Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Examples: tramadol, nefazodone, flupenthixol, amoxapine</td>
</tr>
<tr>
<td>Strong CYP3A4 Inhibitors</td>
<td>Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Examples: ritonavir, indinavir, fosamprenavir, indinavir, saquinavir</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducers</td>
<td>Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.</td>
<td>Examples: rifampin, carbamazepine, phenytoin, St. John’s wort</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).</td>
<td>Examples:</td>
</tr>
<tr>
<td>Other Adverse Events</td>
<td>Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.</td>
<td></td>
</tr>
<tr>
<td>Prevention or Management</td>
<td>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.</td>
<td></td>
</tr>
</tbody>
</table>

Drugs Having No Clinically Important Interactions with INGREZZA

Table 3: Prevention or Management of INGREZZA Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 Inhibitors</td>
<td>Concomitant use of strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Examples:</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducers</td>
<td>Concomitant use of INGREZZA with strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.</td>
<td>Examples:</td>
</tr>
<tr>
<td>Prevention or Management</td>
<td>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.</td>
<td></td>
</tr>
</tbody>
</table>

Other interactions of INGREZZA with other drugs are presented in Table 4.

Table 4: Prevention or Management of INGREZZA Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 Inhibitors</td>
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<td>Prevention or Management</td>
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<td></td>
</tr>
</tbody>
</table>

Inhibitors

Strong CYP2D6 Inhibitors: CYP2D6 inhibitors that increase INGREZZA exposure (Cmax and AUC) are contraindicated. | Examples: | |

The induction potency of St. John’s wort may vary widely based on preparation.

Drugs Having No Clinically Important Interactions with INGREZZA

Dosage adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2C19, CYP2E1, or CYP3A4/5 based on in vitro study results.

OVERDOSAGE

Human Experience

The pre-marketing clinical trials involving INGREZZA in approximately 850 subjects do not provide information regarding symptoms with overdose.

Management of Overdose

No specific antidotes for INGREZZA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).

For further information on INGREZZA, call 844-INGREZZA (844-467-3902).

Distributed by Neurocrine Biosciences, Inc.
San Diego, CA 92130

INGREZZA is a registered trademark of Neurocrine Biosciences, Inc.
CP-IBUS-US-003956 07/2020
Important Information

INDICATION & USAGE
INGREZZA® (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
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WARNINGS & PRECAUTIONS (continued)
Parkinsonism
INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS
The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >Placebo) include: anticholinergic effects, balance disorders, falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the adjacent page for Brief Summary of Prescribing Information and visit Neurocrine.com/INGREZZAPI for full Prescribing Information.

Improving Response in Antidepressant Therapy

Focus on Deplin®

Intended for US healthcare professionals only. DEPLIN is a prescription medical food for use only under the supervision of a physician for the clinical dietary management of depression and schizophrenia and is specially formulated to meet the distinctive nutritional requirement for these conditions.

For more information about DEPLIN, please see Product Information found on DEPLIN.com.
Improving Response in Antidepressant Therapy: Focus on Deplin®

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Psychiatric Teaching Attending
Central Regional Hospital
Butner, North Carolina

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John Zajecka, MD
Professor of Psychiatry
Director, Woman's Board Depression Treatment Research Center
Rush University Medical Center
Chicago, Illinois

Case Studies and Expert Commentary
Andrew Cutler, MD
Clinical Associate Professor of Psychiatry
SUNY Upstate Medical University
Syracuse, New York

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The clinical manifestations of depression were described more than 2500 years ago, although current terminology including "depression" was not established until the late 19th century, and the pathophysiology of this common disorder is still being elucidated.

A recent search of the PubMed database using the key words "depression" + "pathophysiology" identified 3628 articles published within the past 2 years alone. Because major depressive disorder (MDD) is highly variable, complex, multifactorial, and etiologically heterogeneous, its pathophysiology provides the foundation for rational therapy.

The proposed underlying pathophysiologic mechanisms broadly include diathesis (vulnerability)-stress, environmental effects on genes (epigenetics), cellular (oxidative) stress, and neuroinflammation, the latter defined as an inflammatory response within the brain or spinal cord, mediated by proinflammatory cytokines (small protein molecules such as interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor-alpha [TNF-α] that are produced by several immune cells), reactive oxygen species (unstable molecules, sometimes called "free radicals," that can contribute to inflammatory processes), and immune mediators (Figure 1).

Pathophysiology of MDD: Focus on Inflammation

Bidirectional Relationship Between Depression and Inflammation

The relationship between depression and inflammation is well documented. Patients with MDD typically have increased levels of proinflammatory cytokines and C-reactive protein (CRP).

The Evolving Pathophysiology of MDD and the Role of Folate

Patients with MDD typically have increased levels of proinflammatory cytokines and CRP. Proinflammatory cytokines and CRP may predict the development of depressive disorders, and administration of proinflammatory cytokines or inflammatory stimuli (eg, typhoid vaccine or endotoxin) can induce depressive symptoms.

Patients with MDD show higher cerebrospinal fluid (CSF) levels of proinflammatory cytokines and increased expression in postmortem brains of TNF-α messenger RNA (mRNA), monocyte chemoattractant protein-1 mRNA (MCP-1, a cytokine that regulates migration and infiltration of inflammatory cells), and Toll-like receptor-3 and -4, which play a role in innate immune responses. Some viral pathogens induce cytokine production and are associated with depressive symptoms. These findings suggest a bidirectional interaction between cytokines and mood (ie, inflammation increases the risk of depression and depression increases the risk of inflammation). Conversely, blockade of proinflammatory cytokines can reduce depressive symptoms, and not all patients with MDD display elevated markers of inflammation, which are more common in the presence of stress, nonpsychiatric comorbidities, and obesity.

Evolving Paradigm of the Pathophysiology of Depression

The 3 neurobiological correlates of MDD are 1) dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, 2) depletion of brain serotonin, and 3) alteration of the continuous production of adult-generated neurons in the hippocampus. The HPA axis, sympathetic nervous system, and serotonergic, adrenergic, and dopaminergic central pathways—in concert with genetic factors and glucocorticoid and leptin (a hormone released from adipocytes in adipose tissue) receptors—all play roles in the association between inflammation and MDD. Briefly, activation of the HPA axis in the central nervous system (CNS), which typically is caused by stress, leads to increased hypothalamic secretion of corticotropin-releasing hormone.
The evolving pathophysiology of MDD and the role of folate

Valerie Holmes, MD

The clinical manifestations of depression were described more than 2500 years ago,1 although current terminology including “depression” was not established until the late 19th century,2 and the pathophysiology of this common disorder is still being elucidated.3 A recent search of the PubMed database using the key words “depression” + “pathophysiology” identified 3628 articles published within the past 2 years alone. Because major depressive disorder (MDD) is highly variable, complex, multifactorial, and etiologically heterogeneous,4,5 its pathophysiology provides the foundation for rational therapy. The proposed underlying pathophysiologic mechanisms broadly include diathesis (vulnerability)-stress,6 environmental effects on genes (epigenetics), cellular (oxidative) stress, and neuroinflammation, the latter defined as an inflammatory response within the brain or spinal cord, mediated by proinflammatory cytokines (small protein molecules such as interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor-alpha [TNF-α] that are produced by several immune cells), reactive oxygen species (unstable molecules, sometimes called “free radicals,” that can contribute to inflammatory processes), and immune mediators7 (Figure 1).

Pathophysiology of MDD: Focus on Inflammation

Bidirectional Relationship Between Depression and Inflammation

The relationship between depression and inflammation is well documented.8–10 Patients with MDD typically have increased levels of proinflammatory cytokines and C-reactive protein (CRP). Proinflammatory cytokines and CRP may predict the development of depressive disorders, and administration of proinflammatory cytokines or inflammatory stimuli (eg, typhoid vaccine or endotoxin) can induce depressive symptoms. Patients with MDD show higher cerebrospinal fluid (CSF) levels of proinflammatory cytokines and increased expression in postmortem brains of TNF-α messenger RNA (mRNA), monocyte chemoattractant protein-1 mRNA (MCP-1, a cytokine that regulates migration and infiltration of inflammatory cells), and Toll-like receptor-3 and -4, which play a role in innate immune responses.11 In addition, some viral pathogens induce cytokine production and are associated with depressive symptoms. These findings suggest a bidirectional interaction between cytokines and mood (ie, inflammation increases the risk of depression and depression increases the risk of inflammation).10 Conversely, blockade of proinflammatory cytokines can reduce depressive symptoms, and not all patients with MDD display elevated markers of inflammation, which are more common in the presence of stress, nonpsychiatric comorbidities, and obesity.8

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Figure 1. Interactive Pathophysiologic Matrix of MDD.
Pathophysiology of MDD

(CRH), followed by increased release of adrenocorticotropic hormone (ACTH) from the anterior pituitary and then increased secretion of glucocorticoids from the adrenal cortex. Activation of the HPA axis is also associated with increased sympathetic tone, characterized by decreased release of acetylcholine, increased release of norepinephrine, and the release of proinflammatory cytokines in the brain ("infamed brain"). In addition, there is disruption in synaptic plasticity due to decreased brain-derived neurotrophic factor (BDNF, a key modulator of neuromplasticity) and alterations in dopamine, serotonin, and norepinephrine signaling. These interactive pathways are summarized in Figure 2 and together contribute to the cognitive and emotional features of depression (eg, anhedonia, depressed mood, feelings of decreased self-worth, reduced ability to concentrate, and suicide ideation).

**Inflammation plays a key role in the pathophysiology of depression.**

In addition to recruiting peripheral immune activating cells, cytokines activate microglia (resident macrophages in the brain). Activated microglia then release proinflammatory cytokines such as IL-6 and TNF-α, which induce activation of the HPA axis and subsequent secretion of glucocorticoids by the adrenal cortex. Glucocorticoids in turn modulate not only the HPA axis but also microglial activation, creating what could be described as a self-perpetuating proinflammatory state.

Proinflammatory cytokines also influence the synthesis, release, metabolism, and reuptake of key mood-relevant neurotransmitters in the brain, including the monoamines dopamine, serotonin, and norepinephrine. Serotonin and norepinephrine reuptake inhibitors modulate the development of cytokine-induced depressive-like behavior in research settings. For example, studies have shown that the CSF concentration of IL-6 is elevated in patients with MDD and that there is a significant positive correlation between depression scores and CSF IL-6 levels.

Figure 2. Evolving Paradigm of the Pathophysiology of MDD.

*Decreases efficiency of monoamine synthesis. SHT=5-hydroxytryptamine; ACH=acetylcholine; ACTH=adrenocorticotropic hormone; BDNF=brain-derived neurotrophic factor; CRH=corticotropin-releasing hormone; DA=dopamine; IL-1=interleukin-1; IL-6=interleukin-6; NE=norepinephrine; TNF-α=tumor necrosis factor-alpha.

Inflammation plays a key role in the pathophysiology of depression via 3 major pathways: (1) Stress stimulates the release of glucocorticoids from the adrenal cortex, CRH from the hypothalamus, and the peripheral proinflammatory cytokines IL-1, IL-6, and NF-κ. CRH is the primary regulator of HPA axis activation. (2) HPA overactivity leads to alteration of autonomic balance favoring sympathetic (NE) over parasympathetic (ACH) signaling and increased sympathetic tone, promoting the release of proinflammatory cytokines from macrophages. Sympathetic signaling is activated under stress; parasympathetic signaling is associated with stress reduction. The 2 systems have complementary functions, operating in tandem to maintain homeostasis. Proinflammatory cytokines interfere with monoaminergic (DA, 5HT, and NE) and neurotrophic (eg, BDNF) signaling. (3) In addition, obesity and lipid accumulation in adipocytes, especially abdominal adipocytes, leads to an increased release of inflammatory cytokines. The "leaky gut" theory postulates that many factors including stress and unhealthy diet damage the gut barrier, increase intestinal permeability, and allow lipopolysaccharides (large molecules consisting of a lipid and a polysaccharide that activate peripheral inflammatory cells) to traverse the previously impermeable barrier. Lipopolysaccharides and other endotoxins contribute to an immune-mediated inflammatory response, which includes the release of proinflammatory cytokines.
The concentration of the proinflammatory cytokine IL-6 is increased in the CSF of patients with MDD.

Among the many known neurotrophins (growth factors that regulate many aspects of neuronal function), BDNF is the most abundant in the CNS, where it is synthesized mainly in the hippocampus and hypothalamus.20 BDNF modulates neurotransmitter release and neuronal differentiation, adaptation, growth, and survival, collectively defined as neuroplasticity. Reduction of functional neurotrophic factors such as BDNF may contribute to the pathophysiology of depression by attenuating neuroplasticity.21 Several studies have demonstrated the reduced expression of BDNF in depressed persons and increased levels of BDNF following antidepressant therapy.20

Relationship Among Obesity, Adipose Tissue, Proinflammatory Cytokines, and Depression

Obesity/Adipose Tissue Contribute Proinflammatory Cytokines

Depression and obesity share alterations in cell-mediated immune responses14 and demonstrate similar activation of inflammatory and immune pathways leading to neuroinflammation.13 In particular, lipid accumulation in the form of white adipose tissue (so-called “bad fat”) in the abdomen activates innate immune mechanisms.15 Specifically, adipocytes in white adipose tissue secrete hormonal and immunostimulatory factors including so-called adipocytokines (ie, adiponectin, leptin, resistin, visfatin) as well as IL-6 and TNF-α, which are believed to be key links between obesity and inflammation.16 Activated macrophages in white adipose tissue also produce MCP-1, and lipid accumulation in adipocytes increases the production of MCP-1.16 MCP-1, in turn, leads to further accumulation of mononuclear cells and production of cytokines. This cyclic series of events results in a chronic inflammatory milieu that appears to mediate the link between obesity and depressive disorders.

Bidirectional Relationship Between Depression and Obesity

Studies have confirmed a bidirectional relationship between depression and obesity, ie, depression increases the risk of obesity and obesity increases the risk of depression.16

Depression increases the risk of obesity and obesity increases the risk of depression.

A meta-analysis of 15 longitudinal studies confirmed a bidirectional association between depression and obesity (especially abdominal adiposity).21 Specifically, obese persons had a 55% increased risk of developing depression over time, and depressed persons had a 58% increased risk of becoming obese.22 Results from a well-characterized cohort of almost 66,000 US women followed between 1996 and 2006 in the Nurses’ Health Study also provided evidence that depression and obesity are bidirectional.22 Depression was associated with a significantly increased risk of obesity at follow-up, and this association was more apparent in women with physician-diagnosed depression and who used antidepressant medication. The converse analysis showed that baseline obesity was also associated with a moderately increased risk of depression at follow-up. Both associations were only partially explained by lifestyle factors and baseline comorbidities. Research suggests several mechanisms for the relationship between depression and obesity.27 Some experts propose that depression causes or contributes to obesity through its potential effect on binge eating and that pharmacotherapy for depressive disorders may lead to weight gain. Alternatively, others suggest that

NHANES Survey Identifies a Connection Between Obesity and Depression

Data from the National Health and Nutrition Examination survey, a continuous survey of a nationally representative sample of about 5000 persons across the United States,22 were analyzed for the years 2005–2010 and found that almost 43% of adults with depression were obese (defined as BMI ≥30 kg/m²) compared with 33% without depression.22 Women with depression were more likely to be obese than women without depression, a finding that was consistent across all age groups. Among men, rates of obesity did not differ by depression status until age 60 and over, after which men with depression were more likely to be obese than men of the same age without depression.22 The survey also found that 1) as the severity of depression increased, so did the percentage of all adults with obesity; 2) both moderate to severe depressive symptoms and antidepressant use were associated with increased obesity; 3) moderate to severe depressive symptoms were associated with a higher rate of obesity both in persons who were taking antidepressant medication and in those who were not; and 4) antidepressant use was associated with a higher rate of obesity regardless of severity of depressive symptoms. The highest prevalence of obesity (54.6%) was seen in persons who had moderate or severe depressive symptoms and took antidepressant medication. However, it could not be determined whether depression preceded obesity or the opposite, as both were assessed concurrently in this epidemiological study.23 In contrast, longitudinal studies have demonstrated a bidirectional relationship between depression and obesity (ie, depression increases risk of obesity and obesity increases the risk of depression).24
Pathophysiology of MDD

obesity causes or contributes to depression. For example, the stigma attached to obesity (particularly among women) may contribute to depression, and limitation of activity due to obesity or obesity-related chronic disorders may increase the risk of depression. Finally, depression and obesity may be linked through some common cause or third factor, either environmental or biological. There is evidence to suggest that inflammation represents the underlying link between adiposity and depression and their effects on comorbidities.23

Inflammation and Increased Monoamine Synthesis May Lead to Antidepressant Treatment Resistance

Studies have shown that inflammation is associated with greater depressive symptom severity, resistance to commonly used antidepressants, a differential response to the selective serotonin reuptake inhibitor (SSRI) escitalopram versus the tricyclic antidepressant nortripyline or the norepinephrine-dopamine reuptake inhibitor bupropion, and a higher likelihood of hospitalization in patients with MDD.5,29,30 Chamberlain et al measured blood CRP levels in 4 groups: patients with treatment-resistant MDD, treatment-responsive patients with MDD not currently experiencing symptoms, patients with depression who were not currently receiving medication, and healthy volunteers.31 Mood assessments were performed with the Hamilton Rating Scale for Depression (HAM-D). Compared with healthy volunteers, CRP was elevated significantly in the treatment-resistant group but not significantly in the treatment-responsive and untreated groups, demonstrating an association between CRP and treatment resistance.31 The authors concluded that MDD is associated with increased CRP, particularly in treatment-resistant depression.31

Using a somewhat similar study design, Lindqvist et al measured the blood levels of IL-6, TNF-α, CRP, and biomarkers of oxidative stress in untreated patients with MDD and healthy controls.32 The investigators then treated about half the MDD patients with an SSRI for 8 weeks and repeated the measurements; all patients with MDD were assessed with the HAM-D before and after treatment. Compared with healthy controls, MDD patients had significantly higher levels of IL-6, TNF-α, and 2 markers of oxidative stress (F2-isoprostanes and 8-OH-2-deoxyguanosine). Compared with MDD responders to SSRI antidepressant treatment, nonresponders had significantly higher levels of F2-isoprostanes at baseline and after treatment. Nonresponders showed a significant increase in 8-OH-2-deoxyguanosine over the course of treatment, whereas responders showed a significant decrease in IL-6 during treatment. The authors concluded that antidepressant response was associated with changes in inflammatory and oxidative stress markers.32

Inflammation contributes to an inadequate response to typical antidepressants.

Studies also indicate that low-grade inflammation—defined as elevated serum levels of proinflammatory cytokines and CRP and/or activated circulating or resident immune cells including microglia—contributes to an inadequate response to antidepressants (eg, SSRIs/SNRIs, TCAs).33 A systematic review of 19 studies found that elevated serum levels of IL-6 and CRP identify a form of MDD with a relatively poor outcome and nonresponsiveness to agents with a predominantly serotonergic mechanism of action.33 What are the therapeutic implications of these findings? Most important is that monoamine-modulating antidepressants may not be very effective in the setting of increased inflammatory signals and oxidative stress, both of which can reduce the central synthesis of monoamine neurotransmitters. Increasing the synthesis of serotonin, norepinephrine, and dopamine with L-methylfolate (also known as 5-methyltetrahydrofolate) may enhance the effectiveness of antidepressants that are dependent on adequate levels of these monoamines.34

Role of Folate in Physiology and MDD Pathophysiology

Folate functions as a coenzyme or co-substrate in the metabolism of amino acids, the conversion of homocysteine to methionine, and the synthesis of DNA and RNA.35 Methylation of deoxyuridylate to thymidylate in the formation of DNA is required for proper cell division, and impairment of this reaction can lead to megaloblastic anemia, one of the hallmarks of folate deficiency. Folate also has a role in neurotransmitter synthesis in the brain.35

L-Methylfolate, Monoamine Synthesis, and Inflammation

The conversion of dietary folate to L-methylfolate is a multi-step process. A key step in this process is the conversion of dihydrofolate to the bioactive form L-methylfolate by the enzyme methylenetetrahydrofolate reductase (MTHFR).34 L-Methylfolate is the only form of folate that crosses the blood-brain barrier and is immediately available for synthesis of serotonin, norepinephrine, and dopamine.35

L-Methylfolate is the only form of folate that crosses the blood-brain barrier and is immediately available for synthesis of serotonin, norepinephrine, and dopamine.

L-Methylfolate is a cofactor in the metabolic pathway leading to the synthesis of monoamine neurotransmitters (Figure 3). L-Methylfolate modulates the formation of tetrahydrobiopterin (BH4).
a critical cofactor for the synthesis of monoamines that activates the rate-limiting enzymes tyrosine hydroxylase for the synthesis of norepinephrine and dopamine and tryptophan hydroxylase for the synthesis of serotonin.\(^34\) During this process, BH4 is oxidized to dihydrobiopterin (BH2), which can be regenerated to BH4 through pathways supported by L-methylfolate.\(^37\) However, BH4 is highly labile and is relatively unstable in the presence of inflammation and oxidative stress, resulting in its oxidation and irreversible degradation to dihydroanthopterin (XPH2).\(^37\) Proinflammatory cytokines such as IL-6 have been shown to reduce BH4 in sympathetic neurons, and cytokine influences on BH4 through oxidative stress may be a mechanism for inflammation to reduce monoamine availability in important regions of the brain.\(^37\)

**Association Between Folate and Depression**

Research has demonstrated that low serum or red blood cell (RBC) folate levels are associated with increased risk for depression, more severe depressive symptoms, longer and more severe depressive episodes, no response to antidepressant therapy, lower probability of achieving remission, later onset of clinical improvement, and increased risk of depressive symptom relapse.\(^38\)\(^-\)\(^41\)

**Low serum or RBC folate levels are associated with an increased risk for depression.**

A meta-analysis of 43 studies that included 8510 persons with depression and 27,282 without depression was performed to identify an association with folate.\(^38\) The results showed that individuals with depression had significantly lower serum folate levels compared to those without depression; dietary intake of folate and serum folate levels differentiated those with depression from those without depression.\(^38\) All studied populations—adult, geriatric, perinatal, and child/adolescent—had significantly lower levels of serum folate than their nondepressed counterparts, although RBC folate levels did not identify a difference. The authors noted that, despite the large burden of disease and mortality associated with depression, the best available treatment modalities including antidepressant therapy are not effective for almost 60% of patients, which suggests that core underlying mechanisms of depression are not being targeted.\(^38\) They concluded that clinicians should consider folate supplementation for their patients, although additional research is warranted.\(^38\)

**Genetic Polymorphisms Impair Conversion of Dietary Folate and Folic Acid to L-Methylfolate**

The MTHFR gene encodes MTHFR.\(^42\) Single nucleotide polymorphisms (SNPs) have been identified in MTHFR that are associated with impaired folate metabolism, lower plasma folate concentrations, changes in folate form distribution, and elevated plasma homocysteine concentrations, all of which have been correlated with MDD.\(^42\)\(^,\)\(^43\) One common SNP that reduces the activity of MTHFR is the C677T polymorphism of MTHFR, a point mutation with the substitution of the nucleotide cysteine for thymine at position 677, causing the substitution of the amino acid alanine with valine in the enzyme.\(^44\) This SNP encodes a thermolabile MTHFR that is less active at higher temperatures.\(^45\) Individuals with 2 copies of this variant tend to have lower serum folate levels compared to controls. More than 25% of Hispanics, up to 15% of North American Caucasians, and 6% of African Americans are estimated to be homozygous for the C677T variant. Supplementation with folate as folic acid, folinic acid, or L-methylfolate has been shown to reduce depressive symptoms in MDD.\(^46\) Because L-methylfolate is not MTHFR-dependent regardless of a patient’s genotype,\(^47\) this formulation may offer advantages in depressed patients with a reduced-function MTHFR variant and decreased MTHFR activity.

**Summary and Conclusions**

MDD may be associated with increased neuroinflammation, which is known to interfere with monoamine turnover, possibly reducing the efficacy of antidepressant agents.

- Depression is a complex heterogeneous disorder, the pathophysiology of which includes...
Pathophysiology of MDD

diathesis (vulnerability)-stress, epigenetics, cellular (oxidative) stress, and neuroinflammation.

- Pathogenetic mechanisms in depression include activation of the HPA axis (CRH-ACTH-glucocorticoid pathway); increase in sympathetic tone and proinflammatory cytokines; decreased BDNF with loss of neuroplasticity; and alterations in dopamine, serotonin, and epinephrine signaling.

- Obesity and the leaky gut contribute proinflammatory cytokines to the underlying inflammatory process.

- Inflammation and the associated increase in monoamine synthesis may result in reduced effectiveness of and increased resistance to antidepressant therapy.

- Clinicians can consider obtaining CRP levels in their depressed patients to help rule out an underlying inflammatory process that may be contributing to the depressive disorder.

- L-Methylfolate is a key cofactor in the metabolic pathway leading to synthesis of monoamine neurotransmitters, and reduced folate levels are associated with reduced levels of monoamine neurotransmitters.

- SNPs may impair the functioning of MTHFR, thereby limiting the synthesis of L-methylfolate, which results in more treatment-resistant MDD.

- Unlike other folate formulations, L-methylfolate is not MTHFR-dependent and may be a better choice in depressed patients with a reduced-function MTHFR variant and decreased MTHFR activity.

- Deplin® is a branded form of L-methylfolate, the biologically active form of folate that crosses the blood-brain barrier to support the synthesis of monoamines. Dietary supplements containing folic acid or other forms of folate available over-the-counter (OTC) are not subject to the same labeling and manufacturing regulations as are medical foods such as DEPLIN.

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References


Achieving sustained remission of major depressive disorder (MDD) with restoration of vocational and interpersonal functions is the primary objective of antidepressant therapy. Failure to accomplish this therapeutic goal is associated with a high probability of relapse or recurrence, the risk of which can be reduced with continuation therapy to preserve remission and maintenance therapy to prevent recurrence and enable recovery. Unfortunately, up to 70% of patients with MDD fail to achieve a complete remission of symptoms following initial antidepressant therapy; and many who do remit experience relapse or recurrence, despite maintenance treatment. Patients who fail their initial treatment often do not respond to a second antidepressant and frequently experience chronic depression and impaired psychosocial functioning. Treatment-resistant depression—defined by the Food and Drug Administration (FDA) as MDD with an inadequate response to at least 2 antidepressants given at adequate doses for an adequate duration during the current episode—occurs in up to 30% of patients and is associated with a substantial burden of disease. Interventions that provide both short-term and sustained remission and subsequently reduce the impact of MDD on functioning and quality of life are critically needed. In addition, MDD is accompanied by a number of other, equally important needs (Table 1).

Options for Adjunctive Treatment of Depression

Strategies for the early management of patients with an inadequate response to antidepressant therapy (including initial antidepressant therapy) include switching to another antidepressant, use of adjunctive therapy, or combining antidepressant modalities (eg, psychotherapy, electroconvulsive therapy [ECT]). Adjunctive therapy may be more appropriate for patients with a partial response to the antidepressant and includes a multitude of treatment options. Clinicians should first consider the range of treatments with the best empirically based evidence, such as atypical antipsychotics (AAPs), esketamine, lithium, thyroid hormone (T3), vagus nerve stimulation, transcranial magnetic stimulation, ECT, and L-methylfolate. Clinicians should always consider the risk-benefit ratio when choosing an antidepressant treatment, as many of these treatments are associated with adverse events. Among these treatment options, AAPs represent one of the few medication classes with treatment options that are specifically FDA-approved for adjunctive therapy in MDD. Unlike typical antipsychotics, which act almost exclusively on dopamine neurotransmission, AAPs theoretically work by modulating serotonin and norepinephrine as well as dopamine neurotransmission, which may explain the effectiveness of these agents in MDD. Adding an AAP to antidepressant therapy reduces depressive symptoms in patients with MDD, although the effect size is small and treatment-related side effects, including the possible risk of metabolic syndrome and movement disorders (eg, akathisia, tardive dyskinesia), can be moderate to severe. In clinical trials, intranasal esketamine provided clinically significant improvement of symptoms in patients with treatment-resistant depression with a side effect profile that includes transient, mild to moderate side effects, including increased blood pressure, sedation, and dissociation during the treatment.

Table 1. Unmet Needs in MDD.

- In patients with inadequate response, guidelines that address when to change antidepressants, use adjunctive treatments, or combine antidepressant therapies
- Treatments with a quicker onset and sustained efficacy
- Improved short- and long-term safety, tolerability, and side effect profiles of antidepressants and other interventions for unipolar depressive disorder
- An understanding of the role of biomarkers to guide therapy for individual patients over time, in conjunction with clinical judgment
- Ability to identify which empirically based interventions are capable of improving specific dimension/domain-based outcomes (eg, cognition, fatigue)
- Improved patient and family education and collaboration with other healthcare professionals about treatment options, time to onset of response, side effects, and how to manage side effects at all stages of treatment
- Alignment of expectations of treatment outcomes between patients and clinicians (eg, patients rank quality of life and positive affect higher, while physicians rank functioning and depressive symptoms higher)
- Identification of clinical features and other variables (eg, racial, ethnic, cultural, and biomarkers) in the clinical presentation of MDD and response to treatment

What Is DEPLIN?

DEPLIN is a prescription medical food specifically formulated to support the nutritional requirements of these patients. It is a prescription medical food such as DEPLIN. The rationale for requiring a medical food such as DEPLIN. The rationale for requiring a medical food such as DEPLIN.
L-Methylfolate, the biologically active form of folate that crosses the blood-brain barrier, is also a potentially effective and well-tolerated option for adjunctive treatment of MDD. Studies conducted as early as the 1960s identified an association between folate deficiency and depression, and patients with depression characteristically demonstrated low serum folate levels or decreased dietary folate intake compared to those without depression. In a study of 33 patients with treatment-resistant depression, 36% had low cerebral folate deficiency, defined as normal blood levels of folate together with low cerebrospinal fluid levels of L-methylfolate. Clinically, folate deficiency has been linked to an increased risk of depression with more severe symptoms, protracted episodes, lack of response to antidepressants, lower rates of remission, delayed clinical improvement, and greater risk of relapse. The use of folate or derivatives should be considered as adjunctive therapy for patients with MDD demonstrating an inadequate response to antidepressant treatment.

In order to cross the blood-brain barrier, folic acid must be converted to L-methylfolate. Conversion of folic acid to L-methylfolate is a multistep process, beginning with intestinal absorption of dietary folic acid (or dietary folate, which is hydrolyzed to folic acid in the gut prior to absorption). Unlike other folate formulations, L-methylfolate bypasses the multistep process required for the biosynthesis of L-methylfolate from dietary folic acid or folinic acid and is unaffected by functional gene-level mutations such as single nucleotide polymorphisms (SNPs), which can disrupt this multistep process. In addition, L-methylfolate precursors (metabolites that may accumulate) may bind to folate transport receptors necessary for L-methylfolate to cross the blood-brain barrier and limit the amount of L-methylfolate that can enter the central nervous system. The metabolic steps in this process are summarized in Figure 1.

After crossing the blood-brain barrier, L-methylfolate modulates the formation of tetrahydrobiopterin (BH4), an essential cofactor that activates tyrosine hydroxylase for the synthesis of norepinephrine and dopamine and tryptophan hydroxylase for the synthesis of serotonin. BH4 is degraded to BH2 during these enzymatic reactions, but it can be generated to BH4 through pathways supported by L-methylfolate. Note that BH4 is irreversibly degraded to XPH2 under conditions of inflammation and oxidative stress (Figure 1). This pathway is the core explanation for why DEPLIN can be of benefit to patients with an inadequate response to antidepressant therapy. L-Methylfolate appears to enhance synthesis and sustain optimal levels of serotonin, norepinephrine, and dopamine.

Studies have shown that L-methylfolate can improve the response to antidepressants in patients with MDD who fail to respond to an adequate trial of an antidepressant.

What Is DEPLIN?

DEPLIN is a prescription medical food containing the bioactive form of folate, L-methylfolate, for the dietary management of depression and schizophrenia, and is specially formulated to meet the distinctive nutritional requirements of these conditions. DEPLIN has been extensively studied as adjunctive treatment for MDD in randomized and open-label clinical trials and real-world settings, and has been in clinical use for more than 15 years.

Dietary supplements containing folic acid or other forms of folate available over-the-counter (OTC) are not subject to the same labeling and manufacturing regulations as are medical foods such as DEPLIN. The usual dose of DEPLIN is one 15-mg capsule daily, taken with or without food. The rationale for requiring a prescription for DEPLIN underscores the importance of medical monitoring of its use in patients with MDD and avoiding the potential negative outcomes of inadequately treated MDD.

Pharmacokinetic studies show that DEPLIN and folic acid are not interchangeable. In a study comparing the bioavailability of a single oral dose of 5 mg DEPLIN with that of a single oral dose of 5 mg folic acid in persons with homozygosity for the 677C→T mutation of methylenetetrahydrofolate reductase (a genetic polymorphism...
that is common in people with depression and that can interfere with the metabolism of folate.24 DEPLIN was 7 times more bioavailable at peak concentration than folic acid.32 These results confirm that DEPLIN has a different pharmacokinetic profile than folic acid and is directly available following intestinal absorption, whereas folic acid first must be metabolized to tetrahydrofolate.32

Short- and Long-Term Clinical Evidence Supporting DEPLIN

Clinical evidence indicates that L-methylfolate supplementation should be used in patients with documented low levels of folate and its metabolites and as adjunctive therapy in patients who do not respond to traditional antidepressant therapies.22,25 The well-designed, rigorous, short- and longer-term clinical studies of DEPLIN in patients with MDD were conducted mainly at a dose of 15 mg daily.

The efficacy, safety, and potential role of biomarkers were evaluated in 2 multicenter, randomized, double-blind clinical trials in adult patients with selective serotonin reuptake inhibitor (SSRI)-resistant MDD;15 2 post hoc analyses of these trials;32 a 12-month, open-label extension trial1; a real-world retrospective cohort study;28; and a retrospective analysis of patient charts.28 Table 2 provides an overview of these studies.

In the first randomized, double-blind trial, 148 outpatients were enrolled in 2 consecutive 30-day periods and randomly assigned in a 2:3:3 ratio to receive adjunctive L-methylfolate (DEPLIN) for 60 days (7.5 mg/day for 30 days followed by 15 mg/day for 30 days), placebo for 30 days followed by DEPLIN (7.5 mg/day) for 30 days, or placebo for 60 days, all with continued SSRI therapy.15 There was no significant difference observed in outcomes across the 3 treatment groups at the 7.5-mg dose. The second randomized, double-blind trial enrolled 75 outpatients and utilized the same design as the first study except the DEPLIN dose was 15 mg/day during both 30-day periods. In the second trial, adjunctive DEPLIN at 15 mg/day showed significantly greater improvement compared with placebo on both primary outcome measures (response rate and degree of change in depression symptom score on the 28-Item Hamilton Depression [HAM-D] Rating Scale) and 2 secondary outcome measures of symptom severity. DEPLIN was well tolerated in both studies, with rates of adverse events no different from those reported for placebo. The investigators concluded that “15 mg/day, but not 7.5 mg/day, of adjunctive L-methylfolate may constitute an effective, safe, and relatively well tolerated augmentation strategy for patients with major depression who have had no response or a partial response to SSRIs.”15

15 mg/day of adjunctive DEPLIN “may constitute an effective, safe, and relatively well tolerated augmentation strategy for patients with major depression who have had no response or a partial response to SSRIs.”15

Given the bidirectional relationship of inflammation to both depression and obesity, as well as the association between low folate status and MDD, 2 post hoc exploratory analyses of the second randomized, double-blind trial were performed to assess the effect of 15 mg DEPLIN vs placebo as a function of baseline biomarker levels or genotype.5,29 The analyses focused on biomarkers of inflammation (eg, interleukin-8 [IL-8], tumor necrosis factor-alpha [TNF-α], high-sensitivity C-reactive protein [hsCRP]) and metabolic status (eg, obesity defined as body mass index [BMI] of ≥30, insulin, and the adipokine leptin).

Table 2. Overview of DEPLIN Clinical Trials in MDD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 115</td>
<td>Multicenter, randomized, double-blind (two 30-day phases) trial in SSRI-resistant MDD</td>
<td>N=148; &gt;12 QIDS-SR, tx with SSRI &gt;8 weeks (stable for 4 weeks)</td>
<td>• PBO → PBO</td>
<td>Improvement in HAM-D17 / Response* rates according to HAM-D17</td>
</tr>
<tr>
<td>Trial 215</td>
<td>Multicenter, randomized, double-blind (two 30-day phases) trial in SSRI-resistant MDD</td>
<td>N=75; &gt;12 QIDS-SR, tx with SSRI &gt;8 weeks (stable for 4 weeks)</td>
<td>• PBO → PBO</td>
<td>Improvement in HAM-D17 / Response* rates according to HAM-D17</td>
</tr>
<tr>
<td>Post hoc analyses5,29</td>
<td>Exploratory analyses evaluating effects of biological, inflammatory, and/or genetic markers on treatment response</td>
<td>N=74</td>
<td>–</td>
<td>Effect of biomarkers on response to HAM-D28</td>
</tr>
<tr>
<td>Open-label extension1</td>
<td>12-month, open-label, extension trial of Trials 1 and 2</td>
<td>N=68</td>
<td>15 mg</td>
<td>Reduction in HAM-D17 score at 12 months</td>
</tr>
<tr>
<td>Real-world study30</td>
<td>Retrospective cohort study evaluating patients prescribed DEPLIN</td>
<td>N=502</td>
<td>7.5 mg or 15 mg</td>
<td>Reduction in PHQ-9 from baseline</td>
</tr>
</tbody>
</table>

*Response defined as a reduction of ≥50% in HAM-D17 score during treatment or a final score of ≤7. HAM-D17=Hamilton Depression Rating Scale-17 item; HAM-D28=Hamilton Depression Rating Scale-28 item; MDD=major depressive disorder; PBO=placebo; PHQ-9=Patient Health Questionnaire; QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Rated; SSRI=selective serotonin reuptake inhibitor; tx=treatment.
Clinical studies of DEPLIN in patients with major depressive disorder (MDD) have shown that adjunctive therapy with DEPLIN 15 mg can result in significantly greater improvement compared to placebo. This was demonstrated in a 12-month open-label extension of a randomized, double-blind trial, which showed a greater improvement in Hamilton Depression Rating Scale (HAM-D) scores among patients treated with DEPLIN 15 mg compared to placebo. Patients continuing management of their condition with DEPLIN 15 mg after the double-blind acute therapy trial showed additional and sustained reduction in depression symptoms over time, indicating further improvement in depression symptoms over time.

**Patients with obesity (BMI of ≥30) and elevated levels of inflammatory markers (hsCRP, TNF-α, and IL-8) showed an increased response to DEPLIN 15 mg, although treatment with DEPLIN for depression should not be limited to patients with these characteristics.**

The second post hoc analysis confirmed the effect of elevated inflammatory biomarkers (hsCRP, S-adenosylmethionine [SAM]/S-adenosylhomocysteine [SAH] ratio, 4-hydroxynonenal [4-HNE]) on treatment response with DEPLIN. In addition, despite a limited sample size, it showed that the presence of most (but not all) genetic polymorphisms related to folate metabolism also predicted a greater response to DEPLIN.5 These analyses suggest that the presence of certain inflammatory biomarkers and genetic markers may help identify patients with SSRI-resistant MDD who may be particularly responsive to adjunctive therapy with DEPLIN 15 mg.

The long-term efficacy, safety, and tolerability of DEPLIN 15 mg was investigated in a 12-month open-label extension of the 2 randomized, double-blind trials.1 Outcome criteria included response (≥50% improvement in the Hamilton Depression Rating Scale (HAM-D) total score from the start of the double-blind study), remission (total HDRS-17 score of ≤7), recovery (≥6 months of remission from the start of the open-label study), relapse (HDRS-17 score of >15 within 6 months of achieving remission), and recurrence (HDRS-17 score of >15 after 6 months of remission at the time of recovery). Sustained recovery was defined as recovery that was sustained through the final study visit at 12 months from the start of the open-label trial.1 Patients continuing management of their condition with DEPLIN 15 mg after the double-blind acute therapy trial showed additional and sustained reduction in depression symptoms over time (Table 3).1 Overall, 61% of patients achieved remission and 38% achieved full recovery, which were sustained over the 12 months.1 Among non-responders at the end of the double-blind trial, 60% of 53 patients converted to remission and 26% converted to full recovery (statistical significance not reported). There were no recurrences in patients who recovered, no serious adverse events, and no discontinuations as a result of adverse events. As in the double-blind trials, DEPLIN had a safety and tolerability profile comparable to placebo.1 Despite the limitation of the

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Table 3. Outcomes of Subjects in 12-Month Open-Label Phase of DEPLIN 15 mg (N=68).1

<table>
<thead>
<tr>
<th>Status at End of Double-Blind Acute Phase</th>
<th>Achieved Remission During Open-Label Phase</th>
<th>Achieved Recovery</th>
<th>Sustained Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (n=11)</td>
<td>NA</td>
<td>91% (n=10)</td>
<td>100%</td>
</tr>
<tr>
<td>Response without remission (n=4)</td>
<td>75% (n=3)</td>
<td>50% (n=2)</td>
<td>100%</td>
</tr>
<tr>
<td>Nonresponse (n=53)</td>
<td>60% (n=32)</td>
<td>26% (n=14)</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>61% (n=35/57)</td>
<td>38% (n=26/68)</td>
<td>100%</td>
</tr>
</tbody>
</table>

NA=not applicable. Adapted with permission.1
open-label study design, the authors concluded that DEPLIN may be an early option in patients who do not respond adequately to antidepressant monotherapy.1

Patients in the long-term (12-month) extension trial showed additional and sustained reductions in depressive symptoms with DEPLIN 15 mg/day. As in the double-blind trials, DEPLIN had a safety and tolerability profile comparable to placebo.

A real-world retrospective cohort study evaluated 554 patients with MDD, 502 of whom received DEPLIN along with their antidepressant for 3 months (adjuvant therapy) and 52 of whom were treated with DEPLIN alone (monotherapy).30 Depressive symptoms, quality of life, and medication satisfaction were assessed with the self-reported Patient Health Questionnaire-9 (PHQ-9).30 In this clinical setting, patients who received adjunctive DEPLIN along with their antidepressant achieved statistically significant improvements in depressive symptoms, quality of life, and functioning and reported greater satisfaction with DEPLIN compared with their previous medication.

Overall, the response rate was 67.9% and the remission rate was 45.7%, with a compliance rate of >90%. Interestingly, treatment response rates were similar for patients who took DEPLIN as monotherapy or adjunctive therapy.70 A retrospective chart review compared outcomes in 242 patients with MDD and a Clinical Global Impression–Severity (CGI-S) score of 4 to 5, 147 of whom were treated with an SSRI or a Clinical Global Impression–Severity (CGI-S) score of 4 to 5, 147 with an SSRI or SNRI alone and 95 with an SSRI or SNRI plus DEPLIN 7.5 mg or 15 mg daily.30 DEPLIN-treated patients showed a significantly greater improvement in CGI-S scores at 60 days and a significantly more rapid improvement at both doses with no between-group difference in adverse events.28

Appropriate Patient Types for DEPLIN Therapy

Based on the results of these studies and other factors, what are the patient selection criteria for DEPLIN in MDD? Data from clinical trials show that DEPLIN is effective adjunctive therapy for MDD in patients who have had no or only partial response to antidepressant treatment.5,29,30 The data also show that DEPLIN is beneficial for long-term use,1 with no significant differences in adverse events compared to placebo and none of the adverse events associated with other adjunctive agents, such as weight gain or movement disorders.1,15,28

Evidence suggests specific patient selection criteria include obesity, clinical and/or laboratory evidence of inflammation or an underlying inflammatory process, and/or certain polymorphisms of genes regulating folate metabolism (Table 4).5,29 In addition, a number of factors and conditions can lead to low folate states, and patients who have MDD with certain clinical profiles particularly may benefit from DEPLIN. These profiles are summarized in Table 4 and include medications such as anticonvulsants, antibiotics, methotrexate, and oral contraceptives.24 Tailoring the assessment for these factors should involve a current and prospective monitoring of the medical illness, other newer treatments, and possibly laboratory or genetic markers.

Table 4. Patients With MDD Who May Benefit From DEPLIN (But Not Limited to These Patients).

<table>
<thead>
<tr>
<th>Condition or Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or partial response to antidepressant therapy</td>
<td>15,28,30</td>
</tr>
<tr>
<td>Obesity</td>
<td>29</td>
</tr>
<tr>
<td>Clinical evidence of a chronic inflammatory state or a disorder associated with inflammation</td>
<td>5,29</td>
</tr>
<tr>
<td>Biomarkers suggestive of an inflammatory process</td>
<td>5,29</td>
</tr>
<tr>
<td>Systemic metabolic disorders (eg, diabetes, cardiovascular disease)</td>
<td>30</td>
</tr>
<tr>
<td>Gut dysbiosis</td>
<td>35</td>
</tr>
<tr>
<td>Functional polymorphism(s) of folate metabolism genes</td>
<td>24,32</td>
</tr>
<tr>
<td>Concurrent use of medication known to reduce folate levels and/or inhibit dihydrofolate reductase, which is required for the first conversion step of both dietary folate and folic acid supplements to L-methylfolate</td>
<td></td>
</tr>
<tr>
<td>- Antibiotics</td>
<td>24</td>
</tr>
<tr>
<td>- Anticonvulsants used as mood stabilizers (valproate, lamotrigine)</td>
<td>24,25</td>
</tr>
<tr>
<td>- Metformin</td>
<td>26</td>
</tr>
<tr>
<td>- Oral contraceptives</td>
<td>27</td>
</tr>
<tr>
<td>- Methotrexate and other folic acid antagonists</td>
<td>24</td>
</tr>
<tr>
<td>Need to avoid side effects of AAPs and/or not candidates for esketamine</td>
<td>14</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>24,28</td>
</tr>
<tr>
<td>Preference for nutritional products with perceived holistic/wellness health benefits</td>
<td>16</td>
</tr>
</tbody>
</table>
When there is an inadequate response to current antidepressant therapy, clinicians are encouraged to consider assessing for the multiple factors that may contribute to the lack of achieving and sustaining remission, including the impact of potentially modifiable factors, genetics, and inflammation (eg, obesity), and continue to monitor and tailor treatment to the individual’s needs over time.

Summary and Conclusions

Up to 70% of patients with MDD experience an inadequate response to antidepressant therapy, and many are unable to tolerate adjunctive therapy with AAPs. DEPLIN is a prescription medical food, and it is 7 times more bioavailable at peak concentrations than OTC/supplement folic acid. Clinical studies support its use as adjunctive therapy across a range of patients with MDD with no response or a partial response to antidepressant monotherapy. These studies also suggest that obesity and biomarkers of inflammation may be predictive of a greater response to DEPLIN. DEPLIN is effective for short- and long-term use in this setting, with a favorable tolerability and safety profile characterized by no significant differences in adverse events compared with placebo and none of the adverse events associated with some other adjunctive agents for MDD. Therefore, clinicians should consider the use of DEPLIN early in the course of treatment or whenever there may be an inadequate response to antidepressant therapy.

References


Mr A

“It’s been hard for me to get going. I just want to lie down all day, and I can’t get much sleep at night.”

Chief Complaint
Mr A, a 53-year-old man, was referred by his primary care physician after partial response to escitalopram. Current MDE is 4 months.

History of Present Illness
• Patient reports significant anhedonia, insomnia, fatigue, low motivation, difficulty concentrating at work, feelings of hopelessness, financial and family health concerns, and mildly increased appetite with cravings for sweets
• First MDE occurred during graduate school; treated with counseling only
• Second MDE occurred about 10 years later, precipitated by stress at work and home; treated with fluoxetine for 6 months with a good response
• Third MDE occurred about 8 years later, precipitated by a financial crisis; treated for 12 months with only a partial response
• Current MDE; treated with escitalopram 10 mg/day; dose was increased to 20 mg/day after 4 weeks with only minimal improvement

Other Medical Conditions
• Obesity (BMI=33)
• Mild hypertension
• Type 2 diabetes
• Hyperlipidemia

Family/Social History
• Married financial analyst with 2 adult sons and a supportive wife
• Mother and a maternal uncle have a history of depression
• Two paternal aunts have a history of alcohol abuse
• Family history of type 2 diabetes, hypertension, hyperlipidemia, and hypothyroidism
• Non-smoker; moderate social drinker; does not abuse drugs

Workup/Evaluation
Exam reveals an overweight man with mild psychomotor retardation and decreased attention and concentration. Gives short answers and sometimes needs to be reminded of questions. He has dark circles under eyes. Reports some hopelessness but denies suicidal ideation or intent. No psychotic or manic symptoms. Displays good insight. Orientation and memory are intact.
• PHQ-9=19 (moderate-to-severe depression)
• GAD-7=5 (mild anxiety)
• Laboratory tests (including thyroid function tests) normal, except for
  – Elevated hsCRP
  – Genetic testing (folate metabolism screening panel) identified the MTHFR CT variant and the MTR A2756G variant

Current Medications
• Amlodipine
• Rosuvastatin
• Fish oil
• Losartan
• Metformin
• Coenzyme Q10

References
This case exemplifies what I would call the “ideal” or obvious candidate for Deplin®. The patient is a partial responder to an SSRI, which is the population studied in Papakostas et al1 (study reviewed in article 2 by Dr Zajecka in this supplement). Mr A also has markers of metabolic dysregulation (BMI ≥30), inflammation (hsCRP ≥2.25 mg/L), and a genetic predisposition (MTHFR CT allele [CT or TT] and MTR A2756G variant) that are predictive of an enhanced response to DEPLIN.2,3 In addition, he has obesity and type 2 diabetes, both of which are associated with an increased risk for depression. In fact, the relationship between depression and diabetes is bidirectional.4 I was concerned about using an atypical antipsychotic due to the risk of weight gain, metabolic disturbance, and tardive dyskinesia.

In addition to obesity, diabetes, and the MTHFR CT variant, Mr A has other risk factors for low L-methylfolate due to interference with enzymes in the conversion from folate to the biologically active L-methylfolate. These include age, regular use of alcohol, and poor nutrition.5,6 In addition, certain medications can interfere with enzymes in this pathway, including the metformin that he takes for diabetes.7

Optimal care of patients with MDD calls not only for judicious use of psychopharmacologic agents but also implementation of various dietary and lifestyle interventions. For example, I referred Mr A to a nutritionist as he had an unhealthy diet, which clearly contributed to his obesity and, as a result, to his inflammatory profile. I also recommended an exercise regimen with a goal of at least 30 minutes of aerobic activity no less than 3 times/week. The goal was to reduce his BMI to <30, which has been shown to decrease the risk for depression.8 Exercise also increases blood flow to the brain, which may produce an anti-inflammatory effect as well as increase the release of endorphins and endocannabinoids.

After adding DEPLIN 15 mg/day as part of his overall therapy, Mr A reported gradual improvement. After 4 weeks, he began to feel more optimistic, was more engaged in his work, and interacted more with his family. At the 8-week follow-up visit, he reported an increased interest in activities of daily living.

“I feel more on top of things.” He continued to have some mild fatigue, insomnia, and anxiety, but these symptoms were much less troublesome than previously.

Andrew Cutler, MD

Dr Cutler is Clinical Associate Professor of Psychiatry at SUNY Upstate Medical University in Syracuse, New York.

References
Ms R

"I used to do arts and crafts and other fun stuff with my kids, but now I just lie on the couch and let them watch TV or play video games. I feel like such a bad mother."

Chief Complaint

Ms R, a 35-year-old woman, was referred by a friend. She was started on sertraline by her primary care physician 4 months ago with minimal response for depression but some decrease in anxiety. Current MDE is 8 months.

History of Present Illness

- Patient reports feeling stressed and anxious about COVID-19 and worrying about many different things. Symptoms include depressed mood, anhedonia, fatigue, lack of motivation, insomnia, decreased appetite, feelings of worthlessness, and guilt, mostly related to her roles as a wife and mother
- First MDE at age 16 after breakup with boyfriend; no treatment
- Second MDE at age 22 after another breakup; treated with sertraline by her gynecologist and psychotherapy, where she also dealt with sexual abuse and relationship issues

Family/Social History

- Married with 2 daughters ages 6 and 8 years old
- Difficult childhood with emotionally abusive, alcoholic stepfather; subjected to sexual abuse at age 10 to 12 years by her stepfather’s brother
- Mother has a history of anxiety and depression
- Biological father has a history of alcohol and drug abuse
- Smokes 1 pack of cigarettes daily; marijuana several times a week since her early 20s to help control anxiety; and has increased her alcohol use during the pandemic, currently drinking vodka most afternoons and evenings

Workup/Evaluation

Exam reveals a thin, anxious woman who is fidgety. Not manic or psychotic. Admits to feeling hopeless and worthless, but no suicidal ideation or intent. Good insight. Orientation and memory are intact.

- PHQ-9=22 (severe depression)
- GAD-7=14 (moderate anxiety)
- Meets DSM-5 criteria for GAD and for moderate alcohol use disorder, but not for BPD, OCD, panic disorder, SAD, or PTSD
- Diagnoses: MDD, recurrent, severe, without psychotic features; GAD, partially treated; and alcohol use disorder

Current Medications

- Sertraline
- Oral contraceptives

References


Explain the rationale for using DEPLIN as an adjunctive treatment in patients with MDD. Describe the potential side effects and any precautions to consider.
Ms R is a good candidate for Deplin® for several reasons. First, clinical studies support the adjunctive use of DEPLIN in patients with a partial or inadequate response to SSRIs,1 and, accordingly, it should be considered in this clinical setting. DEPLIN is L-methylfolate, the biologically active form of folate. It is a cofactor in the synthesis and release of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine through the regeneration of BH4,2 which may explain how DEPLIN works in depression overall (see discussion of folate physiology in article 1 by Dr Holmes in this supplement). This patient has a history of childhood trauma and adversity, which are associated with increased inflammatory cytokines and risk of depression in adulthood.3 Inflammation and oxidative stress lead to the degradation of BH4, which is reversed by L-methylfolate.4 This helps explain the greater response to DEPLIN observed in MDD patients with evidence of inflammation.5 L-Methylfolate also acts as a methyl donor for DNA methylation, a process necessary for epigenetic gene silencing, which can be disrupted in patients with childhood adversity or inflammation.6 Finally, L-methylfolate is central to one-carbon metabolism, which is involved in anti-inflammatory and anti-oxidative processes.7,8 For these reasons, DEPLIN is an especially good choice for MDD patients with a history of adversity or trauma.

Ms R also illustrates another rationale for the use of DEPLIN. She uses alcohol and tobacco, both of which can interfere with the conversion of folate to L-methylfolate.9 In addition, she suffers with chronic stress and anxiety, which can also cause inflammation and predispose to depression.10 DEPLIN may be a particularly good choice for MDD patients who use alcohol and/or tobacco and for those with chronic stress.

After 4 weeks of adjunctive treatment with DEPLIN, Ms R reported some improvement in her mood and feeling a little more optimistic, together with what appeared to be a brighter and less anxious affect, although she still had difficulty initiating activities with her daughters. After 8 weeks, she reported additional gradual but significant improvement in most of her symptoms, including feelings of worthlessness and guilt. She also resumed creative activities with her daughters and noted that she had more energy, although “not completely back to normal,” and was trying to decrease her alcohol use with some success. “I don’t feel like I need a drink every day anymore.” She did continue her chronic marijuana and tobacco use, however. She plans to continue to take sertraline and adjunctive DEPLIN to prevent another MDE.11

Andrew Cutler, MD

Dr Cutler is Clinical Associate Professor of Psychiatry at SUNY Upstate Medical University in Syracuse, New York.

References
Improving Response in Antidepressant Therapy
Focus on Deplin®

Intended for US healthcare professionals only. DEPLIN is a prescription medical food for use only under the supervision of a physician for the clinical dietary management of depression and schizophrenia and is specially formulated to meet the distinctive nutritional requirement for these conditions.

For more information about DEPLIN, please see Product Information found on DEPLIN.com.