The National Suicide Prevention Lifeline is getting an upgrade. On July 16, 2022, the Lifeline will change from its previous number (800-273-8255) to just 3 digits: 988. Although the old number will remain available for calls, individuals may call, text, or chat 988, where they will be connected with trained counselors.1 CONTINUED ON PAGE 9

Research in the field of pharmacogenomics has grown exponentially over the past 2 decades, resulting in a vast literature exploring the impact of gene variations on medications’ pharmacokinetics and pharmacodynamics. In tandem with this growth, there has been an increase of interest in using pharmacogenomic testing (PGx) to inform prescribing decisions and to help recognize and address the role of genetics in medication management. It has been proposed that addressing genetic variations in patients by individualizing prescribing can maximize treatment benefit and reduce undesirable outcomes. However, this proliferation of resources and options can be confusing and, without proper science, can lead clinicians down incorrect and even dangerous paths.

The 3 pillars of knowledge for rational medication prescribing are pharmacokinetics, pharmacodynamics, and pharmacogenomics. One of the greatest pioneers in psychiatric pharmacogenomics was David A. Mrazek, MD, during his tenure at the Mayo Clinic College of Medicine and Science in Rochester, Minnesota. Mrazek authored a textbook1 CONTINUED ON PAGE 6
A clinician’s job is to cultivate, tend to, and support the mental health of patients—and we recognize your job is admirable and challenging. As we do in all issues of *Psychiatric Times™*, our job is to bring you the most relevant clinical pearls from the forefront of psychiatry so that you can best support your patients.

This month marks the rollout of 988, the new National Suicide Prevention Lifeline. Although additional funding and logistics may still be under consideration, this system, once perfected, will undoubtedly be a game changer for suicide prevention. How will the system work and how will it affect your practice? We spoke to experts like Christine Yu Moutier, MD, chief medical officer of the American Foundation for Suicide Prevention, and Tony Thrasher, DO, DFAPA, president of the American Association for Emergency Psychiatry, to bring you the most comprehensive first look at this monumental effort.

Based on your feedback, one of the challenging areas in psychiatry is managing psychosis. In Part 2 of our Special Report on this topic, Amy Harrington, MD, and Xiaoduo Fan, MD, MPH, explore methamphetamine-associated psychosis, more relevant than ever with approximately 1.6 million adults using the drug annually. Additionally, Maria Ferrara, MD, shares the specific risks women face for first-episode psychosis. Calling for gender-sensitive care. We hope that these articles will aid you in your own practice by providing tools to care for every potential patient.

Our continuing medical education this month reviews the pathophysiology of anti-N-methyl-D-aspartate receptor encephalitis. Through case vignettes that demonstrate potential presentations, Eric Allen Garrelis, MD, and colleagues support your understanding of this autoimmune condition down to a cellular level.

From cover to cover, this issue of *Psychiatric Times™* shares clinical conversations packed full of the latest research, relevant discussions, and pertinent information to help best you in your job. As always, we have you covered.

**Mike Hennessy Jr**
President and CEO, MJH Life Sciences®
INDICATION
Qelbree is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
In clinical studies, higher rates of suicidal thoughts and behaviors were reported in patients with ADHD treated with Qelbree than in patients treated with placebo. Closely monitor all Qelbree-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.

CONTRAINDICATIONS
• Concomitant administration of a monoamine oxidase inhibitor (MAOI), or dosing within 14 days after discontinuing an MAOI, because of an increased risk of hypertensive crisis
• Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range

WARNING & PRECAUTION
• Suicidal thoughts and behaviors: Closely monitor all Qelbree-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.

REFERENCES:

Please see the brief summary of full Prescribing Information on adjacent pages, or visit QelbreeHCP.com.
Risk Summary

Qelbree® (viloxazine extended-release capsules), for oral use

Qelbree is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days following discontinuing an MAOI, because of an increased risk of hypertensive crisis.

Qelbree should not be taken when receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors

Higher rates of suicidal thoughts and behaviors were reported in pediatric and adult patients with ADHD treated with Qelbree than in patients treated with placebo.

Among 1019 patients exposed to Qelbree 100 mg to 400 mg in short-term trials, a total of nine patients (0.9%) reported suicidal ideation (N=6), behavior (N=1) or both (N=2). Eight patients reported suicidal ideation or behavior on the Columbia Suicide Severity Rating Scale (C-SSRS), a validated scale that assesses suicide risk. An additional patient treated with Qelbree reported suicidal behavior during the clinical trial, but did not report it on the C-SSRS. Among 463 patients treated with placebo in these studies, two patients (0.4%) reported suicidal ideation on the C-SSRS. No patients treated with placebo reported suicidal behavior. No completed suicides occurred in these trials.

Among 183 adults treated with Qelbree, a total of three patients (1.6%) reported suicidal ideation on the C-SSRS, versus 0 of 183 adults treated with placebo. No adults treated with either Qelbree or placebo reported suicidal behavior on the C-SSRS in the study. No attempted or completed suicides occurred in the trial.

Patients treated with Qelbree had higher rates of insomnia and irritability. Although a causal link between the emergence of insomnia and irritability and the emergence of suicidal impulses has not been established, there is a concern that these and other symptoms such as depressed mood, anxiety, agitation, akathisia, mania, hypomania, panic attacks, impulsive behavior, and aggression may represent precursors to emerging suicidal ideation or behavior. Thus, patients being treated with Qelbree should be observed for the emergence of precursor symptoms. Closely monitor all Qelbree-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.

Consider changing the therapeutic regimen, including possibly discontinuing Qelbree, in patients who are experiencing emerging suicidal thoughts or behaviors or symptoms that might be precursors to emerging suicidal ideation or behavior, especially if these symptoms are severe or abrupt in onset, or were not part of the patient’s presenting symptoms. Advise family members or caregivers of patients to monitor for the emergence of suicidal ideation or behavior, and to report such symptoms immediately to the healthcare provider.

Effects on Blood Pressure and Heart Rate

Qelbree can cause an increase in heart rate and diastolic blood pressure.

In a clinical study in patients 6 to 11 years of age, 34/154 (22%) of patients treated with Qelbree 100 mg daily had a ≥20 beat per minute (bpm) increase in heart rate at any time point in the clinical trial, compared to 15/159 (9%) of patients who received placebo. This finding was observed in 84/268 (31%) who received the 200 mg dose, compared to 39/262 (15%) of patients in the placebo group, and in 26/100 (26%) of patients who received the 400 mg dose, compared to 24/103 (23%) of patients who received placebo. In a clinical study in patients 12 to 17 years of age, 22/99 (22%) of patients treated with Qelbree 200 mg daily had a ≥20 bpm increase in heart rate at any time point in the clinical trial, compared to 15/104 (14%) of patients who received placebo. This finding was observed in 69/205 (34%) who received the 400 mg dose, compared to 35/201 (17%) of patients in the placebo group.

In patients aged 12 to 17 years, 52/205 (25%) of patients treated with Qelbree 400 mg daily had a ≥15 mmHg increase in diastolic blood pressure at any time point in the clinical trial, compared to 26/201 (13%) of patients in the placebo group. In a clinical study in adult patients (18 to 60 years of age), 52/178 (29%) of patients treated with Qelbree 200 mg daily (19/200 mg to 600 mg) had a ≥20 beat per minute (bpm) increase in heart rate at any time point in the clinical trial, compared to 23/181 (13%) of patients who received placebo. Of patients treated daily with Qelbree 200 to 600 mg, 23/178 (13%) had a ≥ 15 mmHg increase in diastolic blood pressure at any time in the clinical trial, compared to 16/181 (9%) of patients in the placebo group.

Assess heart rate and blood pressure prior to initiating treatment with Qelbree, following increases in dosage, and periodically while on therapy.

Activation of Mania or Hypomania

Nonadrenergic drugs, such as Qelbree, may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating treatment with Qelbree, screen patients to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a personal or family history of suicide, bipolar disorder, and depression.

Somnolence and Fatigue

Qelbree can cause somnolence and fatigue. In the short-term, placebo-controlled clinical trials in pediatric patients 6 to 17 years of age with ADHD, somnolence (including lethargy and sedation) was reported in 10% of Qelbree-treated patients compared to 4% of placebo-treated patients. Fatigue was reported in 6% of Qelbree-treated patients compared to 2% of placebo-treated patients.

In adults, somnolence was reported in 6% of Qelbree-treated patients versus 2% in placebo-treated patients. Fatigue was reported in 12% of Qelbree-treated patients versus 3% of placebo-treated patients.

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 Qelbree.

ADVERSE REACTIONS

Clinical Trials Experience

The safety of Qelbree has been evaluated in 1118 patients 6 to 17 years of age with ADHD exposed to one or more doses in short-term (6 to 8 week), randomized, double-blind, placebo-controlled trials. A total of 682 pediatric patients were treated for at least 6 months, and 347 pediatric patients for at least 12 months with Qelbree.

The safety of Qelbree has been evaluated in 189 adult patients (18 to 60 years of age) with ADHD exposed to one or more doses in a short-term (6 week) randomized, double-blind, placebo-controlled trial. A total of 497 adults with ADHD have been exposed to one or more doses of Qelbree.

Eighty-four adult patients were treated for at least 6 months, and 22 adult patients for at least 12 months.

The data described below reflect exposure to Qelbree in 826 patients (6 to 17 years) who participated in randomized, double-blind, placebo-controlled trials with doses ranging from 100 mg to 400 mg. The population (N=823) was 65% male, 55% female, 54% White, 41% Black, 4% multiracial, and 1% other races.

Adverse Reactions Leading to Discontinuation of Qelbree Treatment:

Approximately 3% (n=27) of the 826 patients receiving Qelbree in clinical studies discontinued treatment due to an adverse reaction. The adverse reactions most commonly associated with discontinuation of Qelbree were somnolence (n=3), nausea (n=3), headache (n=2), irritability (n=2), tachycardia (n=1), fatigue (n=1), and decreased appetite (n=1).

Most Common Adverse Reactions (occurring at ≥5% and at least twice the placebo rate for any dose): somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.

Table 1 and 2 below lists adverse reactions that occurred in at least 2% of patients treated with Qelbree and more frequently in Qelbree-treated patients than in placebo-treated patients. Table 1 data represents pooled data from pediatric patients treated with Qelbree and more frequently in Qelbree-treated patients than in placebo-treated patients. Table 2 represents data from adults with ADHD who were enrolled in a flexible-dose, randomized, placebo-controlled trial of Qelbree at doses of 200mg to 600mg.

Table 1. Adverse Reactions Reported in ≥2% of Pediatric Patients (6 to 17 Years of Age) Treated with Qelbree and at a Rate of Greater than Placebo-Treated Patients in Placebo-Controlled ADHD Studies

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Placebo N=463 (%)</th>
<th>100mg N=154 (%)</th>
<th>200mg N=167 (%)</th>
<th>400mg N=305 (%)</th>
<th>All Qelbree N=836 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somnolence*</td>
<td>4</td>
<td>12</td>
<td>16</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Headache*</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>0.4</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Infections and infestations</td>
<td></td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>8</td>
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<tr>
<td></td>
<td>Upper respiratory tract infections</td>
<td></td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Body as a Whole - General disorders</td>
<td></td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>.02</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal system disorders</td>
<td></td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain*</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
The clinical trials, but did not report it on the C-SSRS. Among 463 patients treated both (N=2). Eight patients reported suicidal ideation or behavior on the Columbia

For full prescribing information see package insert.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

(200 to 600 mg), 23/178 (13%) had a ≥ 15 mmHg increase in diastolic blood

In a clinical study in patients 12 to 17 years of age, 22/99 (22%) of patients treated

Qelbree can cause an increase in heart rate and diastolic blood pressure.

behavior, and to report such symptoms immediately to the healthcare provider.

or behavior, especially if these symptoms are severe or abrupt in onset, or

emergence of suicidal thoughts and behaviors, especially during the initial few

emergence of suicidal impulses has not been established, there is a concern that

suicidal ideation on the C-SSRS, versus 0 of 183 adults treated with placebo.

clinical worsening, and for emergence of suicidal thoughts and behaviors.

treated with placebo. Closely monitor all Qelbree-treated patients for

reported in patients with ADHD treated with Qelbree than in patients

Tables 1 and 2 below lists adverse reactions that occurred in at least 2% of

Table 1. Adverse Reactions Reported in ≥2% of Pediatric Patients (6 to 17 Years of Age) Treated with Qelbree and at a Rate Greater than Placebo-Treated Patients in Placebo-Controlled ADHD Studies

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>Placebo N=367 (%</th>
<th>Qelbree 200 mg to 600 mg N=189 (%</th>
<th>Qelbree 400 mg N=305 (%</th>
<th>All Qelbree N=636 (%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia*</td>
<td>1</td>
<td>1.5</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Irritability</td>
<td>1</td>
<td>1.5</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>17.9</td>
<td>17.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Somnolence*</td>
<td>2</td>
<td>6.4</td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>5.4</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Gastrointestinal system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>8.3</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>5.5</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>1</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>8.3</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3</td>
<td>8.3</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*The following items were combined: Somnolence: somnolence, lethargy, sedation

Headache: headache, migraine, migraine with aura, tension headache

Insomnia: initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, terminal insomnia

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with Qelbree

Monoamine Oxidase Inhibitors (MAOI)

Clinical Impact: Concomitant use of Qelbree with an MAOI may lead to a potentially life-threatening hypertensive crisis.

Intervention: Concomitant use of Qelbree with an MAOI or within 2 weeks after discontinuing an MAOI is contraindicated.

Sensitive CYP1A2 Substrates or CYP1A2 Substrates with a Narrow Therapeutic Range

Clinical Impact: Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total exposure, but not peak exposure, of sensitive CYP1A2 substrates, which may increase the risk of adverse reactions associated with these CYP1A2 substrates.

Intervention: Coadministration with viloxazine is contraindicated.

Moderate Sensitive CYP1A2 Substrate

Clinical Impact: Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total, but not peak, exposure of sensitive CYP1A2, which may increase the risk of adverse reactions associated with these CYP1A2 substrates.

Intervention: Not recommended for coadministration with Qelbree. Dose reduction may be warranted if coadministered.

CYP2D6 Substrates

Clinical Impact: Viloxazine is a weak inhibitor of CYP2D6, and increases the exposure of CYP2D6 substrates when coadministered.

Intervention: Monitor patients for adverse reactions and adjust dosages of CYP2D6 substrates, as clinically indicated.

CYP3A4 Substrates

Clinical Impact: Viloxazine is a weak inhibitor of CYP3A4 which increases the exposure of CYP3A4 substrates when coadministered.

Intervention: Monitor patients for adverse reactions and adjust dosages of CYP3A4 substrates, as clinically indicated.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Qelbree during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-855-965-2388, or visiting online at www.womensmentalhealth.org/preg.

Risk Summary

Based on findings from animal reproduction studies, viloxazine may cause maternal harm when used during pregnancy. Discontinue Qelbree when pregnancy is recognized unless the benefits of therapy outweigh the potential risk to the mother. Available data from case series with viloxazine use in pregnant women are insufficient to determine a drug-associated risk of major birth defects, miscarriage or adverse maternal outcomes.

In animal reproduction studies, oral administration of viloxazine during the period of organogenesis caused fetal toxicities and delayed fetal development in the rat and maternal toxicities in the rabbit at doses approximately equal to the maximum recommended human dose of 600mg in adults, based on mg/m².

Oral administration of viloxazine to pregnant rats and mice during pregnancy and lactation caused maternal toxicities and deaths and fetal toxicities at doses equal to or less than the MRHD of 600mg in adults, based on mg/m², respectively.

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

Lactation

Risk Summary

There are no data on the presence of viloxazine in human milk, the effects on the breastfed infant, or the effects on milk production. Viloxazine is likely present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Qelbree and any potential adverse effects on the breastfed child from Qelbree or from the underlying maternal condition.

Geriatric Use

Clinical trials of Qelbree in the treatment of ADHD did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients.

Renal Impairment

Dosage reduction is recommended in patients with severe (eGFR of < 30 mL/min/1.73m² [MDRD]) renal impairment. No dosage adjustment of Qelbree is recommended in patients with mild to moderate (eGFR of 30 to 89 mL/min/1.73m² [MDRD]) renal impairment. The exposure of viloxazine increases in patients with renal impairment.

OVERTOSAGE

Human Experience

The pre-market clinical trials with Qelbree do not provide information regarding symptoms of overdose.

Literature reports from post marketing experience with immediate-release viloxazine include cases of overdose from 1000 mg to 6500 mg times 1.7 to 10.8 the maximum recommended daily dose. The most reported symptom was drowsiness, Impaired consciousness, diminished reflexes, and increased heart rate have also been reported.

Treatment and Management

There is no specific antidote for Qelbree overdose. Administer symptomatic and supportive treatment as appropriate. In case of overdose, consult a Certified Poison Control Center (1-800-222-1222) or www.poison.org.

RA-QEL-B8-HCP-V2 Revised: 04/2022 Based on: PI 04/2022
and a comprehensive manuscript laying the foundation for this young field. In view of new research and calls for action, this piece will share updates to further help readers make sense of the array of available information.

Looking to the Experts
Anticipating the need to vet gene/drug interactions with evidence-based clinical applicability, 2 objective organizations were created and they continue to curate this data:

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides a continuously updated open-access online database to document the degree of evidence for all drugs that have been studied.

- The International Society of Psychiatric Genetics (ISPG) focuses only on psychiatric medications.

In 2009, the Pharmacogenomics Global Research Network and PharmGKB, which has been managed at Stanford University in California since 2001 and is financially supported by the National Institutes of Health/National Human Genome Research Institute/National Institute of Child Health and Human Development, joined in the development of CPIC. The mission of CPIC is to evaluate all evidence-based, peer-reviewed publications and maintain an open-access database to inform clinicians about gene/drug practice guidelines for all classes of drugs.

This is an important distinction from the role of the ISPG because a gene may be “actionable” for a specific nonpsychiatric drug with adequate published clinical data but not for all drugs that interface with that gene, including psychiatric drugs. A current example of this is the discontinuation by CPIC that the drug efavirenz has an “actionable” prescription modification based on a patient’s genotype at cytochrome P450 2B6 (CYP2B6), but there are no clinically relevant data as to how—or whether—the CYP2B6 genotype will impact the prescribing of bupropion, which is primarily metabolized by CYP2B6.

CPIC was created to guide the clinical interpretation and implications of specific drug-gene combinations and how existing pharmacogenetic information should be used. CPIC guidelines are published to help clinicians better understand how to consider PGx information when it is available to optimize drug therapy, not to advise which medications should be evaluated or when pharmacogenetic testing should be obtained.

A significant advance in psychiatric pharmacogenomics occurred in 2015 when CPIC published a comprehensive guide summarizing the evidence base for clinical decision-making when prescribing selective serotonin reuptake inhibitors affected by the genotypes of CYP2D6 and CYP2C19. The following year, CPIC published additional guidelines for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.

The second organization, ISPG, also maintains an active and evidence-based website, which it updates as new information is established. Its most recent genetic testing statement for psychiatric disorders includes the following:

“We recommend [human leukocyte antigen] HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups.”

“Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial.”

Additionally, the US Food and Drug Administration (FDA) recognized that caution is needed when considering DNA variations and antidepressant use. They noted, “The FDA is aware that health care providers have made changes to patients’ medication based on genetic test results that claim to provide information on the personalized dosage or treat-
ment regimens for some antidepressant medications, which could potentially lead to patient harm. Subsequent to this warning in 2018, the FDA created a regularly updated Table of Pharmacogenetic Associations.

Significantly, all 3 of these databases—CPIC, ISPG, and FDA—concluded that, at the present time, evidence-based clinical research on psychiatric medications supports the use of PGs testing for only 5 genes at: 3 cytochrome P450 genes (CYP2D6, CYP2C19, and CYP2C9) and 2 HLA genes (HLA-B*15:02 and HLA-A*31:01) (Table 1). Importantly, a group of experts assembled by the ISPG performed a comprehensive review of all available data on pharmacogenomic testing in psychiatry, published in 2021, which reached the same conclusions.

The practicing clinician can order testing for any of these 5 evidence-based genes individually from most laboratories. If the labs do not perform the test themselves, they can send it out for processing, with a usual quick turnaround for the results. The resulting report will vary depending on the gene requested. For cytochrome P450 metabolic enzyme genes, the result is typically reported by defining the presumptive phenotype of predicted enzyme activity based on the genotype of the 2 alleles of that gene for the patient (Table 2). The predicted enzyme activity is listed as one of 4 types of metabolic activity: ultrarapid, normal (previously called “extensive”), intermediate, and poor. HLA reports will list the allele as present or absent.

**CYP2D6**

Approximately 60 human CYP450 metabolic enzymes have been identified. Of these, 6 are responsible for 90% of human drug oxidation: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Not coincidentally, the 2 enzymes that are most studied have the highest number of alleles, which results in more potential phenotypes along the functional spectrum of poor metabolism—CYP2D6 with more than 100 alleles differentiated to date, and CYP2C19 with more than 30. These 2 CYP450 enzymes play an important role in the metabolism of many common psychiatric drugs (Table 1).

It has been hypothesized that the large number of alleles for the CYP2D6 gene is a result of evolutionary pressure on this detoxifying enzyme as humans migrated to novel geographic environments that contained different dietary nutrients. A mutation in the CYP2D6 gene that creates a new allele providing greater efficiency in metabolizing and detoxifying new food products would be preserved; hence, the high degree of genetic polymorphism of the CYP2D6 gene may align with the migratory patterns of our ancestors. There is well-established ethnic variability of the CYP2D6 enzyme, with 10% of Caucasian individuals and 2% of Asian individuals being genotypic poor metabolizers. One percent of the US population consists of genotypic ultrarapid metabolizers, with the highest incidence occurring in individuals of Middle Eastern or North African descent.

**HLAs**

HLAs are a large family of genes that code for proteins making up the major histocompatibility complex, an important human immune defense system. The HLA is a significant component of the protein complex on the surface of cells that assist the immune system in the identification of self from “foreign invader” by inserting small peptides from inside the cell to the cell’s surface, where they can be monitored by the immune system. As an example, the HLA-B gene has polymorphic alleles that code for proteins with differing quaternary structures. There are occasional alleles whose protein product will combine with a specific drug, flagging the resulting complex as “foreign invader” and leading to an aggressive immune response that can be lethal to the patient.

Under most circumstances, if the allele for the HLA is present, the associated drug should not be prescribed for that patient. These results are pharmacodynamic in nature, and the presence of a specific HLA allele often is significantly increased in specific ethnicities. The most dramatic established example of this pharmacogenomic test in psychiatry is that a clinician should almost never prescribe carbamazepine to an individual who tested present for the HLA-B*15:02 allele. This allele occurs 10 to 50 times more commonly in patients of Asian descent than in other populations. As a result of this significant life-threatening risk, the FDA issued a boxed warning for carbamazepine advising that at-risk populations should be screened for the presence of HLA-B*15:02 before initiating carbamazepine, and those who have this allele should not receive the drug unless the prescriber determines the benefit robustly outweighs this risk. The exposure of a patient with the HLA-B*15:02 allele to carbamazepine can result in a severe cutaneous reaction, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Other drugs that share this risk include oxcarbazepine, phenytoin/fosphenytoin, lamotrigine, and gabapentin.

The second HLA that has crossed the threshold to clinically actionable data is HLA-A*31:01, specifically for carbamazepine. Prescribing carbamazepine in the presence of this allele significantly increases the risk of developing a syndrome named Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The onset of DRESS usually occurs between 2 and 8 weeks after starting carbamazepine. Its symptoms can include increased eosinophils, a rash, fever, facial edema, enlarged lymph nodes, and possible damage to the kidneys or liver. In patients prescribed carbamazepine who have the HLA-A*31:01 allele, the odds ratio for developing DRESS in all populations is 13.2. This odds ratio is increased to 57.6 in European populations and to 23 in Chinese populations.

### Table 1. The 5 Current Evidence-Based Genes for Psychiatric Medications per CPIC and ISPG

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene description</th>
<th>Drugs affected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Cytochrome P450 2D6</td>
<td>Numerous antidepressants, numerous antipsychotics, atomoxetine</td>
<td>More than 100 alleles differentiated to date</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Cytochrome P450 2C19</td>
<td>Citalopram, escitalopram, sertraline, tricyclic antidepressants</td>
<td>More than 30 alleles differentiated to date</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Cytochrome P450 2C9</td>
<td>Phenytoin/fosphenytoin</td>
<td></td>
</tr>
<tr>
<td>HLA-B*15:02</td>
<td>Human leukocyte antigen, A type, allele 15:02</td>
<td>Carbamazepine, oxcarbazepine, phenytoin/fosphenytoin</td>
<td>SJS/toxic epidermal necrolysis</td>
</tr>
<tr>
<td>HLA-A*31:01</td>
<td>Human leukocyte antigen, A type, allele 31:01</td>
<td>Carbamazepine</td>
<td>DRESS</td>
</tr>
</tbody>
</table>

**Pharmacogenomic Panels**

During the past decade, specialty labs have offered psychiatric panels to look at gene arrays to guide medical providers about what drug to use for a particular psychiatric disorder based on the totality of the results of all genes in the panel. Most often these labs describe their use of proprietary algorithms that their expert scientists developed to assemble their recommendations. Curiously, many of these panels contain a significant number of genes that have not reached the actionable threshold as established by CPIC, ISGP, and the FDA.

Additionally, expert consensus publications and editorials from thought leaders in psychiatry published since 2016 have consistently concluded that psychiatric pharmacogenomic panels (ie, combinatorial pharmacogenetic tests) are not currently evidence-based, and clinical decisions should not be based on their reports. Common genes that are not evidence-based but are included in many of these pharmacogenomic panels include DRD2, UGT2B15, HTR2A, HTR2C, SLC6A4, MTHFR, COMT, CYP1A2, CYP3A4, and CYP2B6. Publications exist concluding that some of these gene panels have somewhat better patient outcomes in comparison with “treatment as usual,” but these studies are almost entirely funded by the CPIC, Clinical Pharmacogenetics Implementation Consortium; DRESS, drug reaction with eosinophilia and systemic symptoms; ISPG, International Society of Psychiatric Genetics; SJS, Stevens-Johnson syndrome.
pharmacogenomic labs that manufacture and market these panels. The Unknown
Every major scientific and medical advance is often accompanied by a brief euphoric feeling that we have finally opened a door to exponential progress in our attempt to understand our role on this planet, in this galaxy, and in this universe. In fact, the progress we have made in all the sciences over the past 200 years is quite remarkable. At age 62 years, I have settled on what I believe to be an optimistic as well as realistic understanding of what we know in each moment moving forward in time. It is encapsulated by the phrase “the more we learn, the less we know.”

The field of pharmacogenomics has progressed at a truly remarkable rate. The resulting advances in diagnoses and treatments in hematology and oncology are dramatic and highly consequential. We in psychiatry are beginning to bear the fruits of pharmacogenomic research. Additionally, all the data vetted are available freely and with open access.

Furthermore, we have much to learn in the young field of genetics before we can confidently determine the functional phenotype of a specific gene in our patient because of a wide range of processes that alter the genotype that pharmacogenomic testing provides. Epigenetic modifications on a gene’s promoter sequence can dramatically affect the amount of gene product that is produced. Epigenetic modifications on histones surrounding the chromosome can increase or decrease access to a gene and determine the amount of gene product transcribed.

Concluding Thoughts
The young and exciting field of psychiatric pharmacogenomics is providing a third pillar of understanding to aid in our competent and informed prescribing of drugs, joining the more well-established pillars of pharmacokinetics and pharmacodynamics. On a positive note, more than 30,000 research articles related to pharmacogenomics have been published since the first rough draft of the human genome was published in 2003. The challenge for clinicians is to keep up with the flood of new research and findings. This article has been an attempt to summarize the state of pharmacogenomic applications in clinical psychiatry at the present time.

REFERENCES
New 988 Suicide Hotline

Additionally, if functioning as intended, operators will be able to counsel callers 24 hours a day and dispatch specially trained responders, hopefully reducing armed law enforcement interventions and emergency department (ED) visits.

“Having a 3-digit number sends the message that mental health emergencies are as important and require the same level of response as other types of health emergencies, and it makes it easier for clinicians to counsel their patients on how to access emergency mental health care,” Margie Balfour, MD, PhD, chief of quality and clinical innovation at Connections Health Solutions and associate professor of psychiatry at the University of Arizona, told Psychiatric Times™.

Currently, when individuals call the Lifeline, they hear a greeting and then a list of options: “Press 1 to connect to the Veterans Crisis Line” and “Press 2 (“Oprima dos”) for the Spanish sub-network.” Callers who do not choose either of these options are routed to a local Lifeline crisis center based on their area code. If the local center is unable to take their call, they are rerouted to another center within the network.

The Lifeline’s network has more than 200 crisis centers in place. From its inception in 2005 through 2020, the Lifeline has received 20,478,698 calls. After the past few years of crisis, 988’s introduction may prove an opportunity for restructuring mental health emergency response beyond suicide.

“Far more than just a rebrand of the National Suicide Prevention Lifeline, the implementation of 988 provides an opportunity to reform and improve our nation’s crisis response system,” Christine Yu Moutier, MD, chief medical officer of the American Foundation for Suicide Prevention, told Psychiatric Times™. She added that 988 “is an opportunity to reimagine crisis response and increase the involvement of trained mental health professionals who are equipped to address the needs of a person in crisis.”

Easier Number, More Calls

Right now, the lifeline receives approximately 4 million calls or texts per year. In 2020, of more than 940,000 total callers, 22.57% had suicidal thoughts within the past 24 hours, 4.03% were believed to be at imminent risk of suicide, and 0.90% were in the midst of a suicide attempt during the call. About 24.60% of callers required emergency services to be dispatched to their location. All these calls, in addition to calls from local crisis centers and certain 911 calls, will be redirected to 988.

Use of the Lifeline is expected to grow exponentially in coming years, potentially attracting more than 10 million individuals, according to some estimates. By 2026, volume could reach up to 24 million callers or texters per year. This has led to increasing questions and concerns over whether the hotline will be able to meet the already vast demand. According to New York Times data analysts, approximately 17% of the 2 million calls in 2021 were abandoned before the caller could receive help. This may be a result of long hold times and limited staffing in call centers.

Among many goals, 988 hopes to answer 95% of all incoming calls within 20 seconds. “The infrastructure of local crisis call centers must be strengthened to address the needs of millions of people in distress every year. Building capacity at the state level is critical so calls do not go unanswered, wait times do not increase, and people get the help they desperately need. These centers must be adequately staffed to respond to the projected increase in call volume and ensure training is provided for crisis center staff and volunteers,” Moutier shared with Psychiatric Times™.

Infrastructure and Logistics

Since the Lifeline’s launch, the national network and the network administrator have been funded through the Substance Abuse and Mental Health Services Administration (SAMHSA), whereas local Lifeline crisis centers have received funding through varied federal, state, local, and private sources. SAMHSA has significantly increased federal funding resources for the national network and local crisis call centers to help ensure a smooth transition to 988. The current crisis system has been historically underfunded and undervalued, but new funding developments may help meet the growing need.

“If we are going to do this, then we must fund mental health at the level we fund law enforcement and paramedics. There is a massive discrepancy—multiples of salaries’ discrepancy—there. We must pay people to be on call 24/7. It is going to take a pretty significant financial dedication,” Tony Thrasher, DO, DFAPA, president of the American Association for Emergency Psychiatry and medical director of crisis services in the Milwaukee County Behavioral Health Division in Wisconsin, told Psychiatric Times™.

In 2022, planned federal funding is $282 million. Of that, $177 million will go toward strengthening network operations including expanding paid and trained staffing for backup, specialized services, and chat and text centers; building up data and telephony infrastructure; strengthening standards, training, and quality improvement; and ensuring evaluation and oversight. The remaining $105 million will go to local crisis centers for expanding capacity to increase response rates, providing follow-up so individuals are effectively engaged with local behavioral health crisis services, staff are sufficiently paid, and staff/volunteers are adequately trained to provide evidence-based interventions even in high-risk populations.

Nonprofit Lifeline administrator Vibrant Emotional Health is also providing funding through grants to 49 states and US territories through the Lifeline’s 988 State Planning Grant Initiative. The funds will be used to develop coordination, capacity, and communications surrounding the launch of 988. The National Suicide Hotline Designation Act (S.2661) allows states to collect revenue to sustain and expand local crisis services. Fees will be collected on both land and cell phone bills to provide ongoing financial support for crisis call centers. The Biden administration recently announced it will allot an additional $700 million to local crisis centers in its fiscal year 2023 budget, but each state will need to maintain its sustainable revenue stream and infrastructure for 988. States that fail to do so face increased risk of individuals in crisis not getting the support they need.

Despite this increased funding, as of May 2022, at least 13 states—Alabama, Colorado, Idaho, Indiana, Kentucky, Minnesota, Nebraska, Nevada, New York, Oregon, Texas, Virginia, and Washington—have passed 988 implementation laws that include fee measures to pay for the expected increase in calls. At least 11 states—California, Florida, Idaho, Kansas, Massachusetts, Michigan, New Jersey, New York, Ohio, Vermont, and Washington—have introduced new or additional legislation. Without significant supplemental state funding and staffing, the Lifeline may have difficulties delivering on goals. The focus will be on these states to iron out the details of how 988 will function in practice.

“Like any big undertaking, the devil is in the details—and 988 is a huge undertaking. You are taking a network of 200 or so suicide hotlines and trying to create a uniform system, which is hard enough,” said Balfour. “Opening up access without a crisis system in place could potentially make problems like ED boarding worse. We need to build that crisis system of care, and that will take time. There is legislation in Congress to start laying the foundation for that—creation of national standards, funding for planning and infrastructure, and parity coverage by health insurance. Although 988 has the potential to catalyze a huge transformation of crisis services, that will be a stepwise process that will happen over years.”
Thoughts From the Editor in Chief

**John J. Miller, MD**

The 988 initiative is a milestone in our ongoing efforts to bring parity to mental health awareness, accessibility, treatment, and destigmatization. However, due to numerous barriers primarily related to lack of funds and the current fragmentation of access to mental health crisis clinicians around the country discussed in this issue, in my opinion, it could very likely take 10 to 20 years to achieve the functional, effective system for which the 988 initiative is striving.

Will the implementation of 988 on July 16, 2022, result in a decrease in suicides in the United States? I believe it will. Sadly, many individuals who commit suicide will not dial 988. During my 31 years of clinical psychiatry practice, the patients I have treated who ultimately died by suicide did so with careful planning, leaving behind family, friends, and mental health providers who all felt blindsided.

However, 988 will provide an immediate, accessible lifeline for those individuals who are feeling suicidal and hopeless but also have ambivalence and emotional turmoil that motivates them to reach out for help. Significantly, any bystander—family, friend, or stranger—who is concerned about the immediate mental health of a person will now have an option to activate a mental health crisis response to professionally assess the crisis and intervene with resources appropriate to the situation.

Although technically 988 is replacing the current 10-digit phone number for the National Suicide Prevention Lifeline, the establishment of 988 will become a much broader safety net for the many diverse mental health crises requiring immediate intervention: suicide risk, unpredictable actions of a person in an acute psychotic episode, a substance abuse crisis, or assistance with an oppositional and angry family member, to list just a few. Once the 988 infrastructure is fully developed, integrated throughout the country, staffed, and operational it has the potential to greatly reduce the current burden of these mental health emergencies that are responded to by 911 calls. The person in crisis will likely engage in a more therapeutic manner with a mental health clinician than with a 911 response team.

Throughout the COVID-19 pandemic we have seen an explosion of mental health crises straining and draining our current mental health system. The implementation of 988 on July 16 will require a massive increase in funds, education of clinicians, and growth of our mental health system at all levels to not only meet the current needs but to put services in place that will be required to competently deliver the outcomes that 988 promises. What good would 911 be without the response teams, hospitals, and associated resources that allow for a rapid, competent response once the crisis is identified?

In my opinion, 988 will greatly affect the practices of all mental health providers. Currently, providers are greatly affected by mental health crises whether or not they want to acknowledge it. Throughout the country, long waiting lists exist for evaluations for all types of mental health treatment. These include therapy; psychopharmacology; day treatment programs; residential programs; medical consultation appointments to aid in accurate diagnosis and treatment; methadone or buprenorphine outpatient treatment; substance use disorder admissions for detoxification and transition to longer-term care; and follow-up visits for established patients in acute crisis. The launch of 988 will further strain these already overburdened elements of the mental health care system.

Additionally, I challenge mental health providers of all types to be more available outside of the formal appointment to serve as the first line when a client calls in crisis. Many private practice mental health practitioners instruct their patients to call 911 or go to the emergency department (ED) if they are in acute crisis. Although in some circumstances this is appropriate, it is likely that many 911 calls and ED visits resulting from this approach could readily be addressed by the individual’s primary mental health provider. This would greatly reduce the burden on the larger mental health system that already exists, and the situation will only improve with 988.
Thoughts From the Editor in Chief

In contrast, at least 7 in 10 adults trust social media for the Trevor Project, 36% of adults do not trust police beyond 911 for patients, caregivers, and witnesses to a 2002 study of 911 response times, mortal- ity rates in medical emergencies rose if response time increased beyond 5 minutes. \(^{13} \) For dispatchers, dealing with traumatic or verbally abusive calls is correlated with lower organizational commitment, a higher desire to leave the job, and greater emotional exhaustion. \(^{14} \) Trauma exposure also affects ambulance operations, with some reporting angry outbursts, trouble sleeping, nightmares, flashbacks, and increased alcohol consumption. \(^{15,16} \)

Training initiatives for 988 dispatchers may need to keep this in mind. According to SAMHSA, current training is primarily determined by each individual crisis center based on its organizational needs. However, the Lifeline Core Clinical Training is in development, and will consist of self-paced online courses covering essential skills for crisis counselors who answer calls/chats/texts within the Lifeline network. Further training to address the specific needs of populations at higher risk of suicide is also in development. \(^{17} \)

### Working Toward Decriminalization

Approximately 1 in 10 individuals with mental health disorders have interactions with law enforcement prior to receiving psychiatric care, \(^{18} \) and up to 10% of police calls are for mental health emergencies. \(^{19} \) Individuals with serious mental illness account for 17% of use-of-force cases and 20.2% of suspects injured in police interaction. \(^{20} \)

Furthermore, injury, death, and other adverse outcomes are 10.7 times more likely for individuals with mental health disorders. \(^{21} \) Negative outcomes are also disproportionately experienced by people of color. \(^{22} \) The 988 hotline will provide an option for the 988 suicide and crisis hotline volunteer and job opportunities. Sub- stance Abuse and Mental Health Administration. Updated May 12, 2022.

### Will It Impact Outcomes and Care?

According to a national poll, 46% of adults have never heard of 988. \(^{23} \) With nearly half of adults unfamiliar with 988, will this resource help clinicians and their patients? \(^{24} \) According to a poll, asking 2 questions: Will 988 help reduce suicide?

Approximately 63% of respondents said they believed the implementation of 988 will reduce suicide. \(^{25} \) However, on affecting practice, respondents were not totally convinced, with a 50/50 split. What are your thoughts on 988? We would love to hear.

**PTEditor@MMHGroup.com.**

### References


23. Will 988 help reduce suicide? Do you think this will impact your practice? Approximately 63% of respondents said they believed the implementation of 988 will reduce suicide. \(^{24} \) However, on affecting practice, respondents were not totally convinced, with a 50/50 split. What are your thoughts on 988? We would love to hear. PTEditor@MMHGroup.com.

### Medical Connections

When mental health professionals and law enforcement work together, they may be more able than ever to help keep individuals in mental health crisis out of the emergency room and out of jail. In this installment of Wellbeing Checkup, Margie Balfour, MD, PhD, of Connections Health Solutions and Dr. Jason Winsky of the Tucson Police Department provide an update on the latest crisis system developments, including the 988 mental health hotline number.

**medicalworldnews.com/view/wellbeing-checkup-making-connections**

Want to share your story? Email us at PTEditor@mmhgroup.com.
Decreased adherence to antipsychotic treatment is common in schizophrenia and associated with poorer outcomes, including illness relapse, cognitive impairment, substance use, suicide, and mortality.\(^1\)\(^2\) Estimates of antipsychotic adherence with poorer outcomes, including illness relapse, patient nonadherence is common in schizophrenia and associated with objective measures (eg, pharmacy refill records or blood levels) yield significantly lower rates on adherence than subjective measures.\(^3\) Furthermore, objective methods (eg, pharmacy refill records from the pharmacy within 1 year. The authors also compared antipsychotic nonadherence to that for other medication groups—including oral antidiabetics, antihypertensives, and statins—in the same patients with schizophrenia. Covariates included age, sex, time since first schizophrenia diagnosis, concomitant medications, medical comorbidities, history of suicide attempt, and substance use disorders. For each antipsychotic, the authors calculated the nonadherence proportion (the number of undispensed prescriptions divided by the total number of prescriptions) with 95% confidence intervals (CI). Odds ratios (OR) and 95% CI were calculated for sociodemographic and clinical factors associated with primary antipsychotic nonadherence. They also tested whether levels of primary adherence between oral antipsychotics varies as a function of efficacy or tolerability.

The mean participant age was 42 years, 52% of participants were male, and 49% were diagnosed more than 20 years ago. The most common concomitant psychiatric medications were benzodiazepines (47%), antidepressants (36%), and mood stabilizers (24%). Approximately 32 percent (n = 9506) of subjects were nonadherent to any antipsychotic treatment (ie, at least 1 undispensed prescription). By contrast, primary nonadherence was lower for antidiabetics (18%), antihypertensives (21%), and statins (14%) in patients with schizophrenia. Several factors were related to primary nonadherence (Table 1), with the strongest association being for age below 25 years (OR, 1.77). Both benzodiazepines (OR, 1.47) and mood stabilizers (OR, 1.29) were also related to primary nonadherence.

Overall, 7.4% of antipsychotic prescriptions had not been dispensed (Table 2). At the group level, there were more undispensed prescriptions for oral (10.3%) than LAI (7.3%) antipsychotics. Based on previous data, both antipsychotic efficacy and tolerability were related to adherence, indicating that agents with lower adverse effects and greater efficacy were more likely to be dispensed.\(^6\)

### Study Conclusions
The study authors concluded that about 1 in 3 outpatients with schizophrenia had primary antipsychotic nonadherence, which was higher than that for their somatic medications (14% to 21%).
Further, patients using clozapine had the lowest nonadherence, and patients using LAI antipsychotics had lower nonadherence than those using oral agents. Younger age, female sex, more recent diagnosis, and substance use were all associated with primary nonadherence. Study strengths included the use of a nationwide sample and register-based data. Limitations included the focus on primary nonadherence (e.g., patients may not take antipsychotic medication as prescribed).

The Bottom Line
Antipsychotic selection should consider multiple factors—including efficacy, tolerability, route of administration, concomitant medications, and patient comorbidities—to minimize nonadherence and associated adverse outcomes.

**REFERENCES**

**More Than a Knockout: Structural Brain Effects in MMA Sparring**

In its first year back in person since the COVID-19 pandemic, the American Psychiatric Association 2022 Annual Meeting featured more than 300 sessions and 1000 posters discussing clinical updates, diversity and health equity, and technological issues. The meeting’s theme, “Social Determinants of Mental Health,” attracted leaders in the field from across the globe. Here you will find selected highlights. Additional coverage can be found at www.psychiatrictimes.com/conferences/apa.

In a first-of-its-kind study, researchers examined the practice sparring’s effects of mixed martial arts (MMA) fighters and resulting brain changes. Although previous studies have looked at other sports that involve repetitive brain injury, the real risk for MMA fighters occurs during practice sessions, explained study co-author Aaron J. Esagoff, a medical student at Johns Hopkins University School of Medicine. While fights and matches only happen a few times per year, individuals can spend hundreds of hours sparring and practicing. MMA is a hybrid combat sport that includes moves from boxing, wrestling, karate, judo, and jujitsu.

“With MMA and a lot of combat sports, you are going to get hit in the head a good amount. And when you get hit a lot of times, that can lead to damage and disease,” Esagoff told attendees. The increasing awareness of repetitive brain trauma and its relationship to neuropsychiatric sequela inspired Esagoff and colleagues to conduct the study of MMA fighters.

To better understand the effects of the repetitive head impacts, the investigators conducted a cross-sectional study of 92 active professional MMA fighters, looking at the relationship between customary sparring practice rounds per week on white matter hyperintensity volume and regional brain volumes. In doing so, Esagoff and colleagues found customary sparring practice rounds per week were significantly associated with increased white matter hyperintensity volume, which he noted may be indicative of damage (e.g., axonal injury, vascular damage, etc.). However, the investigators also found that customary sparring practice rounds per week were associated with increased relative size of the left and right caudate nucleus. The authors hypothesized that practice may help protect from injuries during official fights that damage the caudate.

“The one takeaway would be that sparring and practice is not all good or all bad, as there are some good effects, some not-as-good effects,” concluded Esagoff. “But it’s all an association for now; we’re not able to conclude anything with confidence.”

Esagoff’s co-authors included Michael J.C. Bray, MS; Andres A. Pasuizaca; Matthew E. Peters, MD; Bharat R. Narapareddy, MD; and Charles B. Bernick, MD.—HAD
Artificial Intelligence Revolution Holds Enormous Potential for Psychiatry

Artificial intelligence (AI) is here to stay, and it’s really very important for the psychiatric field to take a leading role in developing it,” said P. Murali Doraiswamy, MBBS, FRCP, of the Duke University School of Medicine in Durham, North Carolina.

Doraiswamy was joined in a panel discussion by Robert M. Califf, MD, MACC, commissioner of food and drugs for the FDA, and moderator Samantha Boardman, MD, psychiatrist and author of Everyday Vitality: Turning Stress Into Strength.

“If I [were] a computer programmer describing the unmet needs in the mental health field, I would use a formula…something like this: 40, 40, 30, 0. This means only 40% of [individuals] who need care get access to the care they want; of those, only 40% get optimal care; of those, only 30% achieve remission; and 0%…get preventive care in terms of resilience,” Doraiswamy said. “That’s the problem in this field—and the hope and promise is that AI and technology can help with some of this.”

Doraiswamy noted that $4 billion has been invested in AI, which has been doubling every 3 months for the past few years and transforming multiple fields. In psychiatry, digital health coaching, stigma reduction, triage and suicide prediction, clinical decision support, and therapeutic apps have already had an impact, with therapeutic wearables, robots and virtual reality avatars, protocol standardization, quality control and practice management, and population forecasting on the horizon.

Mental health and wellness apps are particularly lucrative, with more than 5000 currently on the market and around 250 million individuals having accessed them in the past 2.5 years. Although some of these apps are FDA-approved—such as EndeavorRx for the treatment of pediatric attention-deficit/hyperactivity disorder and Somryst for chronic insomnia—it is important to note that many are neither approved nor overseen by the FDA unless they make a disease claim. In addition, many of these digital tools also provide inaccurate information, send data to third parties, and are based on “black box” algorithms rather than randomized controlled trials. However, recent data show that 82% of individuals believe robots can support their mental health better than humans can, because robots are unbiased, judgment free, and able to provide quick answers.

Clinicians have cited potential harms of AI, including diagnostic and treatment errors; a loss in creative clinical thinking; greater risks of dehumanization and jeopardization of the therapeutic process due to lack of empathy; and less privacy and more fatalism in general. Clinicians also worry that the machine’s reaching a diagnosis could become a “black box” process and that, if time saved is used by administrators to increase patient loads, it might increase clinician burnout.

Another potential concern for clinicians is job security given the fully automated psychiatrist, which is another form of AI in development. Doraiswamy emphasized that a development like this should be regarded as an enhancement of psychiatric practice. “This is not going to replace you,” said Doraiswamy. “This is a personal assistant that’s going to be sitting in the waiting room doing the initial interview invite, get all the intake ready, and then summarize this information and have it ready for you so that you can make a diagnostic assessment.”

Clinicians have also cited benefits of AI, including better outcomes through more standardized protocols and elimination of human error; less bias in regard to race or gender; and scalability of treatment. They say AI can encourage patients to answer truthfully and accept support more objectively, use big data more efficiently than humans, provide practical guidance for trainees, and help elucidate etiologies of diseases that are not well understood.

The evidence for the predictive benefits of AI for psychiatry is also growing. Recent research has found support that AI may be able to detect Alzheimer disease 5 years before diagnosis and predict depressive episodes and risk of suicide. In addition, it is possible that machine learning may be able to anticipate a mental health crisis using only data from electronic health records. “By and large, this shows you the promise,” noted Doraiswamy. Because DeepMind—owned by Google—recently released a general-purpose AI agent, “it’s probable that you could have one AI program that could help with all 159 diseases in the DSM-5,” Doraiswamy told attendees.

To maximize the potential benefits of AI and ensure that psychiatry leads this revolution, Doraiswamy recommended that the field develop clinical practice guidelines; provide proper education and training; ensure that cases are relevant and human centered; advocate for equitable, accountable AI; implement quality improvement methods into workflow; create benchmarks for “trusted and safe” apps; and work with payers to develop appropriate reimbursement.

“We need to step back and acknowledge that digitization in our society and broad access to the internet are having profound effects that we don’t yet understand—and that as we develop technologies with the plasticity that these technologies have, as opposed to traditional medical devices, you can change the software very quickly,” Califf said. “It’s a tremendous potential benefit, but it also carries very specific risks that we need to be aware of.”

“Some very reasonable [individuals] might argue that AI and psychiatry don’t belong even in the same sentence—that AI should play no role whatsoever in mental health care, and that the psychotherapeutic relationship is sacrosanct,” Boardman concluded. “But in a world where there are so many unmet mental health needs, I think there’s a very good argument that AI can not only improve care and diagnostics and increase access, but also reduce stigma and even flag potential issues and symptoms before they appear and reduce burnout among professionals.”—EO
New Data Shows Trauma’s Ripple Effects

In a disaster, we naturally tend to pay attention toward the most immediate victims, so people who are impacted physically and with physical injuries and damages,” Gaëlle Rached, MD, MSc, told attendees during a new research presentation at the APA annual meeting. But what about the family members who live thousands of miles away?

Rached, a research postdoctoral fellow at Northwestern University, shared details about the events of August 4, 2020, when the residents of Beirut experienced a massive explosion as a result of improperly stored ammonium nitrate at the city’s port. More than 200 individuals were killed, and many more were injured and left homeless. Although Rached was in the city and saw firsthand the devastation and trauma, she found herself taken aback by the reports from expat friends and colleagues.

“They heard about the blast from social media, and they tried reaching out to their families, but they weren’t able to reach them,” she told attendees. “The lines weren’t connecting. They spent hours trying to reach them and thinking and imagining the worst... Can you imagine sitting at home looking at these headlines and wondering what your family is going through? Can you imagine seeing these videos shared over on social media and being stuck abroad due to COVID, not being able to help?”

As she talked with her colleagues about these experiences, she realized that the traumatic experiences were similar, “but somehow a little bit different.”

In general, expatriates are exposed to stressful living conditions, which makes them more susceptible to developing mental health problems, Rached noted. Yet their general mental health is not well studied, and even less is known about such in the context of traumatic events. Thus, Rached and colleagues conducted a 7-month study to examine the impact of the Beirut explosion on expats.

The study consisted of 670 Lebanese citizens or first generation from Lebanese descent who were residing abroad (not in Lebanon) and at least 18 years old. Of that population, 268 experienced the explosion and/or had close family members physically impacted by it. The median age was 31, and the majority (62.2%) were female. Participants came from all over the world, with the highest percentages coming from the United States and France. Study co-authors included Muriel Slim; Dimitri Fiani, MD; Margarita Abi Zeid Daou, MD; and Souraya Torbey, MD.

Participants were screened using the Hopkins Symptoms Checklist and the PTSD Checklist for DSM-5. Preliminary analysis found almost 60% of the 268 who had more personal experience had scores on the PTSD Checklist indicative of PTSD. Furthermore, about 41% of participants screened higher than the threshold for anxiety and depression on the Hopkins Symptom Checklist. Both younger age and female sex were associated with higher scores, even months after the event occurred.

Rached explained her results show expatriates’ mental health are negatively affected by traumatic events in their home countries:

- Months following the traumatic event
- Regardless of how long the expat has been away from their home country
- Regardless of if they experienced the event or witnessed it firsthand

“My simple message would be that there are 200 million expats around the world right now. Look out for expats in your life—your friends, your coworkers, your colleagues—especially when the country is going through traumatic events,” Rached concluded. —HAD

New Weapon in the Fight Against Opioid Use Disorders

The opioid epidemic has raged on despite the development of evidence-based treatment for opioid use disorders,” explained Kimberly Hu, MD. “About 70% of the nearly 71,000 drug overdose deaths in 8 states involved opioids. That’s a huge, staggering number.”

Recognizing the role that insufficient access to medications plays in this epidemic, Hu and colleagues at the Ohio State University Wexner Medical Center designed and implemented an opioid use disorder (OUD) curriculum for third-year medical students. In the study, the students (n=405) were provided with in-person or virtual buprenorphine waiver training and in-person clinical experiences between January 2019 and April 2021. Pre- and post-intervention tests, along with self-reported clinical management surveys, assessed the students’ ability to screen patients with OUD and manage acute and chronic pain. Paired sample t-tests were estimated to assess improvement in knowledge and approach to clinical management principles.

Hu, a resident at the Ohio State University Wexner Medical Center, and colleagues found a statistically significant increase in both their knowledge as seen in the pre- and post-test scores as well as their self-reported understanding of management principles. A follow-up study at the end of the year also provided positive feedback. Hu reported: “83% [of the participants] said that they felt they knew how to manage acute pain, about 62% felt that they knew how to manage chronic pain, and about 77% said that they knew how to screen the patient for opioid use disorder.”

This is important no matter which specialty the students pursue, as these students will be able to ‘‘link patients with resources early and make sure that there aren’t patients slipping through the cracks,’’ Hu explained.

She noted that educating third-year medical students gives them—and their future patients—an advantage. “They’re a little over halfway through medical school, and then they’ll go into residency in a number of different specialties. So giving them this knowledge early helps them to incorporate [the information and skills] as they continue their training.”

Hu noted that the educational program is ongoing and supported by the Substance Abuse and Mental Health Services Administration. Her study co-authors included Julie Niedermier, MD; Amanda Sturt, PhD; Casia Horsemann, MD; and Julie Teater, MD.

“If we can educate the next generation physicians and increase access to care, this is one way we can combat the opioid crisis,” Hu concluded. —HAD

“About 70% of the nearly 71,000 drug overdose deaths in 8 states involved opioids. That’s a huge, staggering number.”
Clearing the “Brain Fog” in Long COVID

How can we “clear the fog” surrounding brain fog? Experts addressed the cognitive dysfunction, or brain fog, observed in patients with long COVID—as well as patients with fibromyalgia or chronic fatigue syndrome or those undergoing chemotherapy treatment.

Maria Tiamson-Kassab, MD, of the Moores Cancer Center at UC San Diego Health in California, introduced the session, which was delivered on behalf of the Academy of Consultation-Liaison Psychiatry. Durga Roy, MD, FACLP, of Johns Hopkins Bayview Neuropsychiatry Clinic and Johns Hopkins University School of Medicine in Baltimore, Maryland, discussed symptoms and pathophysiology of brain fog in long COVID, as well as some ways clinicians can help patients with brain fog after long COVID. Additional speakers included Jon Levenson, MD, of Columbia University Irving Medical Center, and Susan Abbey, MD, FRCPC, of the University of Toronto.

Tiamson-Kassab explained that brain fog is a nonmedical term used to describe what patients feel in any condition that causes confusion, memory loss, inability to concentrate or focus, and difficulty with word finding or multitasking. It is a symptom in many conditions, including long COVID, fibromyalgia, chronic fatigue syndrome, pregnancy, multiple sclerosis, and systemic lupus erythematosus, as well as in cancer treatments and certain medications. Neurocognitive domains affected in brain fog include planning; decision-making; processing speed; complex, divided, and selective sustained attention; free and cued recall; and working, procedural, and autobiographical memory.

Cognitive dysfunction is a particular concern in long COVID, as many patients have reported symptoms such as brain fog weeks or months after initial SARS-CoV-2 infection and can appear weeks after infection. In all cases, the symptoms cannot be sufficiently explained by any alternative diagnosis, and they can present even if the initial SARS-CoV-2 infection was mild or asymptomatic.

Although a range of symptoms may present, “fatigue and cognitive impairment appear to be the most debilitating symptoms of long COVID,” Roy explained. However, the exact cause of brain fog and other symptoms in long COVID is not yet clear. “We have to be cognizant of the fact that, potentially, anxiety and depression could be factors that are driving the fatigue and cognitive impairment,” Roy said. “And pathophysiology can stem from numerous hypotheses, neuroinflammation, or neurotropism, but the idea is that the frontal limbic pathway seems to consistently be something that we’re hearing about when it comes to cognitive problems in long COVID.”

In terms of treatment, Roy recommended both pharmacologic and nonpharmacologic interventions targeting mental fatigue and cognition. Pharmacologic interventions may include medications such as methylphenidate, donepezil, modafinil, luteolin, nicotinamide riboside, vitamin C or probiotic supplementation, monoclonal antibodies, or adaptogens. Suggested nonpharmacologic interventions include cognitive behavioral therapy, graded exercise therapy, pacing, and rehabilitation.

With studies on brain fog in long COVID still new and in development, Roy emphasized a need for more research to improve treatment and patient quality of life. “This is definitely a syndrome that we don’t know very much about,” Roy said. “It’s something that we really need to study more in order to get a better grasp on what’s going on.”—EO

“Fatigue and cognitive impairment appear to be the most debilitating symptoms of long COVID.”

-DURGA ROY

Scan for more coverage of the American Psychiatric Association 2022 Annual Meeting, including video interviews.
It’s Time to Think of Women
Mental Health Services for First-Episode Psychosis

Maria Ferrara, MD, PhD

As the World Health Organization reminds us,1 gender is a critical determinant of health, including mental health. Psychosis affects 3 in 100 individuals worldwide and typically develops around age 21 years.2 It includes diagnoses such as those of the schizophrenia spectrum and affective disorders. Early intervention services hold the promise of changing the trajectory of psychosis by providing specialized, coordinated care to individuals experiencing their first episode of psychosis (FEP).3 Evidence shows that FEP services can improve short-term and long-term outcomes for the individual4 (eg, employment) and for their community5 (eg, reduced disruptive public behavior, legal charges). What remains unknown, and maybe overlooked, is that women experiencing FEP might encounter gender-based disparities in accessing and receiving specialized care.6

Crucial questions arise: Are men and women equal when it comes to accessing mental health care for FEP? Do men and women with psychosis have the same care needs?7,8 How can we tailor FEP services to accommodate women’s needs?

Gender differences regarding the clinical characteristics of the psychosis spectrum have been extensively described9,10. Men and women differ in incidence and age at onset,11 in symptoms at care presentation, and in course of illness. Compared with men, women also carry different risk factors for psychosis,12 including hormonal and psychosocial influence.

Several factors have been identified that could affect access to and quality of care received by women with FEP. Potential suggestions for overcoming clinical and structural challenges also will be provided.

Factors Affecting Access to Care for Women With FEP

Age at onset: Many FEP programs accept only individuals aged 15 to 35 years, which is consistent with the design of a service providing specific psychosocial interventions to address a set of needs for education and employment targeted to younger individuals. However, this age range might exclude women who have their first episodes later in life. The multinational EU-GEI study including 2774 individuals with FEP reported not only that women were older at first contact with FEP services (age 34 years vs 28 years for men) but also that they had a second peak of new onset of psychosis in their 50s (post menopause).13

In the United Kingdom, a solid attempt has been made to expand access to specialized FEP services to individuals up to age 65 years. A preliminary report suggested that, compared with individuals younger than 35, a higher proportion of referrals and accepted patients over 35 were female, providing further evidence of possible unmet care needs in women over 35 with FEP.14

The challenge exists in how to design FEP services for this older age group with higher care complexity, such as systematic involvement of family social care services and greater economic needs.

Clinical presentation of psychosis and pathways to care: These also differ by gender.15 Women tend to present with prevalent mood symptoms associated with psychosis instead of the classic bizarre behavior and thoughts; therefore, they are more likely to receive a diagnosis of affective psychosis (which is often a criterion for exclusion from FEP programs). Moreover, women are less likely to manifest psychosis through aggressive and disorganized/dangerous behaviors that often lead to hospitalization. As a result, paradoxically, women with acute psychosis are less likely to be identified by means of an admission to the inpatient psychiatric units. Hospitalization is often dramatic and considered an aversive entry to mental health care.16 It still represents one of the main doors through which to access FEP programs.17 Given these premises on clinical presentation, FEP services might consider accepting women with concomitant mood symptoms into treatment, reserving some time to conduct an in-depth differential diagnosis evaluation to clarify the diagnosis, and then referring women to the appropriate service.

Gender stereotypes and societal norms: These also can affect access to care and establishing the correct diagnosis. A woman’s call for help can be labeled as being over dramatic or acting out to gain attention.18 When gender stereotypes are intertwined with gender norms, access to care can be very problematic. Women are often the designated caregivers for infants and elderly relatives, so prioritizing the care of others could further delay their own access to treatment.19,20 Women, more often than men, are employed in precarious jobs with lower salaries and worse benefits (eg, less paid time off, more rigid schedules), challenging smooth access to care.19,20 FEP services should be sensitive to these gender differences and implement gender-targeted, early-detection interventions in outpatient health facilities, such as primary care, obstetric, and gynecologic clinics, where women with unrecognized psychosis may be found.

Factors Affecting Quality of Care for Women With FEP

Sexual and reproductive health: Monitoring for this should be considered an integral part of FEP services, considering that FEP usually manifests during adolescence and most importantly in the reproductive years. Women, by definition, carry a unique risk factor for new onset or relapse of psychosis: pregnancy.21 Quality of care for FEP is also measured by the attention to mental health monitoring when a woman with a past or current history of psychosis is pregnant and in the postpartum period.22 FEP services may facilitate ad hoc consultations with other services (eg, pediatrics, primary care, or obstetrics). A more systematic interagency collaboration is also suggested. For example, patients with FEP might receive best-practice reproductive care during the peripartum period for themselves and simultaneously access to pediatric care for their infants.

Physical health: Both genders can develop metabolic adverse effects due to the pharmacological treatment for psychosis, which contributes to an increase in cardiovascular risk within these populations.23,24 The choice of pharmacological treatment for women with FEP should be especially sensitive to these adverse effects, such as weight gain and hair loss, which are more heavily stigmatized in women.

Mental Health Services for First-Episode Psychosis
Preventive medicine: Women with schizophrenia are less likely than those without a severe mental illness to receive Papncalou study screening for cervical cancer and half as likely as the general population to receive mammography. FEP services can act by providing education and facilitating the appropriate access to women-specific preventive programs.

Trauma-oriented care: Women, more than men, are victims of intimate partner violence that is linked to an increase in risk of manifesting psychotic experiences, especially in cases of multiple victimizations. Moreover, there is a strong association between exposure to traumatic events in childhood and increased risk of psychosis. It is recommended that FEP programs screen for past traumatic events and assess the current risk of trauma for the patient and potential children in the household.

Concluding Thoughts

It is time for gender-sensitive FEP services. Preventive medicine: FEP services can act by providing education and increased risk of psychosis. Concluding Thoughts: It is time for gender-sensitive FEP services.

Dr Ferrara is an assistant professor at the Institute of Psychiatry at the University of Ferrara in Italy and an adjunct assistant professor of psychiatry at the Yale School of Medicine in New Haven, Connecticut.

REFERENCES


20. The Not Dead

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 24 years in Psychiatric Times in a column called “Poetry of the Times.” He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts. His latest book is Freud on My Couch.
Methamphetamine-Associated Psychosis: What Should Clinicians Know?

Amy Harrington, MD; Xiaoduo Fan, MD, MPH

Background

Methamphetamine use in the United States is a growing problem, with approximately 1.6 million adults using it yearly. It can be taken orally, nasally, or intravenously to produce euphoria and mood elevation. Acute intoxication can lead to increased mental acuity and reduction in appetite. It can also inhibit fatigue, which is why it is used concomitantly with sedating substances of abuse such as alcohol or opioids. Withdrawal is associated with somnolence, reduced cognitive ability, and dysphoric or irritable mood, which can contribute to the increased risk of suicide.

There is a robust association between methamphetamine use and the development of psychotic symptoms, such as paranoid delusions, ideas of reference, and auditory hallucinations. Clinical observations suggest that there are 2 distinct types of methamphetamine-associated psychosis (MAP): Some patients have quick resolution of psychotic symptoms with cessation of substance use, but for other patients, psychotic symptoms are slow to remit. In a cross-sectional study, more than half (52%) of patients with MAP saw a remission of their psychotic symptoms within a week of abstinence from methamphetamines. Psychotic symptoms remained in 26% of patients after 1 month and in 16% of patients after 3 months. For those patients who present with persistent psychotic symptoms after methamphetamine use has stopped, it remains unclear if they are already genetically vulnerable and methamphetamine use triggers the development of a psychotic disorder. Clinical management of a patient with onset of psychotic symptoms in the context of methamphetamine use may present a challenge for psychiatric providers in an ambulatory, longitudinal treatment setting.

CLINICAL VIGNETTE

A 27-year-old man presents to an outpatient psychiatric unit for intake 5 days after discharge from an inpatient psychiatric hospitalization. He had no prior psychiatric history until 10 days before the appointment, when he was brought to the emergency department (ED) by police after his landlord called 911. The landlord told police that the patient was acting unusually, making verbal threats to other tenants, and expressing paranoid and persecutory beliefs. He required ketamine 200 mg IM before he was cooperative enough to accept IV fluid hydration. Medical work-up was within normal limits, and urine toxicology testing was positive for methamphetamines.

During the ED evaluation, he became increasingly depressed, reporting suicidal ideation and continued auditory hallucinations. He was admitted to an inpatient psychiatric unit, where he was prescribed risperidone 1 mg orally twice per day. Over the course of his hospitalization, he reported remission of suicidal ideation as well as improvement in hallucinations and his level of paranoia. He was discharged on hospital day 5. At the initial outpatient assessment, he reported adherence with risperidone since discharge and denied any psychotic symptoms. However, he was experiencing sedation during the day. Although he endorsed cravings for methamphetamine, he said he was committed to not resuming substance use. Citing the adverse effects he was experiencing, he wanted to know if he could safely discontinue the antipsychotic medication.

Approach to Treatment

Management in the acute setting: Acute onset of psychotic symptoms in a previously healthy individual requires a comprehensive evaluation. In addition to brain imaging, laboratory work including basic metabolic panel, HIV, rapid plasma reagin, and thyroid stimulating hormone can help rule out possible medical causes. IV fluids may be necessary to replace fluid loss and to address hyperthermia caused by methamphetamine intoxication.

Withdrawal from alcohol or benzodiazepines can present with psychosis, and because methamphetamine is often used in conjunction with other substances, this should be included on the differential diagnosis. Benzodiazepines are the preferred treatment in this situation, and they are used as first-line agents in the treatment of patients with agitation psychosis. Ketamine is widely used for sedation in emergency department settings and can be administered intravenously or intramuscularly. Both first- and second-generation antipsychotic medications can be used in acute management of psychotic symptoms. Neuroimaging studies demonstrate structural changes in the brains of patients who develop psychosis with the use of methamphetamine compared with those who do not develop psychosis. Changes in these brain regions have also been seen in patients with primary psychotic disorders.

Genetic studies also suggest an overlap in genes associated with the development of primary and methamphetamine-associated psychosis. Using a stress-vulnerability model of psychosis in which methamphetamine is an additional “hit” or stressor precipitating the onset of psychotic symptoms, the amount, frequency, and duration of drug use needed to cause MAP could vary greatly based on the individual’s genetic vulnerability.

Approach to Treatment

Management in the acute setting: Acute onset of psychotic symptoms in a previously healthy individual requires a comprehensive evaluation. In addition to brain imaging, laboratory work including basic metabolic panel, HIV, rapid plasma reagin, and thyroid stimulating hormone can help rule out possible medical causes. IV fluids may be necessary to replace fluid loss and to address hyperthermia caused by methamphetamine intoxication.

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agitated psychosis, often in conjunction with anticholinergic medications to prevent possible extrapyramidal symptoms.

**Treatment of prolonged psychosis:** Because MAP involves many of the same dopaminergic circuits as primary psychotic disorders, it is no surprise that many of the same antipsychotic medications can be effective in both conditions. However, it is important to recognize that psychotic symptoms related to methamphetamine use may remit with cessation of substance use, so continuous use of antipsychotic medications may not be necessary. Antipsychotic medications are associated with abnormal movements that can be permanent. They are also associated with metabolic adverse effects that can increase the risk for cardiovascular disease. The potential benefits from continuing an antipsychotic medication in a patient with MAP must be weighed against these potential risks.

A clinician should gather appropriate history to determine if psychotic symptoms or a psychotic prodrome was present prior to methamphetamine use. If there is no evidence of a preexisting psychotic disorder and if psychotic symptoms have remitted with cessation of methamphetamine use, it is reasonable to try tapering the antipsychotic medication. Patients should be seen frequently during this period to assess for the reemergence of psychotic symptoms. It can also be helpful to include a family member or other source of collateral information who can report symptoms they might observe as the antipsychotic is discontinued. Negative symptoms are less commonly seen in methamphetamine-induced psychosis, and if noted on exam, they would suggest that a primary psychotic disorder requiring ongoing treatment is more likely.

Studies suggest that second-generation antipsychotic medications are preferred over first-generation treatment in the treatment of MAP. Haloperidol and olanzapine have comparable effects with regard to psychotic symptoms; however, patients treated with olanzapine appear to tolerate the medication better due to fewer extrapyramidal adverse effects. Haloperidol and quetiapine have also been shown to have comparable therapeutic effects.

In a study comparing risperidone and aripiprazole, both medications resulted in improvement in psychotic symptoms. Participants treated with both medications reported decreases in subjective rating of cravings, although this effect was more robust in the risperidone-treated group. In addition, the dropout rate was higher and tolerability of the drug was lower in the group treated with aripiprazole, suggesting risperidone would be the preferred agent out of the 2 studied.

The evidence that antipsychotic medications, particularly second-generation antipsychotics, may reduce craving for methamphetamine suggests a role for these medications as first-line treatment in MAP. Pharmacological treatment recommendations for MAP are summarized in the Table. More research is warranted to further explore the efficacy of different antipsychotic medications to treat MAP.

**Cessation of methamphetamine use:** Treatment of MAP should focus both on alleviating the psychiatric symptoms as well as promoting abstinence from methamphetamines. The treatment of methamphetamine use disorder is challenging even in patients who have not presented with psychotic symptoms, as there are currently no US Food and Drug Administration (FDA)-approved medications for this indication.

Because replacement therapy has been successful in the treatment of other substance use disorders, such as opioid and tobacco use disorder, numerous studies have explored a role for pharmacologically produced amphetamines to treat methamphetamine use; however, the results so far seem to be disappointing. N-acetylcysteine has been studied as a potential treatment but is currently not recommended as a treatment for this patient population. In a 2021 study of people with moderate to severe methamphetamine use disorder, those receiving bupropion plus extended-release injectable naltrexone showed a small but significant improvement in methamphetamine-negative urine drug tests compared with those randomized to placebo. Oxytocin also has been explored as a possible treatment for a number of substance use disorders, including methamphetamine; the results suggest that oxytocin may be able to augment psychosocial treatments such as group therapy to increase efficacy in substance use disorder treatment.

Nonpharmacologic treatments form the current basis for treatment of methamphetamine use disorder at this time. Psychotherapeutic interventions such as cognitive behavioral therapy and continued management have shown promise in the treatment of methamphetamine use disorder. Although these treatment modalities have not been studied specifically in the MAP population, they may show some promise, particularly in medication-resistant patients. Mindfulness-based relapse prevention (MBRP), which has been shown to reduce relapse in several substance use disorders, has been studied in psychiatric patient populations and can reduce both positive and negative psychotic symptoms, suggesting its potential benefit in the treatment of MAP. Unfortunately, lower than ideal retention in studies of psychotherapeutic treatments suggests a barrier for the effectiveness of these treatments in the absence of other treatments that target physiological craving.

**Table. Pharmacologic Treatment Recommendations for Methamphetamine-Associated Psychosis**

<table>
<thead>
<tr>
<th>Time since last use of methamphetamine</th>
<th>Recommended starting dose</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 24 hours</td>
<td>Titrated to resolution of agitation: Lorazepam 2 mg po, IM or IV</td>
<td>Consider transfer to emergency-level room for management. Incorporate IV hydration. Monitor vital signs and consider cardiac sequelae of intoxication. Rule out medical etiology for acute psychotic symptoms.</td>
</tr>
<tr>
<td></td>
<td>Midazolam 2.5-5 mg IV, or 5-10 mg IM Ketamine 1-2 mg/kg IV or 3-4 mg/kg IM Haloperidol 5-10 mg po or IM Olanzapine 5-10 mg po, IM, or SL Risperidone 1-2 mg po</td>
<td></td>
</tr>
<tr>
<td>Less than 7 days</td>
<td>Titrated to resolution of psychotic symptoms: Risperidone 1-2 mg po bid Aripiprazole 10 mg po daily Quetiapine 100 mg po daily Haloperidol 2-5 mg po or IM bid</td>
<td>Evaluate for suicide risk. Evaluate for withdrawal of comorbid substance use.</td>
</tr>
<tr>
<td>Less than 30 days</td>
<td>Same as above. If symptoms resolve, slow titrate with frequent monitoring for reemergence of symptoms. If symptoms recur, resume antipsychotic medication. If depressive symptoms, consider bupropion 300-450 mg po daily, if tolerated. Otherwise, use SSRI or SNRI as indicated.</td>
<td>Address extrapyramidal adverse effects promptly. Refer for substance use treatment to prevent resumption of methamphetamine use. Obtain history to rule out premorbid psychotic disorder prior to methamphetamine use.</td>
</tr>
</tbody>
</table>

**Concluding Thoughts** As methamphetamine use continues to grow worldwide, mental health providers will encounter MAP with greater frequency in various clinical settings. Further study on both pharmacological and psychosocial treatment approaches for MAP as well as methamphetamine use disorder is still needed.

**Dr Harrington** is medical director in the department of Outpatient Psychiatry Services, associate director of the Addiction Psychiatry Fellowship program, and director of quality in the department of psychiatry at Umass Memorial Medical Center. She is also an assistant professor at the University of Massachusetts Chan Medical School. Dr Fan is a professor at the University of Massachusetts Chan Medical School and is affiliated with Umass Memorial Medical Center.

Dr Fan has received research support or honoraria from Akermes, Allergan, Avanir, Boehringer Ingelheim,
What are some of the key issues in major depressive disorder (MDD)? Here are my idiosyncratic top 8.

### 1. Accessibility

Despite the prevalence of disability, chronicity, morbidity, comorbidity, and premature mortality associated with MDD, most individuals with MDD receive inadequate treatment, if any. Members of low-income and minority populations are especially unlikely to receive treatment. But even in high-income countries, the World Mental Health Survey Initiative showed that only 22% of all individuals with 12-month MDD received minimally adequate treatment. Several factors contribute to this lack of treatment, including stigma about mental health in general and mental health care in particular, lack of knowledge about treatment availability and effectiveness, and the shortage of mental health providers both globally and in the United States.

In addition, out-of-pocket expenses may be prohibitive for individuals. Even for those with mental health insurance, it is increasingly difficult to find a provider, especially a psychiatrist, who accepts insurance. Clinicians who do accept insurance often have long waiting lists with available times that do not work for individuals with children or jobs.

Thus, unmet needs include increasing efforts to destigmatize mental health and its treatment; educating the public and clinicians about recognition, diagnosis, and effective treatments of MDD and its variants; increasing the mental health workforce; and providing better mental health care coverage.

### 2. Diagnostic challenges

Despite the prevalence of disability, chronicity, morbidity, comorbidity, and premature mortality associated with MDD, most individuals with MDD receive inadequate treatment, if any. Members of low-income and minority populations are especially unlikely to receive treatment. But even in high-income countries, the World Mental Health Survey Initiative showed that only 22% of all individuals with 12-month MDD received minimally adequate treatment. Several factors contribute to this lack of treatment, including stigma about mental health in general and mental health care in particular, lack of knowledge about treatment availability and effectiveness, and the shortage of mental health providers both globally and in the United States.

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### 3. Burnout and bereavement

Two additional diagnostic issues of impact in contemporary psychiatry are the relationships of MDD to burnout and bereavement. About 40% of health care workers experience distressing symptoms of burnout, likely even more so since the start of the COVID-19 pandemic. In working in the physician wellness arena, I see many physicians of health care workers experience distressing symptoms of burnout, likely even more so since the start of the COVID-19 pandemic. In working in the physician wellness arena, I see many physicians.
And why not include such common and disruptive symptoms as physical or psychic pain, anxiety, cognitive problems, irritability, or rumination?

Difficult-to-treat depression. The concept of TRD, based solely on failure to achieve remission with 2 or more adequately delivered medication trials, may have outlived its usefulness. A broader, perhaps more empathic, concept of difficult-to-treat depression (DTD) has been proposed to replace TRD. DTD is defined as “depression that continues to cause significant burden despite usual treatment efforts.” It considers not only symptomatic remission and response but also treatment intolerance, “poop-out,” relapse, recurrence, functioning, and quality of life.

The role of “out-of-the-box” interventional therapeutics. When I was training as a psychiatrist more than 50 years ago, we had tricyclic and monoamine oxidase inhibitor antidepressants, and we began the search for medications that were better tolerated, worked more quickly, were more effective for a broader range of patients, and had more sustainable effects. Several new medications and classes of antidepressants have been developed in the ensuing decades, but until very recently the search was focused exclusively on monoaminergic-based strategies. More recently, the discovery of ketamine’s rapidly acting, profound antidepressant and anti-suicidal effects has spurred great interest in finding other, nonmonoaminergic, “out of the box” treatments. Intranasal esketamine was the first of these to be approved, initially as an adjunctive treatment for TRD and more recently for depressive symptoms in adults with MDD and suicidal thoughts and behaviors. At the same time, we are seeing a resurgence of interest in psychedelic therapies. Several studies have suggested safety and rapidly acting effectiveness of psilocybin therapy for

Mood Disorders

Diagnosis of MDD after bereavement but in...
Physicians have rates of MDD similar to the rest of the population but are no more likely—perhaps less so—to access treatment. This is due, in part, to continued stigma related to mental illness, but also to fears regarding the consequences of diagnosis and treatment on standing in the professional community and licensing, promotion, and insurance concerns. No doubt, avoidance of treatment relates to the high suicide rates noted in physicians. Distinguishing features of physician suicide include: female physicians die by suicide more often than males in the general population; suicide is the leading cause of death among female residents; physicians are more likely to have a job problem (hence, attention to improving well-being and reducing burnout cannot be overstated); a higher proportion of physician and nurse suicide deaths are by overdose compared with the general population; depression is a significant risk factor as among nonphysician suicide deaths; and physicians who took their lives were no more likely to receive mental health treatment compared with nonphysicians who took their lives.17,18

Preventing physician suicide requires evidence-based actions that multiple stakeholder groups can take, including regulatory agencies, licensing boards, and hospital privileging boards; specialty boards, professional associations, and continuing education organizations; medical educators; and individual clinicians.19 The key is that each of these constituencies prioritizes the well-being and mental health of the health care workforce—not just physicians, but the entire teams physicians work with—so they can live fully and practice their profession at the top of their game.

The very recently passed Dr. Lorna Breen Health Care Provider Protection Act, which requires the US Department of Health & Human Services (HHS) to take actions to improve mental and behavioral health and prevent burnout among health care providers, is a major step forward. Several national initiatives to address the issues of physician well-being, burnout, and suicide have emerged. What these programs have in common is attention to evidence-based practices, safe and accessible avenues for physicians to address mental health concerns, confidential and timely follow-up, and stigma reduction.20 At UC San Diego, the Healer Education Assessment and Referral (HEAR) Program offers a comprehensive educational program, proactive screening and warm referrals, crisis intervention and critical incident debriefing, ongoing confidential counseling/therapy for house staff, group support, peer supporter training, and interdisciplinary Schwartz Center Rounds.21 Each aspect of this comprehensive program is readily transportable to other institutions.

In summary, although there has been an explosion of knowledge in the neuroscientific basis of mental disorders, genomics, neuroimaging, and neuropsychology, there remains considerable room for growth in how we provide equitable access to evidence-based treatments; define and diagnose MDD; create evidence-informed first-step and next-step, personalized treatment decisions; conceptualize TRD and consider replacing or supplementing it with DTD; develop novel interventions that provide options for better tolerated, more effective, more sustainable treatments; more effectively train future clinicians to competently employ a broader spectrum of evidence-based treatments than the current norm; and shift the culture of medicine to one that prioritizes optimizing our own wellness and mental health.

No doubt readers will have their own ideas of what deserves to be in a top 8 list and may have different perspectives on my somewhat subjective views. We would love to hear from you!
CAPLYTA is indicated in adults for the treatment of schizophrenia and depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate.

**Important Safety Information**

**Boxed Warnings:**
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.** CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies.** Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.

**Contraindications:** CAPLYTA is contraindicated in patients with known hypersensitivity to lumateperone or any components of CAPLYTA. Reactions have included pruritus, rash (e.g., allergic dermatitis, papular rash, and generalized rash), and urticaria.

**Warnings & Precautions:** Antipsychotic drugs have been reported to cause:
- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis,** including stroke and transient ischemic attack. See **Boxed Warning** to the left.
- **Neuroleptic Malignant Syndrome,** which is a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.
- **Tardive Dyskinesia (TD),** a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of TD. Discontinue CAPLYTA if clinically appropriate.
- **Metabolic Changes,** including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.

Help your patients get relief from their bipolar depression with titration-free, once-daily CAPLYTA 42 mg
Choose CAPLYTA

for a broad range of adults with bipolar depression

- Proven efficacy in bipolar depression (bipolar I & II)*
- Once-daily, titration-free dosing—patients start on the effective dose
- Broad access
- Changes in weight and akathisia were similar to placebo at week 6
  • Antipsychotic drugs have been reported to cause metabolic effects and tardive dyskinesia
  Please see Important Safety Information below.

• Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases). Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.
• Orthostatic Hypotension and Syncope. Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.
• Falls. CAPLYTA may cause somnolence, postural hypotension, and motor and/or sensory instability, which may lead to falls and, consequently, fractures and other injuries. Assess patients for risk when using CAPLYTA.
• Seizures. Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.
• Potential for Cognitive and Motor Impairment. Advise patients to use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.
• Body Temperature Dysregulation. Use CAPLYTA with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.
• Dysphagia. Use CAPLYTA with caution in patients at risk for aspiration.

Drug Interactions: Avoid concomitant use with CYP3A4 inducers and moderate or strong CYP3A4 inhibitors.

Special Populations: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Breastfeeding is not recommended. Avoid use in patients with moderate or severe hepatic impairment.

Adverse Reactions: The most common adverse reactions in clinical trials with CAPLYTA vs placebo were:
  • Schizophrenia: somnolence/sedation (24% vs 10%) and dry mouth (6% vs 2%).
  • Bipolar Depression (Monotherapy, Adjunctive therapy): somnolence/sedation (13% vs 3%, 13% vs 3%), dizziness (8% vs 4%, 11% vs 2%), nausea (8% vs 3%, 9% vs 4%), and dry mouth (5% vs 1%, 5% vs 1%).

Please see the accompanying Brief Summary of Prescribing Information on the following pages.

References: 1. CAPLYTA prescribing information, 2021.

Scan QR code to request samples or a visit from a sales representative

See its efficacy at caplytahcp.com
INDICATIONS AND USAGE
CAPLYTA is indicated for the treatment of schizophrenia in adults and depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

DOSEAGE AND ADMINISTRATION
Recommended Dosage: The recommended dosage of CAPLYTA is 4 mg administered orally once daily with or without food. Dose titration is not required.

Dosage in Elderly Patients: Use of CYPP3A Inducers and Moderate or Strong CYPP3A Inhibitors: Concomitant use of CAPLYTA with CYPP3A inducers, moderate or strong CYPP3A inhibitors may result in decreased lumateperone exposure (AUC and Cmax). Avoid concomitant use of CAPLYTA with moderate or strong CYPP3A inhibitors.

Dosage Recommendations for Patients with Hepatic Impairment: Avoid use of CAPLYTA in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

CONTRAINDICATIONS
CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone. Reactions have included pruritus, rash, (e.g., allergic dermatitis, papular rash, and generalized rash), and urticaria.

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), largely in patients taking typical antipsychotic drugs, revealed a risk of death increased to approximately 2.6 times that in placebo groups. 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 placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be cardiovascular in nature. Postmarketing data suggest that elderly patients treated with antipsychotics are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking typical antipsychotic drugs, revealed a risk of death increased to approximately 2.6 times that in placebo groups. 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 placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be cardiovascular in nature.

Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults: In pooled analyses of placebo-controlled trials of antipsychotic drugs, a total of 26,462 patients were treated, and 6,852 patients were treated with placebo. The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than placebo) for CAPLYTA 42 mg were: nausea, vomiting, dyskinesia, parkinsonian akathisia, and somnolence. These adverse reactions were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 8%, 5%, and 4% for total cholesterol, triglycerides, and LDL cholesterol, respectively. Bipolar Depression - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the proportion of patients with a shift from normal to high were 10%, 5%, and 2% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

Weight Gain - Weight gain has been observed with use of antipsychotics. Monitor weight at baseline and frequently thereafter.

Schizophrenia - In pooled data from placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study was similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately -3.2 kg (SD 7.4) at Day 590.

Bipolar Depression - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 4 months in patients with bipolar depression, the mean change in body weight was -1.0 kg (SD 3.1) at Day 175.

Falls: Antipsychotics, including CAPLYTA, may cause somnolence, postural hypotension, and motor and sensory disturbances, which may lead to falls and related fractures. Patients with progeria may have these problems.

Orthostatic Hypotension and Syncope: Antipsychotics may cause hypotension, especially in the elderly. Patients should be monitored for hypotension.

Antipsychotic drugs have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus - Hyperglycemia, in some cases extreme and associated with ketoadiposis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperglycemia in patients treated with CAPLYTA. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Hyperglycemia and Diabetes Mellitus - Hyperglycemia, in some cases extreme and associated with ketoadiposis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperglycemia in patients treated with CAPLYTA. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.
Dysphoria: Esophageal dysmotility and aspiration may have been associated with antipsychotic drug use. Antipsychotic drugs, including CAPLYTA, should be used cautiously in patients at risk for aspiration.

ADVERSE REACTIONS
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. The safety of CAPLYTA has been evaluated in placebo-controlled clinical trials in 2,644 adult patients with schizophrenia. In a 6-week, placebo-controlled trial in which CAPLYTA was administered at a daily dose of 42 mg (n=406) in patients with at least 6 months of exposure and 108 at least 1 year of exposure to the 42-mg dose of CAPLYTA. Schizophrenia - The following findings are based on the pooled short-term (2- to 6-week), placebo-controlled trials conducted with CAPLYTA. Headache and mild to moderate dyspeptic symptoms were reported in 3% and 3% of patients, respectively, during clinical trials, with the incidence of these symptoms being higher in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) were somnolence/sedation, dizziness, nausea, and dry mouth. Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) were as follows: (adverse reaction is followed by percentage of patients treated with CAPLYTA 42 mg (n=406) and patients treated with placebo (n=122) in parentheses). Somnolence/Sedation (24%, 10%), Nausea (9%, 5%), Dry Mouth (8%, 2%), Dizziness (5%, 3%). Clinical judgment was made by the investigator or other practitioners of the need for the therapy, placebos, and other treatments, the severity of the disease, the severity of adverse reactions associated with the therapy, other drug concomitantly used, or other circumstances. The following findings are based on the pooled short-term (6-week), placebo-controlled monotherapy bipolar depression studies in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=372).

In the 6-week, placebo-controlled bipolar depression trial in patients treated with CAPLYTA 42 mg (n=217) and placebo (n=110) patients, adverse reactions were as follows: (adverse reaction is followed by percentage of patients treated with CAPLYTA 42 mg (n=217) and placebo (n=110)) in parentheses. Somnolence/Sedation (13%, 3%), Dizziness (4%, 4%), Nausea (8%, 3%), Dry Mouth (5%, 1%), Diarrhea (4%, 3%), Vomiting (4%, 0%), Abnormal Involuntary Movement (AIMS) scale for dystonia and tremor (total score ranges from 0 to 6), Pooled data from short-term (4- to 6-week), placebo-controlled schizophrenia trials, the frequency of reported events related to extrapyramidal symptoms (EPS), including akathisia, extrapyramidal disorder, muscle spasms, restlessness, muscle stiffess, stiffness, dystonia, dyskinesia, muscle twitching, tardive dyskinesia, tremor, dizziness, abnormal movements (ie, AIMS scale) for dystonia (total score ranges from 1 to 28).

In placebo-controlled clinical trials, the frequency of serious adverse reactions in adult patients treated with CAPLYTA 42 mg (n=217) was as follows (adverse reaction is followed by percentage of patients treated with CAPLYTA 42 mg (n=217) and placebo (n=110)) in parentheses. Somnolence/Sedation (2%, 1%), Dizziness (1%, 2%), Nausea (9%, 5%), Dry Mouth (5%, 1%), Diarrhea (3%, 2%), Upper respiratory tract infection (1%, 2%), Blurred vision (3%, 1%), Increased blood prolactin (2%, 0%), Dizziness, dizziness postural.

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. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with higher potency and higher doses of first-generation antipsychotic drugs. An elevated rate of acute dystonia is observed in males and younger age groups.

Extrapyramidal Symptoms (EPS) - In the short-term, placebo-controlled schizophrenia and bipolar depression studies in which CAPLYTA was administered at a daily dose of 42 mg (n=372), the following findings are based on the pooled data from the Simpson-Angus Scale (SAS) for EPS (total score range from 0 to 60) study (placebo treated patients at 0 mg/day and CAPLYTA treated patients at 2.1 mg/day). The mean change from baseline for CAPLYTA-treated patients and placebo-treated patients were -0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and -0.1 and 0 for the AIMS, respectively.

In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.

In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.
Psychiatry and Psychotherapy

The Great Divorce That Never Happened

Mark L. Ruffalo, MSW, DPsa; and Daniel Morehead, MD

A frequent criticism of psychiatry is that psychiatrists do not learn, practice, or value psychotherapy. Even critics within the field routinely complain that psychiatry has “lost its mind,” whereas outside critics frequently portray toxic biological psychiatrists in competition with humane psychotherapists from other disciplines. The psychiatrist, as the story goes, is interested only in diagnosing and medicating patients—not in understanding, supporting, or working psychotherapeutically with them. This story, widely reported as fact in the media, is an outdated, harmful myth—one that discounts the realities of psychiatric patients—not in understanding, supporting, or working psychotherapeutically with them.

In the mid-20th century, psychotherapy was the treatment of choice for most mental disorders. Even after the development of the first effective psychotropic medications in the 1950s and 60s, psychotherapy remained the mainstay of psychiatric treatment, especially in the psychoanalytically dominated United States. By the late 1980s, however, the field had shifted in a biological direction. The development of selective serotonin reuptake inhibitor antidepressants in particular led to great excitement in the promise of biological investigation and treatment. Nevertheless, psychotherapy continues to be practiced by psychiatrists, with some devoting their academic and clinical careers to the study and practice of psychotherapy.

1 Psychiatry residents receive significant formal instruction in psychotherapy.

One of us (DM) is director of residency training at a psychiatry department in the Northeast; the other (MR) teaches in that program and serves as codirector of the psychotherapy track for a psychiatry residency program in Florida. As such, we have direct knowledge of the quality and extent of training psychiatry residents receive in psychotherapy. By contrast, most critics of psychiatry do not teach in psychiatry departments and have little to no firsthand knowledge of psychiatric residency curriculum.

Training in supportive, psychodynamic, and cognitive-behavioral psychotherapy is nationally mandated for all psychiatry residents. Residents must also learn to integrate psychotherapy with psychopharmacology and spend substantial time practicing psychotherapy during their outpatient training. They attend several yearlong didactic courses in psychotherapy and are individually assigned psychotherapy supervisors (many of whom are psychiatrists). Didactic instruction typically covers a range of psychotherapy topics, such as case clinical formulation, transference, countertransference, and psychotherapeutic technique. Clinically, residents see patients for short-term and longer-term psychotherapy treatments.

Approximately a quarter of psychiatry residencies also offer specific psychotherapy tracks for residents with particular interest in psychotherapy and for those who plan to pursue additional training in specific psychotherapies (e.g., psychoanalytic training) postresidency. Many individuals, even mental health professionals, assume psychotherapy training is weaker for psychiatry than for other mental health disciplines such as psychology and social work. Yet a national survey published in 2006 showed that psychiatry compared favorably to other disciplines for evidence-based forms of therapy training. Thus, the claim that psychiatrists do not learn psychotherapy is false.

2 Psychotherapy is a part of almost all clinical interactions.

Although most psychiatrists nowadays do not offer traditional 45-minute or 60-minute psychotherapy appointments to all their patients, psychotherapy continues to be practiced in some form by most psychiatrists. From a psychodynamic perspective, every interaction between doctor and patient, even in the hospital setting, is an opportunity to relate to the patient psychotherapeutically. Sudak and Taormina have described the integration of cognitive-behavioral therapy into medication management visits, and Iannitelli et al have recently discussed the application of psychodynamic principles during psychopharmacological treatment.

Undoubtedly, most psychiatrists engage in some supportive psychotherapy even during brief visits and even if they do not formally label or bill the sessions as such. Moreover, in their study, Tadmon and Olfson found that 47% of psychiatrists continue to offer 45-minute to 60-minute psychotherapy sessions to patients. Thus, claims that psychotherapy has simply disappeared from psychiatric practice are false.

3 In the past decade, there has been a resurgence of interest in psychotherapy and psychosocial approaches among psychiatry residents.

A 2012 survey of residents reported that 82% of them consider “psychotherapy to be integral to their identity as psychiatrists.” Another survey showed that residents want more psychotherapy training rather than less. Our experience matches the results of such research. In fact, we have observed an increasing number of psychiatry residents interested in learning and practicing psychotherapy during the past decade.

In recent years, psychiatry has become a popular and competitive specialty choice among medical students, who describe their interest in learning the art of engaging deeply with suffering patients and combining psychosocial treatments with biological interventions. Many residents are particularly eager to learn psychotherapy methods and rightfully view psychotherapy as a core, foundational skill in the practice of clinical psychiatry. Meanwhile, some professional organizations are specifically devoted to the advancement of psychotherapy training within psychiatry, such as the American Academy of Psychodynamic Psychiatry and Psychoanalysis.
Many leading psychotherapy scholars are psychiatrists, and this has been the case for decades.

Some of the leading figures in American and global psychotherapy are psychiatrists, including Otto Kernberg, MD; Glen Gabbard, MD; and the recently deceased Aaron Beck, MD, father of cognitive-behavioral therapy. Several psychiatrists who are leading researchers in psychopharmacology have also undertaken research validating medical psychotherapy. Psychiatrists make up a significant percentage of membership of the American Psychoanalytic Association. They are also frequent presenters at national psychotherapy conferences and contributors to psychotherapy journals. The American Journal of Psychotherapy, a leading journal of psychotherapy theory and practice, is a journal of the American Psychiatric Association. Thus, the psychiatric profession remains integral to psychotherapy development and research.

Concluding Thoughts

Psychotherapy continues to be a core aspect of psychiatrists’ training and identity. Psychotherapy training also continues to be a substantial and mandatory component of residency training for all psychiatrists. Contrary to popular assumptions, it is not critical that all psychiatrists conduct traditional psychotherapy as part of their practice. No one becomes alarmed if all cardiologists do not practice cardiac catheterization, and no one becomes alarmed if all psychiatrists do not practice psychotherapy. Psychiatry continues to be a core component of residency training for the general psychiatry residency programs: a proxy for trends in psychotherapy education? Acad Psychiatry. 2020;44(4):423-426.

In brief, if all psychiatrists conduct psychotherapy as part of their training for the general psychiatry residency programs: a proxy for trends in psychotherapy education? Acad Psychiatry. 2020;44(4):423-426.

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Dr Ruffalo is an instructor of psychiatry at the University of Central Florida College of Medicine in Orlando and an adjunct instructor of psychiatry at Tufts University School of Medicine in Boston, Massachusetts. He is a psychodynamic psychotherapist in private practice in Tampa, Florida. Dr Morehead is a psychiatrist and director of training for the general psychiatry residency at Tufts Medical Center in Boston. He frequently speaks as an advocate for mental health and is a author of Science Over Stigma: Education and Advocacy for Mental Health, published by the American Psychiatric Association.

Concluding Thoughts

Psychotherapy continues to be a core aspect of psychiatrists’ training and identity. Psychotherapy training also continues to be a substantial and mandatory component of residency training for all psychiatrists. Contrary to popular assumptions, it is not critical that all psychiatrists conduct traditional psychotherapy as part of their practice. No one becomes alarmed if all cardiologists do not practice cardiac catheterization, and no one should worry that “only” half of all psychiatrists currently offer traditional 45-minute psychotherapy sessions. But all psychiatrists should continue to support psychotherapy’s place in mental health treatment and in the holistic, biopsychosocial treatment that psychiatrists routinely offer.

For decades, critics and leading psychiatrists have worried that psychotherapy among psychiatrists will one day die out and be forgotten. Yet for decades, reports of its demise have been greatly exaggerated.

Amo Bloom does not waste any time. You learn the arc of her story in the first 3 pages of In Love: A Memoir of Love and Loss. The author’s spirited and charming husband, Brian, has developed Alzheimer disease. Amy and Brian adore traveling, sharing water and gum on their airplane trips, including one to Switzerland. They are in love. And Brian has decided to end his life by “accompanied suicide” at Dignitas in Zurich.

First is the book’s dedication: “For Brian.”

Then, the epigraph: “ ‘Please write about this,’ my husband said.”

And on to Part 1: “Sunday, January 26, 2020, Zurich, Switzerland.”

Why read such a book? The whole story is foretold at the outset. There are no surprises. The subject is terribly controversial and downright depressing. But In Love is not about death. It is about life—an ode to Amy and Brian’s deep and touching intimacy that endures to the end. The book is creatively crafted, shifting back and forth in time, the way associative memory moves from past to present and from inner thoughts to outer realities. Along the way, there is a lot for psychiatrists to learn.

Alzheimer disease moves in with a family, quietly at first. Even once a patient or family member finds the courage to seek medical consultation, they likely will still have doubts about whether something is really the matter. If they enter a psychiatrist’s office—for the first time or the hundredth time—they might be thinking that cognitive changes are due to depression, anxiety, stress (of which there is no

In Love: A Memoir of Love and Loss
by Amy Bloom
(Random House; 2022)
240 pages

Amy Bloom
Barbara Schildkrot, MD; Karen Greenberg, MD
shortage), transient postanesthesia memory impairment, sleepless nights, or normal aging. They might describe increasing tension with a spouse, a boss, or adult children. Would you recognize the early signs of this degenerative disease in such presentations?

Approximately 6.5 million Americans are living with Alzheimer disease today, and that number is projected to rise to about 13 million by 2050.1 Whatever your practice may be, you will surely see patients with Alzheimer disease or their family members. We now know that brain changes that characterize the disease begin to appear approximately 10 years before clinical symptoms—long before mild cognitive impairment and very long before mild dementia. Brain MRI, neuropsychological testing, and amyloid and tau PET scans are useful diagnostic tools, and in most cases, it is possible to make a definitive diagnosis based on cerebrospinal fluid biomarkers. Numerous blood assays have already been developed and are being studied to determine which are the best predictors of cognitive decline.

The US Food and Drug Administration (FDA) recently approved Aduhelm (aducanumab) for the treatment of early Alzheimer disease. Aduhelm is a monoclonal antibody that targets beta-amyloid plaques in the brain. Approval of the drug has been controversial, largely because of its small effect size in combination with a high incidence of serious adverse effects, as well as its $28,000-a-year price tag: Medicare will cover Aduhelm only for patients in clinical trials. Nonetheless, the indications for this medication are a wake-up call to clinicians: It is prescribed only for the treatment of mild cognitive impairment or early dementia caused by Alzheimer disease. Early identification is crucial. And while we do not yet have an altogether safe and effective pharmacologic treatment or early dementia caused by Alzheimer disease, a gift and a tragedy. Approval of the drug has been controversial, largely because of its small effect size in combination with a high incidence of serious adverse effects, as well as its $28,000-a-year price tag: Medicare will cover Aduhelm only for patients in clinical trials. Nonetheless, the indications for this medication are a wake-up call to clinicians: It is prescribed only for the treatment of mild cognitive impairment or early dementia caused by Alzheimer disease. Early identification is crucial. And while we do not yet have an altogether safe and effective pharmacologic treatment or early dementia caused by Alzheimer disease.

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The book describes Amy and Brian’s encounters with numerous physicians. Two of them in particular, Brian’s neurologist and psychiatrist, Amy writes, “are for me the villains of this story.” They, along with Brian’s internist, “failed him,” states Amy. There is also a hero for Amy, however; her psychiatrist, who interviewed Brian and wrote a decisive letter to Dignitas describing Brian’s life story and mental status. Would you have written such a letter, participating in the Dignitas process and potentially facilitating Brian’s accompanied suicide?

REFERENCE

HMS Center for Bioethics.

Dr. Schildkraut is an assistant professor of psychiatry, part-time, at Harvard Medical School (HMS) in the Department of Psychiatry at Brigham and Women’s Hospital. She is the author of several books and a blog. Dr. Greenberg is an affiliated physician, Beth Israel Deaconess Medical Center; part-time instructor, HMS; and fellowship alumnus, HMS Center for Bioethics.  

Where did it come from? Take it down! And Brian looked at me with puzzled, irritated concern and said, in effect, What glass? And, Please please stop complaining about this thing that isn’t even there.

I called the neurologist and made an appointment.

In Love revolves around the pivotal decision that followed Brian’s Alzheimer disease diagnosis: “It took Brian less than a week to decide that the ‘long goodbye’ of Alzheimer’s was not for him.” Brian was a lover of life—a “big, handsome man with a big laugh” who thrived on good food and good conversation. When he joined his men’s book club, he announced the reason: “I love a good read, and I love intimacy.” Only 66 years old, he was unswerving in his plan: “I’d rather die on my feet than live on my knees.” … He did not want the onslaught of his disease to steal his ability to end it all.

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Given Brian’s slipping cognition, he asked Amy to find an effective way for him to end his own life without implicating her in a murder. He wanted Amy at his side, and he wanted the method to be peaceful and 100% foolproof in order to avoid catastrophic disability. Amy’s painstaking research uncovered a truth that most Americans do not know: It is simply not possible to end one’s life on one’s own terms in the United States if you have a deteriorating illness.

Medical aid in dying (MAID) is legal in 10 states and the District of Columbia— together, areas in which about 22% of the US population reside—under statutes using language such as “death with dignity” as opposed to the more provocative “physician-assisted suicide.” However, all MAID laws in the United States require that a patient have a prognosis of 6 months or less to live and also be competent to make an informed life-and-death decision. Individuals with neurodegenerative diseases are effectively excluded.

Here is where Dignitas ("To live with dignity") comes in. Brian said, “I don’t want to end my life... but I’d rather it end while I am still myself, rather than become less and less of a person.” Switzerland is one of the many countries that do not require individuals to be terminally ill to access MAID, but it is the only country in the world where foreigners are eligible—hence Amy and Brian’s trip to Zurich, where Dignitas, a nonprofit organization, is headquartered.

The Dignitas admissions process is arduous and includes extensive paperwork, doctors’ letters, multiple telephone interviews, and dental records for identification after death. Once in Zurich, Brian still had to meet twice with a Dignitas physician to get final approval. At each point, Brian was in charge of the choices. After he and Amy took a car to the Dignitas apartment on the outskirts of town, Brian chose to swallow the prescribed antiemetic followed by sodiumpentobarbital. With Amy holding his hand, Brian ended his life, as 3000 others had done before him. For Amy and Brian, access to Dignitas was at once a gift and a tragedy.

How would you have worked with Brian and Amy? Are all suicides the same? Is a thoughtfully planned, accompanied suicide different from a suicide motivated by mental illness and excruciating psychic pain? In Love leaves us with much to contemplate and reflect upon.

The book describes Amy and Brian’s encounters with numerous physicians. Two of them in particular, Brian’s neurologist and psychiatrist, Amy writes, “are for me the villains of this story.” They, along with Brian’s internist, “failed him,” states Amy. There is also a hero for Amy, however; her psychiatrist, who interviewed Brian and wrote a decisive letter to Dignitas describing Brian’s life story and mental status. Would you have written such a letter, participating in the Dignitas process and potentially facilitating Brian’s accompanied suicide?

Psychiatric Times™ has been hosting a spirited debate on this topic since 2018, which is summarized in “Physician-Assisted Suicide: A Pressing Question of Ethics and Humanity.” In Love is a short but compelling read that is likely to elicit strong feelings on both sides of the debate.

Would you have written such a letter, participating in the Dignitas process and potentially facilitating Brian’s accompanied suicide?

Dr. Schildkraut is an assistant professor of psychiatry, part-time, at Harvard Medical School (HMS) in the Department of Psychiatry at Brigham and Women’s Hospital. She is the author of several books and a blog. Dr. Greenberg is an affiliated physician, Beth Israel Deaconess Medical Center; part-time instructor, HMS; and fellowship alumnus, HMS Center for Bioethics.
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What Is an Effect Size?

When we read studies and meta-analyses, we often see the terms statistical significance and effect size. Most of us are familiar with the concept of statistical significance. A finding is said to be statistically significant if it is unlikely to occur by chance. Most often, experimenters set a level of statistical significance of 0.05 or \( P = .05 \). This means that we accept the finding as statistically significant only if there is a less than 5 in 100 or 5% probability of the finding occurring by chance. Whether a finding is statistically significant depends in part on how many participants are in the study. Larger studies are more likely to find statistical significance than smaller ones.

Medical researchers have long used the concept of statistical significance. However, in recent years, many researchers have argued that we overvalue statistical significance and that we need to pay more attention to effect size.

An effect size is a measure of (1) the amount of change in a sample of patients who undergo a treatment or, more commonly, (2) the amount of change in a sample of patients who undergo a treatment compared to a control group. An effect size tells us how much difference a treatment makes.

A treatment effect can be statistically significant but so small as to be clinically meaningless. For example, a meta-analysis evaluated the effect of treating patients with Alzheimer disease with the combination of a cholinesterase inhibitor and memantine. In terms of both cognitive functions and behavioral disturbance, the effect was statistically significant but small enough to be clinically meaningless.

There are many ways to measure effect size. We could measure the change in a biological parameter such as weight lost in kilograms when a patient takes semaglutide versus placebo. We could measure the percentage of weight lost or the percentage of body fat lost.

We could measure the change in a rating scale such as the Patient Health Questionnaire–9 (PHQ-9), used to rate severity of depression, when we treat patients with depression with psychotherapy versus a waiting list control. The range of scores on the PHQ-9 runs from 0 to 27, where an increasing score represents increased depression. We could measure the percentage of patients who meet a defined end point. For example, we could determine the percentage of patients taking an antidepressant who have a 50% reduction in PHQ-9 score. A 50% reduction would be considered a response. On the PHQ-9, a reduction to 4 or less would be considered remission.

We could also assess how many patients taking a medication versus placebo we would have to treat so that 1 additional active-treatment patient would meet a predetermined end point, such as remission. This is called a number needed to treat (NNT). For example, if 40% of patients taking an antidepressant go into remission and 20% of placebo-treated patients go into remission, the NNT is calculated as:

\[
\frac{40}{20} = 2
\]

This means we would have to treat 5 individuals with the antidepressant to achieve 1 remission attributable to the antidepressant. Typically, an NNT of 3 would be considered a strong effect, 5 a medium effect, and 7 a small effect.

Researchers sometimes report a risk ratio. Despite incorporation of the word risk, a high-risk ratio is not always bad. Imagine, for example, a group of patients taking an antidepressant for depression and another group taking a placebo. If 40% of the patients taking the antidepressant achieved remission compared with 20% of the patients taking the placebo, then the risk ratio is:

\[
\frac{40}{20} = 2
\]

The risk ratio of 2 says that the patients treated with the antidepressant were twice as likely to go into remission as the patients who took the placebo.

Experimenters sometimes report odds ratios. Odds ratios are mathematically more complicated than risk ratios; they are nonlinear and not intuitive. It is difficult to make much sense of odds ratios in deciding whether to offer a particular treatment.

Many studies and meta-analyses report effect sizes as standardized mean differences (SMDs). Doing this makes the most sense in meta-analyses. A meta-analysis combines the effect sizes from 2 or more trials. Sometimes different trials use different rating scales. One trial involving a particular antidepressant might use the Montgomery-Åsberg Depression Rating Scale (MADRS), and another might use the Hamilton Depression Rating Scale (HDRS). The highest score on the MADRS is 60, and the highest on the HDRS is 53. For this and other reasons, we cannot simply synthesize the numbers from the 2 scales. To combine the results from different scales, we convert the results from each into an SMD and then we can combine the results.

An SMD is a difference measured as a proportion of a standard deviation. As an example, consider a single trial using 1 scale: the PHQ-9. Imagine a sample of patients with depression who have an average PHQ-9 score of 19. Some patients are more depressed than others, and the sample is distributed on the bell curve in black, as shown in Figure 1.

If we treat some patients with an antidepressant and some with placebo, the sample gets better overall. The bell curve shifts to the left, as illustrated in yellow in Figure 2. The average score is now 12.
Opioid Treatment “Mismatch” Threatens Vulnerable Communities

Richard Payerchin

A “mismatch” between opioid treatment locations and vulnerable communities across the United States could lead to disruptions in care for patients in times of disaster, according to a new study.1 The research is a result of collaboration across the Yale Program in Addiction Medicine and SEICHE Center for Health and Justice and the University of Chicago’s Healthy Regions & Policies Lab at the Center for Spatial Data Science.

Pandemics like COVID-19 and natural disasters, such as tornadoes, hurricanes, and wildfires, could disrupt access to buprenorphine, methadone, and extended-release naltrexone—all medications for opioid use disorder (MOUDs), lead study author Paul Joudrey, MD, MPH, said in a press release.1 Joudrey is assistant professor of medicine and a Yale Drug Use, Addiction, and HIV Research scholar at Yale School of Medicine in New Haven, Connecticut.

“In plain terms, we are not placing enough services in communities that are more vulnerable to disasters and pandemics,” Joudrey further explained. “If a disaster disrupts medication services, people living within these communities are less likely to receive treatment.”

This mismatch between community vulnerability during disaster and the availability of services was the worst for vulnerable suburban communities—a particularly unique finding, Joudrey added.

“Also we also found that in rural communities, because the availability of services was just bad all around, there was no association between vulnerability and access to medications.”

The study compared treatment facility locations with residents’ social vulnerability across 32,434 zip codes in the United States. The social vulnerability index measured 4 issues: socioeconomic status, household composition and disabilities, racial and ethnic minority status and language, and housing type and transportation.

The investigators found that “zip codes with greater social vulnerability did not have greater geographic access to each of the 3 MOUDs, showing the degree to which the United States falls short of ensuring equitable access to all MOUDs, especially during natural disasters.”

In addition, almost 25% of the US continental population lives without access to the medications within a 30-minute drive.

The authors called for MOUD policy and delivery innovations “to address urban-rural inequities and better match the location of services to communities with greater social vulnerability to prevent inequities in opioid overdose deaths during future disasters.”

REFERENCES

Although the effects were statistically significant, the effect size was so small as to not be clinically meaningful on average.
Perspective on Correctional Psychiatry

Amar Mehta, MD:

An Insider’s Behind Bars: CLINICAL CONVERSATIONS

JULY 2022 www.psychiatrictimes.com

nonviolent in hospital settings over prison settings. We make every effort to treat people with primary, and without being recognized.

ation but very often predating their incarceration. Anxiety disorders, sometimes related to their situ-

treatment. That is just a single slice in time, of course, as there are always patients cycling through the system. We try to be as accessible as possible to anyone who wants to tackle these often long-standing issues while incarcerated.

According to some studies, about 65% of prison inmates have a substance use disorder, with another 20% were under the influence of drugs or alcohol at the time of their crime. We know there is a large nexus between substance use disorders and other mental illnesses, especially trauma, and we work hard to identify and treat as many as we can while we have the shared opportunity with these patients.

There also is a high prevalence of mood and anxiety disorders, sometimes related to their situation but very often predating their incarceration and without being recognized.

There are also personality disorders, of course, with a wide range of estimates.

PT: How often do individuals arrive with a diagnosis versus receive a diagnosis after incarceration?

Mehta: All inmates are initially transferred through one of our reception centers for classification and assignment, and they are all screened for mental illness in that process. About 23% to 33% screen into mental health care from that initial step, and that roughly correlates with our total prevalence of psychiatric disorders in the whole prison population (33%). Although a substantial proportion of these individuals had mental health involvement prior to their arrival, for many patients this is their first opportunity to address those issues with the attention they deserve.

PT: Does mental health stigma continue into the correctional psychiatry system? What role does psychoeducation play in this setting?

Mehta: Although stigma has decreased throughout American society in the last couple of decades, there are still misconceptions and biases about mental illness and it still may be perceived as a weakness rather than an illness.

Many groups in prison culture don’t allow their peers to receive these services, no matter how much they may be suffering. Mental health staff have worked to be nonjudgmental, nonthreatening, and approachable while providing services like skills-based groups for people that do not officially belong to the mental health program.

Psychoeducation is a key part of all mental health treatment, but perhaps more than ever in this cohort. Many of our patients have not previously encountered accurate information about mental illness, and this socioeconomic group is chronically underserved in many areas of health care, especially mental health. Thus, psychoeducation is an important part of both treatment and educating the general prison population to recognize signs and symptoms that could benefit from help.

PT: What are the top treatment challenges in correctional psychiatry today, and how do they differ from those in mainstream psychiatry?

Mehta: Health care staffing is a nationwide—and indeed, worldwide—issue. Severe shortages throughout the country make hiring an extremely competitive environment, with special challenges in overcoming the stigma of prison work.

The fact is that these patients have a huge capacity to improve their lives, far more than the average person. The work done with them in a clinical setting echoes throughout their families and communities and can be some of the most rewarding work for clinicians.
The fact is that these patients have a huge capacity to improve their lives, far more than the average person. The work that is done with them in a clinical setting echoes throughout their families and communities and can be some of the most rewarding work for clinicians. Although some illnesses are deeply rooted and slow to change, this is the perfect place for our patients to work on these issues and their mental health.

In addition, limits imposed on correctional psychiatry by conventions and inertia can make it harder to remain nimble and keep up with the most advanced treatment modalities, including telepsychiatry and emerging psychopharmacological and technological breakthroughs.

PT: It sounds as though these challenges can be overwhelming. How do you address them?

Mehta: Quite simply: Through focused, targeted battles. We have made huge strides in establishing the largest correctional telepsychiatry program in the country, and we work hard every day to ensure that our well-trained physicians can practice psychiatry to the fullness of their abilities.

PT: Some of the complaints and struggles from psychiatric clinicians revolve around coverage of care, including psychopharmacology. Are these experiences similar in correctional care settings?

Mehta: One of the best things about working in prison is the focus of attention we are able to bring to the treatment of relevant symptoms. Because our patients have fully state-sponsored health care, our physicians do not have to seek authorization from insurance companies. Laboratory testing is at the discretion of the provider, including [obtaining] blood levels for a very wide variety of medications.

Due to the volume of patients in our system, there are collective bargaining agreements for certain medications. However, the formulary is robust. In addition, nonformulary medications do not require a specific external approval process, and their use is largely left up to the provider to determine clinical appropriateness.

Some specific medications are restricted, such as benzodiazepines primarily prescribed for catatonia, but this can also be seen as a benefit because of the challenges faced by providers in the community.

PT: In some ways, correctional settings may have advantages compared with practicing in the general community.

Mehta: There are a few myths in correctional psychiatry that need to be addressed.

1. “People in prisons are bad people, and they deserve bad things happening to them. Criminals don’t matter as long as they’re locked up, and we can just forget about them.”

At least 95% of all inmates in the United States will be released back into the community. And we incarcerate a lot of people. So whatever happens to them while they are in custody or a correctional setting, they will take that experience back out into the general public.

We need to be setting up these individuals with the best chance to succeed after their release. Currently, the United States has depressingly high rates of reoffending and that is a failure on all of our parts as a society. These individuals can succeed if given the right resources; we could have less crimes committed and less people in prisons. Mental health treatment is a great first step toward making that kind of change a reality.

2. “It’s too dangerous to work in a prison.”

I have worked in emergency departments, inpatient hospitals, outpatient clinics, jails, and prisons in multiple states. Patients in prisons tend to be much more stable than their counterparts in jails because they have been sentenced and have been in custody for some time. This comparison extends to emergency departments as well, to a degree; some inmates will, of course, require treatment at the level of an emergency department at some point, but long periods of decompensation without recognition are rarer with so many eyes on the patient at all times.

Inpatient hospitals may have patients with mental illness who are violent, and these situations generally are handled by health care staff, possibly augmented by security guards. Alternatively, they can transfer the patient. Prisons have trained custody officers throughout the facility who monitor the environment at all times and respond immediately to emergencies to protect staff and other inmates. Plus, outpatient clinics have a huge volume of patients pass through at any given time, while prisons represent a relatively stable population for defined periods of time.

3. “Only bad doctors go to work in prisons.”

As prison salaries have become more competitive due to the need for quality health care, highly qualified physicians have increasingly turned to correctional health care settings for their careers. Dedicated and caring providers with a sense of social justice and the desire to help those that need it the most have found long-term, stable jobs at our prisons. Many clinicians are double or triple board certified, and they are committed to the impact they can make by serving this population.

What are other benefits of working in a correctional setting? What attracted you to the field and practice setting?

Mehta: One big advantage is that no patient in our system is ever completely lost to follow-up. They have the right to refuse treatment, but as long as they participate, they are in a constantly monitored setting with good communication about their level of functioning. Similarly, if laboratory testing is required, it will happen promptly or you will be informed of any refusal promptly. This allows for rapid decisions on titrations and next steps. Relationships with the patient are not complicated by disability evaluations, barriers from insurance coverage, or friction from many common controlled substances. Incarcerated individuals are disproportionately representative of severely underserved populations, and these settings also house the highest concentration of severely mentally ill patients in the United States. Prisons constitute a tightly controlled environment that drastically reduces the variables that can drive a community provider crazy, which I definitely like. I am part of a huge team of like-minded colleagues that work together toward the same goals, and we have stable and equal compensation, good benefits, and a very accommodating work-life balance.

PT: Thank you for sharing your insights. Is there anything else you want to share with readers?

Mehta: Being a psychiatrist for patients in prison is a great way to challenge yourself and achieve the job satisfaction that can only come from knowing your work is critically important. You can elevate your practice of medicine to the highest levels with patients that appreciate your time and effort and stand to benefit a huge amount from your help.

Dr Mehta is deputy director of the Statewide Mental Health Program at the California Department of Corrections and Rehabilitation in Sacramento. Previously, he was the statewide chief of telepsychiatry and directly treated patients in the correctional system for more than 6 years. Dr Mehta is a board-certified physician in adult, child and adolescent, and forensic psychiatry, as well as addiction medicine.

Do you have experiences in correctional psychiatry or other unique areas in psychiatry you would like to share? We’d like to hear about them! Send proposals to PTEditor@mmigroup.com.
Caregiving: Walking the Personal and Professional Tightrope

Susan Wilkinson, MSN, PMHNP-BC

August 16, 2019, in New Haven, Connecticut, was a beautiful summer evening. A delicious dinner at the Study at Yale hotel, where we were staying for the night, wrapped up a packed day of activities. These included a presentation and conversations about evidence-based addictions treatment modalities. The day could not have been better. I remember thinking that this was "addiction treatment done right." A colleague invited a group of us to walk over to the Arelhssea Farm Dairy store for their famous "designer" ice cream. I asked for a minute to go to my room and slip on some comfortable shoes for the 5-minute walk. I never returned. Instead, I called my colleague to tell him and everyone else to go ahead—I had to handle an urgent matter. I had at least 10 missed calls and several text messages from 2 neighbors.

As clinicians, we are trained and encouraged to have an objective approach to treatment, especially with addictions—substance use addictions in my case. In the Substance Abuse and Mental Health Services Administration (SAMHSA) Technical Assistance Publication (TAP) series (particularly TAP 21), the addiction counseling competencies stress the importance of this approach. The knowledge, skills, and attitudes of professional practice are all structured around preserving the patient's autonomy and promoting the clinician's need for objectivity.1

Traditionally, evidence-based modalities including motivational interviewing (MI), motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), contingency management interventions, and community reinforcement and family therapy (CRAFT), to mention a few, all advocate for openness and giving patients the benefit of the doubt—even when the reported interventions seem counterintuitive and deviate from our personal beliefs and values.2

Succinctly, clinicians should prioritize the patient's needs and well-being while "keeping a lid" on whatever frustrations may arise. After all, there may or may not be professional consequences. As clinicians, we are conditioned to not cross these boundaries regardless of our feelings. Often, this is so we can preserve the therapeutic alliance, which in turn facilitates desired treatment outcomes and prevents contention or confrontation with the patient. When it comes to chronic disease prevention and health promotion, the Centers for Disease Control and Prevention's (CDC) National Center for Chronic Disease Prevention and Health Promotion identifies social connectedness as one of the 5 pillars of their framework.3 Additionally, throughout our training, the need to preserve a therapeutic alliance with our patients is emphasized, particularly because a healthy relationship is one of the major protective factors. But what happens if the patient is a loved one?

We are not trained how to respond when the individual struggling with a substance use disorder or addictions is a loved one. There is no manual on how to help ourselves when we are faced with the challenges of the caretaking role for our loved ones. Although we can apply the same skill set to manage and contain our emotions (i.e., regulate ourselves and convey self-control), when it comes to disappointment, frustration, or betrayal by a loved one, those emotions hit a different nerve altogether. Fulfilling the clinician role is entirely different when that patient is not related to us. The shift in dynamics from a professionally trained caregiving role to complex family relationships presents its own set of challenges—all of which amplify the above-mentioned feeling with an almost visceral pain.

Shame and Guilt: Stepsisters of Fear and Control

In 2016, I embarked on a journey to use my training as a psychiatric nurse practitioner to give back to the community I hail from. With a passion for substance use treatment, I set out to volunteer in Uganda. By 2018 it was clear that for me to contribute in a tangible manner, I needed to become licensed to practice in Uganda (which I did). Part of the licensing process required me to undergo 8 weeks of orientation at the main mental health and substance use referral hospital—Bubalika National Referral Mental Hospital—in Kampala. It was during that training and orientation that the state of substance use in the country became clear to me.

Although there were systems and structures to provide care and support to individuals who struggle with substance use conditions, support for caregivers and family members was nonexistent. In fact, shame and guilt were all I saw. Using fear to scare individuals off substances was normalized, although not fruitful. The whole notion of "no one brings meals when your child is struggling with substance use addictions" was and continues to ring true.

SAHMSA defines recovery as "a process of change through which people improve their health and wellness, live self-directed lives, and strive to reach their full potential." Further outlined in the Table are the 4 major dimensions that support recovery.

For the purpose of this article, I will dwell on the community part. To clarify, my formative years were spent in a strict evangelical household in which alcohol consumption was demonized. The little exposure to alcohol use and related dysfunction that I vaguely remember occurred when I was 10 or 11 years old. I do remember that whenever my stepmother consumed alcohol, there was palpable tension in the home. That said, my early childhood exposure to alcohol use disorder–related dysfunction was minimal. In my youth, I was introduced to shaming and ridiculing those who consumed alcohol. My father and stepmother converted to evangelical Christianity. As part of expressing our newfound faith, we as a family bore witness to how Jesus can make a difference "if we turn to him and confess our sins"; we then become born again. As such, I will not claim to have been in involved in any caretaker role for family or friends until my marriage.

Little did I know that in 2019 I would be on the receiving end of the same isolation experienced by family members caring for their loved ones who struggle with substance use disorders and/or other addictions. Having a loved one in the throes of alcohol addiction is a uniquely subjective experience. Not one experience is the same as another. Shame and guilt are powerful tools that can shake even the most grounded of us. Now I am happy to report that my husband is more than 2 years into his recovery and he continues to work at it. I will also add that we (because addiction affects the whole family) continue to work through the hiccups and hang-ups. I will also add that the experience of dealing with my spouse’s alcohol addiction was and continues to be my motivation for the nonprofit I founded at the end of 2019.

When I used the term visceral pain before, I meant that the frustration, perceived betrayal, hopelessness, anger, and disgust all took on a different tone when it came to my loved one’s addiction. I must admit, I was not graceful at all. I teetered between intellectualizing his addiction and minimizing the impact on us all as a family unit. The denial took on a life of its own. I would convince myself that he only overdrank and binged when he was not happy, and that he was far from meeting the criteria for alcohol use disorder. If it were someone else, with the evidence at hand and long history of telling events, I would not hesitate to diagnose them with severe alcohol use disorder.

Table. The Substance Abuse and Mental Health Service Administration’s 4 Major Dimensions That Support Recovery

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Support</th>
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</thead>
<tbody>
<tr>
<td><strong>Health:</strong> overcoming or managing one's disease(s) or symptoms and making healthy choices that support physical and emotional well-being</td>
<td>1</td>
</tr>
<tr>
<td><strong>Home:</strong> having a stable and safe place to live</td>
<td>2</td>
</tr>
<tr>
<td><strong>Purpose:</strong> conducting meaningful daily activities and having the independence, income, and resources to participate in society</td>
<td>3</td>
</tr>
<tr>
<td><strong>Community:</strong> having relationships and social networks that support support, friendship, love, and hope</td>
<td>4</td>
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Denial Protects, Until It Doesn’t

The screeching wheels came to a stop on August 16, 2019. While I was away at the previously mentioned addictions-related event (go figure), an incident happened at my home. This time I could not intellectualize it and I could not wish it away. I remember going into full damage-control mode, something I had trained my brain to do—fault to. I thought to myself, Contain the damage: what happens in the house stays in the house. Deal with this and handle the rest later. Except this time, I was not physically present to contain the damage. In hindsight, this incessant need to control aspects of my life is what perpetuated my denial all along—even with the “glaring open secret” out there for all to see.

I now realize how oblivious I was to the bitterness that had consumed me. The bitterness in turn triggered my childhood trauma that had been locked away safely (or so I thought). Reflecting on this, I was frustrated at my inability to tap into the same skill set I utilize with my patients as a trained clinician. One might wonder why I could not apply the same empathetic skills to my loved one that I apply to my patients. When it came to my own family member, those skills had waned. I now know that the underlying emotion was fear. Fear of losing my spouse and our children growing up without their dad. Fear of others finding out that my spouse was in fact deep in the vicious cycle of alcohol use disorder. Whenever he had his “episodes,” I reacted with anger. Why was he destroying us and everything we had built? To remind you, I have hundreds of hours of training on addictions, the psychopathology of addictions, the resultant consequences of one’s actions, and how to help them. I could not apply this knowledge eluded me.

This experience clouded my clarity regarding all the work that my loved one had put into his recovery. It was then that I knew I needed help. I underestimated the compounded effects of taking care of others in my professional life, as well as being the care giver of a loved one. Self-help books, therapy, exercise, and sleep hygiene all helped, but the triggers were ever present. It did not take much to get me into that negative space where I never want to be.

Invitation to Change

In summer 2021, a friend—a therapist himself—introduced me to the Center for Motivation and Change (CMC) as a resource for my patients. By this time, as a society, we knew things were not good. Before long I was invited to visit the CMC in the Berkshires in Massachusetts. It was through CMC that I was introduced to the Invitation to Change (ITC) model and the Foundation for Change. In November 2021, I completed the level 1 training as a clinician. The goal of the Foundation for Change is to offer a compassion approach to substance use disorders through their ITC approach, which is “a holistic helping framework designed for the families and loved ones of people struggling with substances, as well as the professionals who support them.” Simply put, the ITC approach combines science and kindness. Its bedrock is that “evidence-based strategies are combined with compassion and care, making a wealth of research-supported and clinically tested knowledge accessible, practical, and understandable for everyone who needs it.”

Combining science and kindness—that was it! It occurred to me that while I was busy taking care of everyone, the truth was that I was also starting to show signs of compassion fatigue, which in turn affected my kindness and empathy scales. I had convinced myself that all was under control. Going through the ITC training helped validate my feelings, without taking away or adding anything. I know that I am a better spouse, mother, and clinician today than prior to the training. To put it bluntly, ITC has not given me the tools; rather, it holds all the tools together. ITC is my toolbox in which I continue to gather and store the tools that help me stay organized and feel secure in my capacity as an effective clinician while recognizing my brokenness.

I now have new lenses through which I view addictions treatment and support for families, and my empathy scale has been recalibrated. This has helped me clean up my relationships and find new meaning in what it means to be an ally—the very word I chose as the name of the nonprofit organization I founded in 2019. I like to tell people that we were allies before being an ally was trendy. I will close by reflecting on a direct quote from the SAHMSA website:

“The process of recovery is supported through relationships and social networks. This often involves family members who become the champions of their loved one’s recovery. Families of people in recovery may experience adversities that lead to increased family stress, guilt, shame, anger, fear, anxiety, loss, grief, and isolation. The concept of resilience in recovery is also vital for family members who need access to intentional supports that promote their health and well-being. The support of peers and friends is also crucial in engaging and supporting individuals in recovery.”

Ms Wilkinson is an advanced practice nurse with an interest in addictions and trauma. She is the founder and president of Your Ally Foundation, Inc. Additionally, she is a clinical preceptor at Boston College William F. Connell School of Nursing in Chestnut Hill and Regis College in Weston, both in Massachusetts.

REFERENCES
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• 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.
• 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
Full-spectrum relief for all bipolar I symptoms in depressive and acute manic or mixed episodes in adults

Proven relief for bipolar I depressive symptoms at the starting dose (1.5 mg/day)
- May increase dose to 3 mg on Day 15. Maximum recommended dose is 3 mg/day, depending on clinical response and tolerability

Placebo-like impact on lipids and fasting glucose
- Weight change ≤1.5 lb
- 3% of patients reported weight increase of ≥7% in bipolar I depression studies

The proportion of patients with metabolic shifts was similar to placebo.\(^1\)

**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%).


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CONTRAINDICATIONS: VRAYLAR is contraindicated in patients with a history of a hypersensitivity reaction to cariprazine. Reactions have ranged from rash, urticaria, urticaria, and events suggestive of angioedema (e.g., swelling tongue, lip swelling, face edema, pharyngeal edema, and swelling face).

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. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis (see Warnings and Precautions). Suicidal Thoughts and Behaviors: Antipsychotic drugs may increase the risk of suicide in patients with serious mental illnesses, including bipolar disorder. The incidence of suicidal thoughts and behaviors in short-term trials may not reflect the rates after longer term exposures (see Dosage and Administration and Clinical Pharmacology in the full Prescribing Information for adverse reaction information for adverse reactions associated with use of cariprazine). Incidence of Suicidal thoughts and Behaviors: In placebo-controlled trials up to 8 weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with VRAYLAR and placebo. In the long-term, open-label bipolar disorder studies, 4% of patients with normal hemoglobin A1c baseline and 3% of patients with pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of serious infections or chills were objectively collected using the Simpson Angus Scale (SAS) for treatment-emergent EPS (both akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, and tremor) and restlessness. VRAYLAR and other antipsychotic drugs can cause extrapyramidal symptoms (EPS), including akathisia, hyperreflexia, and tardive dyskinesia. Tardive dyskinesia is a movement disorder that may manifest as orofacial dyskinesia, dystonia, and/or extrapyramidal symptoms (EPS) and akathisia, and patient response for several weeks after a patient has been treated with VRAYLAR and after each dosage increase. Consider reducing the dose or discontinuing the drug. Metabolic Changes: Antipsychotic drugs cause a metabolic syndrome characterized by abnormalities in lipids, weight gain, and glucose tolerance. Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Cerebrovascular Disease: Treatment with VRAYLAR may require treatment with VRAYLAR despite the presence of the syndrome. Late-Occurring Adverse Reactions - Adverse events may first appear several weeks after the initiation of VRAYLAR treatment, probably related to drug accumulation in body tissues. Somnolence, sedation, and related events were also reported with VRAYLAR. VRAYLAR and other antipsychotic drugs should be used cautiously in patients with a history of cardiovascular disease (e.g., myocardial infarction, stroke, or transient ischemic attack) or in patients with severe hypertension, hyperthyroidism, or hypothyroidism.
Adverse Reactions Occurring in 2% of VRAYLAR-Treated Patients and Placebo-Treated Adult Patients in 3-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=488), VRAYLAR 1.5 mg/day (N=539), VRAYLAR 4.5 mg/day (N=575), and VRAYLAR 9 mg-day (N=570). The adverse reactions in the full Prescribing Information shows the incidence of EPS is shown as: Placebo (N=488), VRAYLAR 1.5 mg/day (N=539), VRAYLAR 4.5 mg/day (N=575), and VRAYLAR 9 mg-day (N=570). The adverse reactions in the full Prescribing Information shows the incidence of EPS by adverse event are as follows: all EPS events (13.2%), extrapyramidal symptoms (EPS) (8.8%, 9%, 7%), parkinsonism (2.5%, 3%, 2.5%), akathisia (1.8%, 2%, 1.8%), dystonia (1.6%, 1.8%, 1.6%), tardive dyskinesia (0.7%, 0.7%, 0.7%), restless legs syndrome (2.5%, 2.5%, 2.5%), tardive dyskinesia (2.3%, 2.3%, 2.3%). Adverse Reactions Occurring in 2% of VRAYLAR-Treated Patients and Placebo-Treated Adult Patients in 3-Week Schizophrenia Trials. Percentage values shown in parentheses are as follows: Placebo (N=488), VRAYLAR 1.5 mg/day (N=539), VRAYLAR 4.5 mg/day (N=575), and VRAYLAR 9 mg-day (N=570). The adverse reactions in the full Prescribing Information shows the incidence of EPS is shown as: Placebo (N=488), VRAYLAR 1.5 mg/day (N=539), VRAYLAR 4.5 mg/day (N=575), and VRAYLAR 9 mg-day (N=570). The adverse reactions in the full Prescribing Information shows the incidence of EPS by adverse event are as follows: all EPS events (13.2%), extrapyramidal symptoms (EPS) (8.8%, 9%, 7%), parkinsonism (2.5%, 3%, 2.5%), akathisia (1.8%, 2%, 1.8%), dystonia (1.6%, 1.8%, 1.6%), tardive dyskinesia (0.7%, 0.7%, 0.7%), restless legs syndrome (2.5%, 2.5%, 2.5%), tardive dyskinesia (2.3%, 2.3%, 2.3%).
not recommended

USE IN SPECIFIC POPULATIONS:

Rifampin, carbamazepine.

The full Prescribing Information lists the Clinically Important Drug Interactions with VRAYLAR.

DRUG INTERACTIONS:

– Stevens-Johnson syndrome.

Rare

Infrequent

Frequent

Reaction has been identified during post approval use of VRAYLAR. Because these reactions are

Tissue Disorders:

CYP3A4 Inhibitors:

– Reduced CYP3A4 activity and/or reduced CYP3A4-mediated drug metabolism.

Clinical Impact:

Examples:

CYP3A4 Inducers:

– Increased CYP3A4 activity and/or increased CYP3A4-mediated drug metabolism.

Clinical Impact:

Examples:

Other Specific Populations:

Usage of VRAYLAR is not recommended in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). VRAYLAR has not been evaluated in this patient population. Renal Impairment: No dosage adjustment for VRAYLAR is required in patients with mild to moderate renal impairment (CrCl ≥ 30 mL/minute). VRAYLAR has not been evaluated in this patient population. Smoking: No dosage adjustment for VRAYLAR is needed for patients who smoke. VRAYLAR is not a substrate for CYP1A2; smoking is not expected to have a marked effect on VRAYLAR clearance.

Drug Abuse and Dependence:

– Not a drug with abuse potential.

Hepatic Impairment:

– No dosage adjustment for VRAYLAR is required in patients with severe hepatic impairment (Child-Pugh score between 10 and 15).

OVERDOSAGE:

– Human Experience: In pre-marketing clinical trials involving VRAYLAR in approximately 5000 patients or healthy subjects, accidental acute overdose (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered without sequelae.

– Overdose in animals: Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dose (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated populations 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. Adverse pregnancy outcomes in women of reproductive potential who are exposed to VRAYLAR during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit www.womenshealth.org/atypical/clinical-and-research-program/pregnancyregistry/. Risk Summary – Neonates exposed to antipsychotics 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 pregnancy to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DDcar, has been detected in adult patients up to 12 weeks after following delivery [see Clinical Pharmacology in the full Prescribing Information]. Intervention: Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended [see Drug Interactions and Administration in the full Prescribing Information]]. Examples: rifampin, carbamazepine.

USE IN SPECIFIC POPULATIONS:

Pregnancy - Pregnancy Exposure Registry - There is a possibility that VRAYLAR may increase the risk of miscarriage in women of reproductive potential who are exposed to VRAYLAR during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit www.womenshealth.org/atypical/clinical-and-research-program/pregnancyregistry/. Risk Summary – Neonates exposed to antipsychotics 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 pregnancy to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DDcar, has been detected in adult patients up to 12 weeks after following delivery [see Clinical Pharmacology in the full Prescribing Information]]. Intervention: Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended [see Drug Interactions and Administration in the full Prescribing Information]]. Examples: rifampin, carbamazepine.

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Lessons and Discussions in the Round: Exploring Bipolar Disorder

In an innovative custom series, Psychiatric Times™ asked 3 renowned psychiatric clinicians to lead roundtable discussions across the country, and their takeaways were largely based on the very principle that Sir William Osler shared with his disciples so many years ago: The patient’s insights, experiences, and symptoms will not only help guide the diagnosis but also lead you to the most appropriate treatment strategy.

The roundtable sessions were held in Austin, Texas; Los Angeles, California; and Tampa, Florida, in intimate settings to allow for case review and discussions. Gus Alva, MD, assistant professor at University of California Riverside Medical School in the Department of Neuroscience, kicked off the series on the west coast and led an informative and engaging session based on a case of a 23-year-old woman who presented with moderate depressive symptoms.

Not unlike the types of patients who present to the clinicians attending the sessions, this young woman also had medical complications: type 2 diabetes, managed by metformin 1000 mg taken orally twice daily, and an HbA1c level of 7.8%; hypertension, managed by lisinopril 20 mg taken orally every day; and obesity, with a body mass index of 31.2. Notably, lab values were within normal range and her urine toxicology screen was negative.

The patient had received a diagnosis of attention-deficit/hyperactivity disorder in middle school, which was treated with medication at the time, but she currently manages on her own via mindfulness. She has no history of suicidal thoughts or behaviors, self-injurious behaviors, psychiatric hospitalizations, or problems with substance abuse.

Her chief complaints consist of decreased energy and depressed mood, but she also notes difficulty in paying attention, organizing her day, and accomplishing tasks at work. Although she says the symptoms started abruptly 3 weeks ago, she has reported 2 brief episodes of depression over the past 2 years, each lasting about 2 months. Before this most recent episode, she was functioning “better than usual, requiring little sleep and getting more accomplished.”

During her first depressive episode, she was started on sertraline 25 mg, which was titrated to 50 mg; she improved on this dose combined with psychotherapy. In the second depressive episode, the sertraline was increased to 100 mg. This dose resulted in improvement, but she noted that she felt a little activated and had trouble sleeping. Her primary care provider then decided it was time to refer her to a psychiatrist with this third episode of depression.

Almost immediately, the group was drawn to the issue of substance use, and they were surprised at the negative screen. The attendees discussed the apparent need for patients to self-medicate.

“I have done a fair amount of dual diagnosis work,” Alva agreed. “It’s amazing the proportion of individuals with bipolar disorder that end up in acute detox or rehab settings. And the common theme is, ‘I was trying to slow down my mind and wanted to settle my senses.’”

What’s in a Name?

Alva’s attendees soon found themselves deep in another discussion on labels, diagnoses, and the importance of psychoeducation, topics that resonated across all 3 roundtable sessions. The California group noted that patients are generally more willing to accept a diagnosis of unipolar depression as opposed to bipolar depression. In fact, an attendee said her patient is even more willing to accept the diagnosis of borderline personality disorder.

Bethanie Simmons-Becil, DNP, APRN, PMHNP-BC, APHN-BC, who moderated the roundtable in Florida, found the same discussion relevant among attendees. “A lot of patients are not happy with the diagnosis of bipolar disorder. There is a lot of social stigma involved with bipolar disorder mostly because of social media,” she said during the discussion. “It is always a struggle when you tell a patient—especially for the first time—that [they] might have bipolar disorder.”

Her group discussed the importance of what the diagnosis means for the patient—that it can be a functional disease. Simmons-Becil explains to patients, “You don’t have to go on disability. You don’t have to be out of work. You don’t have to give up your life. These are conditions that can be managed and managed well with medication and have little impact over time, especially if you maintain treatment and regular therapy.
“Listen to your patient; he is telling you the diagnosis.”
—Sir William Osler, MD, FRS, FRCP

which is always incredibly helpful.”

The roundtable participants in Texas also felt it was important to truly engage the patient when making the diagnosis, noted moderator Nidal Moukaddam, MD, PhD. Moukaddam is an associate professor in the Menninger Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine, as well as the Ben Taub Adult Outpatient Services director and medical director of the Stabilization, Treatment & Rehabilitation (STAR) Program for Psychosis, also at Baylor College of Medicine. She also serves on the Psychiatric Times™ Editorial Board.

Moukaddam added that the group did not want to give someone a “diagnosis of bipolar disorder, which is a lifelong disorder, without knowing exactly what the patient has been through.” Getting the right diagnosis takes time. The participants spoke of “dilution of care, and how quick encounters in which patients are not given the time that they need is not a good thing.” Moukaddam added that they agreed it is important “to educate patients and work with them and establish that nice rapport that makes them know ‘your doctor is on your side.’”

Simmons-Becil suggested taking this notion even further, and often shares resources with patients. “Especially for those that don’t have a good support system in their community, give them references to community support groups, not just NAMI [National Alliance on Mental Illness] but also open group therapy and things that might be more beneficial, especially if they’re starting to struggle with social isolation or feeling lonely because of their diagnosis.”

Concluding Thoughts
Ultimately, all 3 moderators were impressed with the dedication of their colleagues who attended the roundtables, which included psychiatrists, psychiatric nurse practitioners, and other clinicians. The groups were all focused on understanding patients’ symptoms and histories to determine the most appropriate treatment for each individual patient. Doing so, the participants noted, makes it easier to help patients better understand their condition and the importance of treatment, so they can work on the road to optimal functioning and overall good health.

“The most important thing to do when somebody comes to you, even if they tell you they have a diagnosis, is to confirm the diagnosis. You want to start by making up your own mind...[and] typically, the part of the history that’s hardest to nail down is mania,” Moukaddam said. “Thus, my first step is confirming the diagnosis. My second would be a lot of psychoeducation; make sure that the patient understands what he’s up against and why he needs treatment.”

Collaboration and discussions, such as what took place in these roundtables, also help propel the field and improve patient care, noted Simmons-Becil. “[This gives] me hope for the psychiatric community, specifically for those of us who prescribe in the psychiatric community, just because the more we work together, the better we do for our patients,” she said.

“The more open communication we have as providers, the less stigma there will be associated with bipolar disorder, and the more willing patients might...be to seek help,” Simmons-Becil added. “Further, for those of us who meet each other in the community and work together, we also realize that we are not alone in this battle, either, and that we have valuable peers, educated professionals, that can support us and work with us to help ensure best outcomes for all of our patients.”
Optimize your practice by learning about a wide range of ADHD management topics including alternative, innovative approaches in supporting your pediatric patients, lifestyle factors that may contribute to ADHD, emerging technological tools, and more!

Psychiatric Times™ most recent podcast titled “Lifestyle Interventions for ADHD” features Editor-in-Chief John J. Miller, MD and distinguished professor and vice chair of research of psychiatry and behavioral sciences at SUNY Upstate Medical University, Stephen Faraone, PhD.

Listen now to the latest podcast episodes exclusively on Psychiatric Times™.
Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (ANMDARE) is an autoimmune condition caused by reversible internalization of the NMDA receptor as the result of autoantibodies produced via an immunologic trigger. The condition was first described in the literature in 2005 by Vitaliani and colleagues, with a description of the autoantibodies coming just 2 years later by Dalmau et al. Since its discovery, it has become the most common autoimmune encephalitis.

Epidemiologically, a vast age range (2 months to 85 years) of affected patients has been documented, with a mean age of onset of around 21 years. There is an increased prevalence among younger women than men (4:1); this sex discrepancy appears to even out after age 45 years. It is frequently described as a paraneoplastic condition due to its popular association with ovarian teratomas; however, this is not always the case, as viral causes have been documented, as well as undetermined causes. This article reviews the most up-to-date literature regarding the pathophysiology of ANMDARE and provides a brief overview of the clinical features, diagnostic imaging findings, and treatments.

Clinical Features
The first described cases of ANMDARE involved 4 women diagnosed with comorbid ovarian teratomas and identified a distinguishable pattern of symptoms. The clinical features of ANMDARE can therefore be described as progressive through 3 stages (Figure 1):

1. The prodromal stage. This first stage presents with flu-like symptoms, such as headache, fatigue, and low-grade fever.
2. The psychotic stage. The prominent positive and negative symptoms indistinguishable from those seen in schizophrenia (eg, hallucinations, delusions, disorganized behavior, and paranoia) are associated with the second stage.
3. The neurologic. In this third stage, there are more neurological symptoms, such as focal or generalized seizures, dyskinesias, and autonomic instability. Other neuropsychiatric symptoms include agitation, irritability, catatonia, depression, speech dysfunction, and memory loss. Some patients experience residual neurologic sequelae posttreatment that may last months to years. These stages represent the most common progression, but other variations are seen. Below are cases discussed in the literature that exemplify this variety, followed by the pathophysiology as we understand it today and a brief overview of laboratory findings, imaging, and treatment.

ACTIVITY GOAL
The goal of this activity is to review the pathophysiology of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (ANMDARE).

LEARNING OBJECTIVES
1. Understand the pathophysiology of ANMDARE to the cellular level.
2. Recognize the various tools used to diagnose ANMDARE as well as the specific findings seen.

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 seeking to improve the care of patients with mental health disorders.

ACCREDITATION/CREDIT DESIGNATION/ FINANCIAL SUPPORT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACME) through the joint providership of Physicians’ Education Resource®, LLC, and Psychiatric Times®. Physicians’ Education Resource®, LLC, is accredited by the ACCME to provide continuing medical education for physicians. Physicians’ Education Resource®, LLC, designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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A 27-year-old woman with no significant psychiatric or systemic medical history presents to the emergency department with a 15-day history of disorganized thoughts, hypochondriacal delusions, auditory hallucinations, insomnia, and short-term memory loss. History of present illness does not reveal headache, fever, seizures, dyskinesia, or autonomic instability. Mental status examination exhibits disorientation to time, abstract thinking deficits, poor attention, speech latency, verbal perseveration, and auditory hallucinations. Initial laboratory studies and imaging are normal; she is admitted to an inpatient psychiatric unit for management of first episode psychosis.

While on the psychiatric unit, the patient displays food refusal, decreased speech, and alternating periods of hypo- and hyperkinetic movement. The initial medication regimen consists of aripiprazole, titrated to 30 mg/day and lorazepam 3 mg/day. Although she shows improvement in her psychotic and behavioral symptoms, her short-term memory symptoms worsen, leading to further neurological work-up.

Brain MRI shows diffuse sulcal enlargement of the cerebellar vermis. Electroencephalography (EEG) shows independent bilateral temporal slow activity without an extreme delta brush pattern. Complete blood analysis is unremarkable. Urine toxicology is negative.

Given the atypical presentation, anti-NMDA receptor antibodies are checked in serum and cerebrospinal fluid (CSF); results of both analyses are positive. All other autoimmune antibodies are negative. CSF also shows mild lymphocytic pleocytosis with lymphocyte predominance. Endovaginal ultrasound shows a mass in her right ovary, which is subsequently diagnosed as an ovarian teratoma.

Further treatment consists of intravenous (IV) immunoglobulin 0.4 mg/kg/d and methylprednisolone 1 g/d for 5 days, which are successful in improving her episodic and visual memory, verbal fluency, and attention as well as in decreasing her psychotic symptoms. Repeated brain MRI and EEG show no specific findings. She is discharged on aripiprazole 30 mg/d, prednisolone 60 mg/d, and monthly IV immunoglobulin 0.4 mg/kg/d for 5 days. Both psychiatric and neurological follow-up reveal marked improvement in all symptoms.

**Pathophysiology**

NMDA-glutamate receptors are ionotropic receptors that regulate multiple neuropsychiatric functions, including learning, memory, and neuroplasticity. They are complexes made up of 4 subunits—2 GluN1 subunits and 2 GluN2 subunits—each with similar structures. These subunits serve as the target for the autoantibodies produced in ANMDARE (Figure 2).

The NMDA receptor is an ionotropic glutamate receptor that regulates multiple neurological functions. It is a heterodimer consisting of 2 NR1 subunits that bind to glycine and 2 NR2 subunits that bind to glutamate. These subunits serve as the target for anti-NMDA receptor antibodies. Binding of each subunit’s respective ligand activates the receptor and opens the ion channel, which is highly permeable to calcium, and allows the receptor to exert its effects.

ANMDARE is ultimately caused by autoantibodies that stimulate reversible internalization of the NMDA receptor. This internalization creates a state of NMDA hypofunctionality, which is described in the NMDA hypothesis of psychosis. It also is the likely cause of the prominent positive and negative psychotic symptoms. It is most widely accepted that the specific site of autoantibody action is at the GluN1 subunit. These autoantibodies cause croslinking of the NMDA receptor, altering their ability to interact appropriately, which leads to their internalization and trafficking through endosomes and lysosomes.

Production of these autoantibodies can largely be divided into 3 categories: paraneoplastic processes, viral infections, and unknown. The most common paraneoplastic trigger is ovarian teratoma. It is hypothesized that neuronal tissue exposing the NMDA receptor is contained within some teratomas. These tumor cells undergo apoptosis and release antigen to antigen-presenting cells (APCs), which engulf free antigen and present it to regional lymph nodes. Because antigens are typically intracellular in tumor cells and cannot be easily accessed by APCs, it is suspected the cytotoxic T cells play a role. Herpes simplex virus (HSV) is the most common viral trigger. It is thought that the inflammatory process of the encephalitis causes neuronal degeneration and formation of inflammatory infiltrates, leading to antigen uptake by APCs or direct delivery to local lymph nodes.

Regardless of the initial immunologic trigger, the downstream effect is the production of memory B cells, activation of naive B cells via CD4-positive cells, and anti-NMDA receptor an-
tibody-producing plasma cells, which pave the way for NMDA receptor disruption, de-stabilization, and internalization. Once naïve B cells are produced and activated, they enter the central nervous system (CNS) and undergo restimulation due to the high prevalence of NMDA receptors in the brain. This results in the production of plasma cells specific to the NMDA receptor.

Research suggests that it is primarily these antibodies produced by plasma cells already in the CNS that contribute most to development of disease compared with systemic antibodies. The site of recognition for the autoantibodies is on the GluN1 subunit of the receptor. The autoantibodies disrupt the stability of the receptor, particularly by interfering with the interaction between the NMDA receptor and EphB2, a protein that functions in a supportive and stabilizing role to the NMDA receptor. It is specifically the disrupted interaction between EphB2 and NMDA that leads to displacement and internalization. Further characterization regarding the mechanism of internalization has not yet been clearly described. Recent studies have begun to explore the possible role of scaffolding and stabilizing proteins in this process, the most notable of which is PDS-95 due to its role in anchoring the NMDA receptor to the cell membrane.

Regarding the progressive stages of ANMDARE, what is known of the current pathophysiology can be correlated to the progression of clinical presentation. The prodromal phase of flu-like illness may be attributed to increased proinflammatory cytokines seen in patients with ANMDARE, such as increased serum IL-2 levels and increased CSF IL-6 and CXCL13 levels. The psychotic symptoms seen in the second stage appear to be most likely related to NMDA hypofunctionality resulting from growing numbers of anti-NMDA antibodies and internalization of the synaptic NMDA receptors.

In later stages of ANMDARE, neurologic symptoms, such as seizures, are the hallmark. Research suggests that during the molecular stages before NMDA receptor internalization, anti-NMDA receptor antibodies act briefly as agonists to NMDA receptors, which lowers the seizure threshold. This is an important detail regarding pathophysiology, because it reveals that NMDA hypofunctionality does not completely explain the core symptoms. Other NMDA hyperfunctional symptoms include catatonia and dystonia; the same mechanism of brief NMDA receptor agonist activity is theorized to be responsible for these symptoms. Finally, many patients with ANMDARE suffer severe cognitive symptoms, which—like the psychotic symptoms—can be explained by NMDA hypofunctionality. Decreased NMDA receptor function leads to decreased neuronal activity in the dorsolateral prefrontal cortex, which is required for working memory, cognitive flexibility, and executive planning.

### Diagnosis

ANMDARE can be diagnosed with the use of laboratory tests (both serum and CSF antibodies), imaging (ie, MRI and 18-fluorodeoxyglucose–positron emission testing (FDG-PET), EEG, and the following ancillary tests.

#### Antibody Tests

The most common autoantibody detected and implicated in the diagnosis of ANMDARE is anti-NMDA receptor. Antibody studies should include CSF analysis. Serum analysis for antibodies can be performed, but they are not completely reliable on their own due to false-negative or false-positive diagnosis. Studies have shown that serum analysis is less consistent and has even shown positive results in patients without ANMDARE. Specifically in cases of ANMDARE caused by HSV encephalitis, other antibodies have been seen alongside NMDA receptor antibodies, such as GABA<sub>A</sub> receptor and dopamine 2 receptor antibodies.

#### CSF Findings

CSF findings are abnormal in most patients with ANMDARE (80%), mostly in those with late-phase disease. Findings include lymphocytic pleocytosis, normal or mildly increased protein levels, and CSF-specific oligoclonal bands. Depending on the course of treatment, antibodies may be seen only in CSF. The CSF titers may be predictive of prognosis and response to treatment.

#### Imaging Findings

MRI findings are normal in 50% of patients with ANMDARE (Figure 3). When findings are present, they are mostly seen on T2 or FLAIR and show signal hyperintensity in the cerebellar or cerebral cortex, hippocampi, basal ganglia, brainstem, frontobasal and insular regions, and sometimes the spinal cord. These findings are mostly mild/transient and occasionally show contrast enhancement.

18F-FDG-PET/CT scan could be helpful in the diagnosis of ANMDARE in patients with normal MRI findings (Figure 3). In a small (n=5) series of cases published by Solnes et al, patients with ANMDARE who demonstrated normal MRI results were all noted to have abnormal 18F-FDG-PET/CT scan results (Table 1). Findings included lobar hypometabolism in a wedge-shaped pattern mostly found in the parietal lobe, followed by the occipital and temporal lobes. One study found frontotemporal hypoperfusion and brain atrophy. Other imaging modalities, such as MR spectroscopy and 9mTc-d-l-hexamethyl-propyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) show transient cortical and subcortical changes.

#### EEG Findings

EEG findings are usually abnormal. The most common finding is nonspecific, slow, disorganized activity, sometimes with electrographic seizures. When patients present with catatonia, they show slow, continuous rhythmic activity in the delta-theta range. Nonepilepti-
form seizures may occur and, hence, video EEG may become increasingly important.

Ancillary Tests. ANMDARE often occurs as a paraneoplastic syndrome, most commonly in the presence of an ovarian teratoma. Very rarely, patients may be diagnosed with a different tumor type, such as Hodgkin lymphoma or neuroblastoma.11,22 Important tests for ovarian teratomas include pelvic CT scans, MRI, and pelvic and transvaginal ultrasound. Tumor markers include B-human chorionic gonadotropin, AFP, CA-125, and testosterone. Other etiologies (aside from tumors) can include infections, such as herpes zoster infection, diphtheria, pertussis, tetanus vaccination, and H1N1 vaccination.22,23 Some patients have associated microdeletion of the short arm of chromosome 6 (which included the HLA cluster) antibody to proliferating and anti-nucleus antibodies.24,25

Concluding Thoughts

Despite the amount of research into ANMDARE, a definitive pathophysiological mechanism has yet to be determined. Most studies investigating the mechanism of this condition have pinpointed the most likely pathology to be determined. Most studies investigating the mechanism have pinpointed the most likely pathophysiology first described only 17 years ago that is responsible for the onset of sudden psychotic symptoms. When correctly diagnosed and treated with immunoglobulin and corticosteroids, ANMDARE resolves and these patients generally rapidly improve. As we continue to understand the complexities of the brain, and as further research reveals more information, it is likely that additional unique pathophysicsy will be discovered as etiological for psychosis, mania, and other psychiatric symptoms. These potential findings may provide pathways for the development of novel treatments to reduce, or even eliminate, these symptoms.

ACKNOWLEDGEMENT

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REFERENCES


Table 1. 18F-FDG-PET/CT Findings in Patients With ANMDARE

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>MRI Brain Result</th>
<th>18F-FDG-PET/CT Result</th>
<th>18F-FDG-PET/CT Findings</th>
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<td>1</td>
<td>ANMDARE</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Hypoperfusion of Right PAR, right FRT, Bilateral OCC</td>
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<tr>
<td>2</td>
<td>ANMDARE</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Hypoperfusion of Bilateral PAR, Right TMP, Bilateral FRT, Bilateral OCC</td>
</tr>
<tr>
<td>3</td>
<td>ANMDARE</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Hypoperfusion of Bilateral PAR, Bilateral OCC</td>
</tr>
<tr>
<td>4</td>
<td>ANMDARE</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Mild Hypoperfusion of Right OCC</td>
</tr>
<tr>
<td>5</td>
<td>ANMDARE</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Hypoperfusion of Left PAR, Bilateral OCC</td>
</tr>
</tbody>
</table>

*This table exhibits abnormal findings discovered on 18F-FDG-PET/CT that were not seen on MRI in patients with diagnosed ANMDARE. This was originally published in Solnes LB et al. J Nucl Med. 2017;58(8):1307-1313. Reproduced with permission.
Hackensack Meridian Health is a leading not-for-profit health care network in New Jersey offering a complete range of medical services, innovative research, and life-enhancing care aiming to serve as a national model for changing and simplifying health care delivery through partnerships with innovative companies and focusing on quality and safety.

Through a partnership between Hackensack Meridian Health and Seton Hall University, the School of Medicine will re-define graduate medical education, research, and clinical practice; reverse the critical physician shortage in both the New York/New Jersey metropolitan area and the nation; and stimulate economic development in northern New Jersey.

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“Ocean Medical Center’s psychiatry program will be a community-based program,” said Ramon Solkhah, M.D., program director for psychiatry as well as founding Chair of Psychiatry & Behavioral Health at the Hackensack Meridian School of Medicine at Seton Hall University.

“Our new psychiatry residency program will improve clinical care and ultimately encourage future health care leaders to build practices in the Jersey Shore area.”

As the area’s premier provider of psychiatric services, Hackensack Meridian Behavioral Health Services has provided comprehensive mental health and substance abuse services to the residents of Monmouth, Ocean, Middlesex, and Bergen Counties for over forty years. Due to continued growth and expansion, we are currently accepting applications for Psychiatrists to join our Mental Health and Addiction Interdisciplinary Teams in the following positions:

**Addiction Medicine:** Ocean University Medical Center (Brick, NJ)

**Carrier Clinic (inpatient):** Adult Staff Psychiatrist (Belleville, NJ)

**Geriatric Psychiatry:** Hackensack University Medical Center (Hackensack, NJ), Ocean University Medical Center (Brick, NJ)

**Inpatient:** Ranitan Bay Medical Center (Perth Amboy, NJ)

**Medical Director for Adult Inpatient Unit:** Riverview Medical Center (Red Bank, NJ)

**Outpatient Addiction:** Jersey Shore University Medical Center (Neptune, NJ)

**Outpatient Child & Adolescent Psychiatrist:** Hackensack University Medical Center (Hackensack, NJ) and Ocean University Medical Center (Brick, NJ)

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- Psychiatrist for Emergency Department

CENTER FOR TRAUMATIC-STRESS, RESILIENCY AND RECOVERY: NYC/LI
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- Outpatient Child & Adolescent Psychiatrist
- Unit Chief, Inpatient Psychiatry
- Staff Psychiatrist, Inpatient Unit
- On Call Psychiatrist
- Addiction Psychiatrist

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- Weekend Outpatient Faculty Attending Psychiatrist

SOUTH OAKS HOSPITAL: Amityville, NY
- Medical Director, Outpatient Child & Adolescent Psychiatry
- Outpatient Child & Adolescent Psychiatrist
- Adult Inpatient Psychiatrist
- Inpatient Child & Adolescent Psychiatrist
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Minimum Qualifications
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Other positions open at CMHII Pueblo include: Staff Psychiatrist Req. 21041, Medical MD Req. 21324, Psychiatrist APN/PA/NP Req. 21326

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Department of Psychiatry
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For more information, please contact Linda Wiley, Physician Recruiter at Linda.Wiley@mainehealth.org.

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Jenny Flaugh, Director, Physician Recruitment, Cleveland Clinic Florida
Email: flaughj@ccf.org

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Qualifications:
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- Open to both new graduates and experienced psychiatrists
- Demonstrated success working individually and as part of a team
- Able to work weekends

Benefits:
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- Sign-on Bonus
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- CME and Tuition Reimbursement
- Flexible scheduling with paid time off
- State of the art equipment
- Healthy work environment
- Flexible work pool with excellent colleagues
- Potential opportunities at our other locations
- If interested, please send CV and a brief letter of interest to Johnny Batista II, Physician Recruiter at Johnny.Batista@atlantichealth.org.

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New Jersey

Atlantic Health System

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- Demonstrated success working individually and as part of a team
- Able to work weekends

Benefits:
- Very competitive salary
- Sign-on Bonus
- Robust benefits package
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- Flexible scheduling with paid time off
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- If interested, please send CV and a brief letter of interest to Johnny Batista II, Physician Recruiter at Johnny.Batista@atlantichealth.org.

North Carolina

CAPE FEAR VALLEY HEALTH

We Want You to Join Our Behavioral Health Team!

Cape Fear Valley Behavioral Health is one of the largest comprehensive, multi-tiered behavioral health services in North Carolina. Behavioral Health Care’s mission is to meet and respond to the mental health needs of the community. We offer evidence-based, best practice treatments. 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:

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INGREZZA 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.

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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 CYP3A4 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 CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily. INGREZZA should be used with caution 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 with other VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <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 2 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling, and hypokinesia. In cases in which 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/ schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 28% were Hispanic or Latino. All subjects continued previous 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=262) (%)</th>
<th>Placebo (n=183) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnia, fatigue, sedation)</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
| Other Adverse Reactions Observed During the Premarketing 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 noninformative, 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
- Neuromuscular Disorders: dystonia, dyskinesia, extrapyramidal symptoms (non-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 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.

**Immune System Disorders:**
- Hypersensitivity reactions (including allergic dermatitis, angioedema, pruritis, and urticaria)

**Skin and Subcutaneous Tissue Disorders:**
- Rash

**Dugs Having Clinically Important Interactions with INGREZZA**

**Table 2: Clinically Significant Drug Interactions with INGREZZA**

<table>
<thead>
<tr>
<th>Monamine Oxidase Inhibitors (MAOIs)</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<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>Avoid concomitant use of INGREZZA with MAOIs.</td>
<td>Isocarboxazid, phenelzine, selegiline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitors</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<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>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.</td>
<td>Nelfinavir, indinavir, ritonavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP2D6 Inhibitors</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine’s active metabolite compared with the use of INGREZZA alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.</td>
<td>Quinidine, verapamil, diltiazem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inducers</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<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>Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.</td>
<td>Erythromycin, clarithromycin, fluconazole, itraconazole, phenytoin, St. John’s wort</td>
</tr>
</tbody>
</table>

**Dugs Having No Clinically Important Interactions with INGREZZA**

**Table 3: Dose Adjustment of INGREZZA in Presence of Specific Drugs**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<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>Digoxin concentrations should be monitored when coadministering INGREZZA with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.</td>
</tr>
</tbody>
</table>

**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.poisonguru.org).

For further information on INGREZZA, call 844-INGREZZA (844-649-7792).

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San Diego, CA 92130
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INGREZZA is a registered trademark of Neurocrine Biosciences, Inc.
HELP YOUR ADULT PATIENTS WITH TARDIVE DYSKINESIA (TD)

Take. Control.

INGREZZA is the simple, once-daily choice to reduce TD severity

THE SIMPLE CHOICE
Once-daily INGREZZA is the simple choice to support patient adherence.†

SYMPTOM REDUCTION
INGREZZA 80 mg reduced uncontrolled movements in 7 of 10 patients at 6 weeks (post hoc analysis).†‡

SAVINGS & SUPPORT
$10 or less out-of-pocket is what most patients pay for INGREZZA.¶

Visit INGREZZAHCP.com/Results to see how you can help your TD patients take control

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

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
INGREZZA 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 & 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. 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.

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.


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